

# Comparison of Detectability of Visual Field Abnormality by Frequency Doubling Technology in Primary Open-angle Glaucoma and Normal-tension Glaucoma

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**Purpose:** To compare the effectiveness of frequency doubling technology (FDT) in detecting abnormalities in primary open-angle glaucoma (POAG) and in normal-tension glaucoma (NTG).

**Methods:** Twenty-nine POAG patients (29 eyes) and 27 NTG patients (27 eyes) were studied. All subjects underwent testing with program C-20 of FDT with appropriate corrective lenses.

**Results:** No significant differences were observed between the two groups in mean age, mean deviation (MD), and pattern standard deviation (PSD) measured by the Humphrey Field Analyzer (HFA). The correlation between MD values determined by HFA ( $x$ ) and FDT ( $y$ ) is represented by  $y = 0.60x - 2.7$  ( $r = 0.78, P < .01$ ) in the POAG group and  $y = 0.59x + 0.6$  ( $r = 0.81, P < .001$ ) in the NTG group. Although the average MD measured by FDT was significantly lower in the POAG group than in the NTG group ( $P < .05$ ), no significant difference was found in average PSD between the two groups. In early glaucoma cases ( $MD \geq -5$  dB by HFA), a larger proportion of cases in the POAG group than in the NTG group had lower significance level of MD determined by FDT than by HFA ( $P < .02$ ). At many test points on the temporal periphery in the FDT, the mean sensitivity was lower in the POAG group than in the NTG group; whereas no significant differences among HFA test points were observed.

**Conclusions:** Frequency doubling technology detected visual field abnormalities in POAG cases more sensitively than in NTG cases. This finding indicates that the pathogenesis of My-cell damage is rather different in POAG and NTG. **Jpn J Ophthalmol 2001;45:503-509**  
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**Key Words:** Frequency doubling technology, Humphrey Field Analyzer, My-cell, normal-tension glaucoma, primary open-angle glaucoma.

## Introduction

In experimental glaucomatous eyes, larger ganglion cells are reported to be damaged predominantly in chronic elevation of the intraocular pressure (IOP), and the magnocellular pathway is thought to be damaged in the early stage of glaucoma.<sup>1</sup> With this background, many psychophysical tests utilizing the characteristics of retinal ganglion cells, such as temporal and spatial frequency properties, were performed on early glaucoma cases to detect dysfunction of the magnocellular mechanism (M-cells).<sup>2</sup>

Frequency doubling technology (FDT; Welch-Allyn, Skaneateles, NY, USA, and Humphrey/Zeiss, St Louis, MO, USA) is a perimeter that detects the dysfunction of a subset of M-cells, the My-cells, which constitute a small percentage of the M-cells and exhibit nonlinear response properties.<sup>3</sup> Recently, FDT is commonly used in the clinical setting. Johnson et al<sup>4</sup> obtained 82% sensitivity and 95% specificity in early glaucoma (mean deviation [MD]  $> -6$  dB), and 82% and 97% sensitivity in moderate ( $-6$  dB  $> MD > -12$  dB) and advanced glaucoma ( $-12$  dB  $> MD > -22$  dB), respectively. Osako et al<sup>5</sup> also reported 97.1% sensitivity and 95.7% specificity in all glaucomas, and sensitivities of 96.6% and 97.4% in early glaucoma ( $MD \geq -5$  dB) and moderate or advanced glaucoma ( $-5$  dB  $> MD$ ), respectively. These reports indicate that FDT is an effective method for assessing glaucoma.

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While the main pathogenesis of primary open-angle glaucoma (POAG) is mechanical damage to the optic nerve head caused by high IOP, the pathogenesis of normal-tension glaucoma (NTG) is thought to be associated with ischemic factors together with mechanical damage.<sup>6-9</sup> Many investigators reported differences in optic disc findings and visual field changes between POAG and NTG.<sup>7,10-18</sup> These facts imply that the process of optic nerve damage is different between these two types of glaucoma.

As large ganglion cells such as M-cells are susceptible to high IOP, the pathogenesis of M-cell damage is expected to be different in POAG and NTG. In this study, we compared the results of FDT in POAG and NTG cases.

### Materials and Methods

A total of 56 glaucoma patients (56 eyes) (mean  $\pm$  SD = 61.6  $\pm$  11.8 years) were evaluated by FDT and Humphrey Field Analyzer (HFA). They consisted of 29 POAG patients (29 eyes; POAG group) and 27 NTG patients (27 eyes; NTG group). All subjects had experience with automated perimetry (HFA), and had corrected vision  $>1.0$  and no ocular media opacity on slit-lamp examination. The diagnostic criteria for POAG are: (1) glaucomatous optic disc change with corresponding visual field abnormalities, (2) maximum IOP  $\geq 22$  mm Hg, and (3) normal open angle. The criteria for NTG are: (1) glaucomatous optic disc change and visual field defects as in POAG, (2) maximum IOP  $\leq 21$  mm Hg with or without glaucoma treatment, (3) normal open angle, (4) no other underlying intra-cranial or sinus disease, and (5) no history of excessive bleeding or shock.

There were no significant differences between the two groups in mean age, MD, and pattern standard deviation (PSD) measured by the HFA (Table 1).

**Table 1.** Background of Subjects

Characteristics*	POAG Group <sup>†</sup> (29 eyes 29 cases)	NTG group <sup>‡</sup> (27 eyes 27 cases)	<i>t</i> -Test
Mean age (years)	62.3 $\pm$ 10.2	60.8 $\pm$ 13.5	<i>P</i> = .64
Refractive error (D) (spherical equivalent)	-0.2 $\pm$ 2.0	-0.7 $\pm$ 2.1	<i>P</i> = .40
IOP (mm Hg)	18.2 $\pm$ 4.2	14.8 $\pm$ 2.8	<i>P</i> < .001
MD (dB) (HFA)	-6.8 $\pm$ 6.3	-6.6 $\pm$ 4.9	<i>P</i> = .91
PSD (dB) (HFA)	7.1 $\pm$ 4.8	7.9 $\pm$ 4.1	<i>P</i> = .53

\*IOP: intraocular pressure, MD: mean deviation, PSD: pattern standard deviation, HFA: Humphrey Field Analyzer.

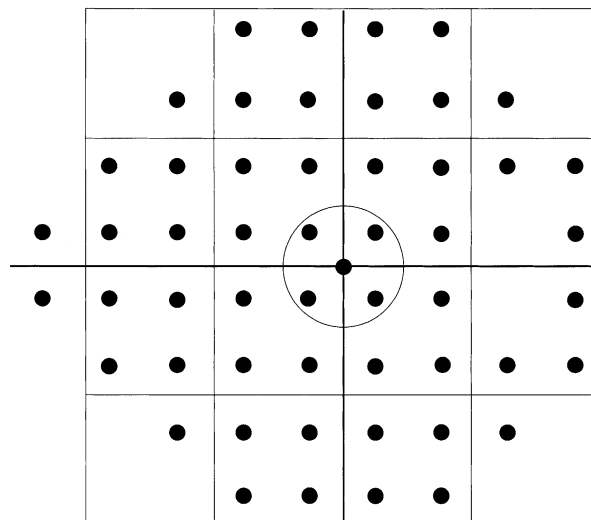
<sup>†</sup>POAG: primary open-angle glaucoma.

<sup>‡</sup>NTG: normal-tension glaucoma.

The mean IOP was higher in the POAG than in the NTG group (*t*-test, *P* < .001). Intraocular pressure was measured at the same time that the FDT test was performed, and cases already treated with topical anti-glaucoma medication were included. The IOP was  $>22$  mm Hg in 6 of the 29 POAG patients (maximum IOP was 26 mm Hg).

Program C-20 of the FDT was applied to each subject with appropriate corrective lenses. The test was performed after the patient had undergone a demonstration program and understood the difference in the stimuli used in the FDT and the HFA. Cases with false-positive errors, false-negative errors, or fixation losses greater than 33%, and cases with severe myopia ( $<-5$  D) were excluded from this study.

The stimulus presentation pattern for the FDT program C-20 consists of 17 stimulus locations; four 10° square targets per quadrant and a central 5° radius target (Figure 1). A particular type of staircase strategy called Modified Binary Search<sup>19,20</sup> is used in FDT, and a contrast threshold for each test location is determined. Each stimulus is presented in a low spatial frequency sine-wave sinusoidal pattern (0.25 cycles per degree) that is temporally modulated at a high frequency (25 Hz). According to this stimulus presentation, the stimulus display is perceived as twice as many as the actual number in the grating pattern. This phenomenon is called "frequency doubling illusion"<sup>21,22</sup> and is applied to the measurement of contrast sensitivity.



**Figure 1.** Stimulus presentation pattern for frequency doubling technology (FDT) and Humphrey Field Analyzer (HFA). Stimulus pattern for C-20 program (FDT) consists of 17 stimulus locations; four 10° square targets per quadrant (□) and central 5° radius target (○). Black dots (●) are stimulus pattern for 24-2 program (HFA).

We studied the correlations in visual field indices (MD, PSD) between FDT (program C-20) and HFA (program 24-2), and compared the average values of the visual field indices. The results obtained by the two different types of perimeters cannot be compared directly because HFA measures differential light threshold and FDT measures contrast sensitivity. We therefore compared the two perimeters using significance levels ( $P$  values) of MD, which indicate how far the patient values deviate from the normal population. Mean deviation is presented as the approximate average sensitivity for all test locations compared to the age-adjusted average value for normal individuals. When the MD value is less than that for 95% of the normal population, the percentile probability ( $P < 5\%$ ,  $P < 2\%$ ,  $P < 1\%$ ,  $P < 0.5\%$ ) is displayed on both perimeters.

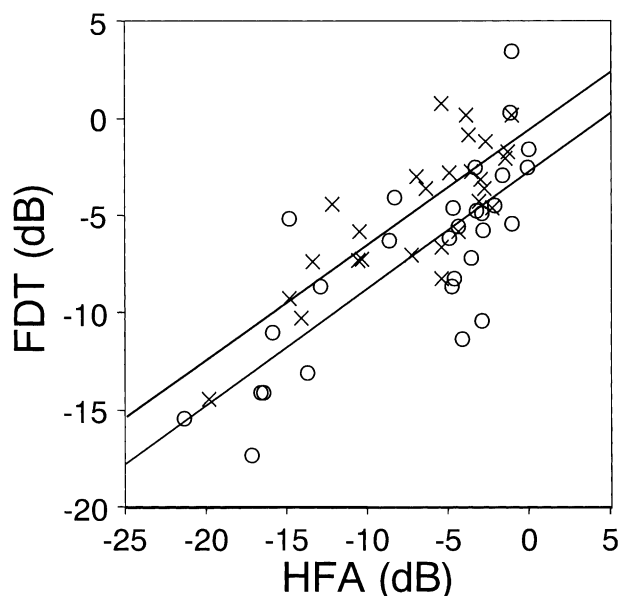
Figure 1 shows the correspondence of test locations of the program 24-2 of HFA and the program C-20 of FDT. To compare retinal sensitivity between POAG and NTG, the average mean sensitivity in the HFA was calculated for each test area adopted by the FDT. All data for the left eye were converted to the right eye format for this analysis.

### Results

The correlation between MD determined by HFA ( $x$ ) and FDT ( $y$ ) is represented by the equation:  $y = 0.60x - 2.7$  ( $r = 0.78$ ,  $P < .01$ ) in the POAG group, and  $y = 0.59x + 0.6$  ( $r = 0.81$ ,  $P < .001$ ) in the NTG group (Figure 2). The regression lines for the POAG and the NTG groups were almost parallel, and the MD values by FDT were generally lower in the POAG than in the NTG group. The average MD by FDT was  $-6.8 \pm 4.9$  in the POAG and  $-4.5 \pm 3.5$  dB in the NTG group, with a significant difference between the two groups ( $t$ -test,  $P < .05$ ).

The correlation between PSD determined by HFA ( $x$ ) and FDT ( $y$ ) is represented by the equation:  $y = 0.31x + 6.0$  ( $r = 0.53$ ,  $P < .001$ ) in the POAG group, and  $y = 0.66x + 2.2$  ( $r = 0.86$ ,  $P < .001$ ) in the NTG group (Figure 3). The average PSD by FDT was  $8.2 \pm 2.8$  dB in the POAG group and  $7.4 \pm 3.2$  dB in the NTG group, with no significant difference between these groups ( $t$ -test,  $P = .36$ ).

The significance levels of the MD values obtained by FDT and HFA for each case were compared. The proportion of cases with lower  $P$  values by FDT than by HFA was 10/29 (34.5%) in the POAG group and 5/27 (18.5%) in the NTG group. The proportion of cases with lower  $P$  values by HFA than by FDT was 4/29 (13.8%) in the POAG group and 8/27 (29.6%)

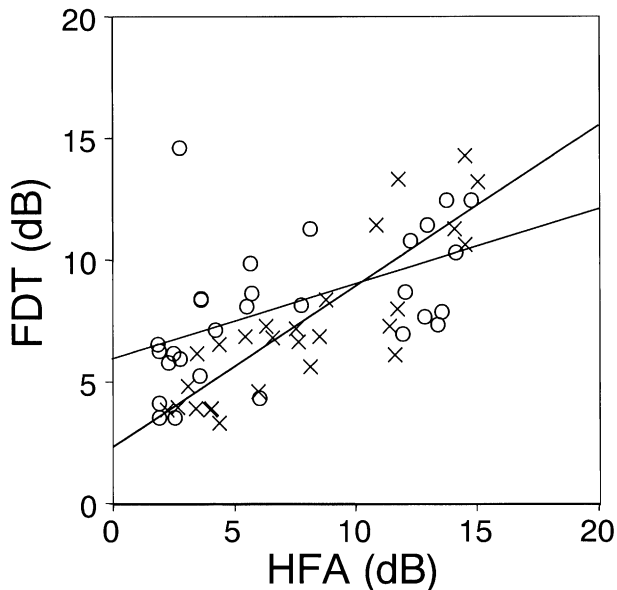


**Figure 2.** Correlation between mean deviation (MD) values determined by frequency doubling technology (FDT) and Humphrey Field Analyzer (HFA). Correlation between MD determined by HFA ( $x$ ) and FDT ( $y$ ) is represented by  $y = 0.60x - 2.7$  ( $r = 0.78$ ,  $P < .01$ ) in primary open-angle glaucoma (POAG) group, and  $y = 0.59x + 0.6$  ( $r = 0.81$ ,  $P < .001$ ) in normal-tension glaucoma (NTG) group. MD values of POAG group are generally lower than those of NTG group. O: POAG, X: NTG.

in the NTG group. The proportion of cases with no difference in  $P$  values between the two perimeters was 15/29 (51.7%) in the POAG group and 14/27 (51.9%) in the NTG group (Table 2). No significant difference was found in the observed frequencies between the POAG and NTG groups ( $\chi^2$  test,  $P = .23$ ).

In the comparison of mean sensitivity at each test location between the POAG and NTG groups, no test location in the HFA showed a significant difference. In contrast, at many test locations on the temporal periphery in the FDT, the mean sensitivity was significantly lower in the POAG than in the NTG group (Figures 4 and 5).

In early-stage glaucoma patients with an MD of more than  $-5$  dB (19 cases of POAG and 14 cases of NTG), the average MD measured by FDT was  $-4.7 \pm 3.6$  dB in the POAG group and  $-2.3 \pm 1.8$  dB in the NTG group, and a significant difference was observed between the two groups ( $t$ -test,  $P < .05$ ). The corresponding average PSD measured by FDT were  $7.8 \pm 2.8$  dB,  $5.7 \pm 1.8$  dB, respectively, with no significant difference ( $t$ -test,  $P = .07$ ). On the other hand, the average MD and PSD measured by HFA were, respectively,  $-2.7 \pm 1.6$  and  $3.9 \pm 2.0$  dB in



**Figure 3.** Correlation of pattern standard deviation (PSD) values determined by frequency doubling technology (FDT) and Humphrey Field Analyzer (HFA). Correlation between PSD determined by HFA ( $x$ ) and FDT ( $y$ ) is represented by  $y = 0.31x + 6.0$  ( $r = 0.53$ ,  $P < .001$ ) in the primary open-angle glaucoma (POAG) group, and  $y = 0.66x + 2.2$  ( $r = 0.86$ ,  $P < .001$ ) in the normal-tension glaucoma (NTG) group. Regression line shows that PSD values obtained from FDT are higher than those obtained from HFA for region of small PSD values in HFA, and this tendency is more obvious in POAG. ○: POAG, ×: NTG.

the POAG group, and  $-2.9 \pm 1.2$  and  $5.5 \pm 2.8$  dB in the NTG group, with no significant differences in these two parameters between the two groups.

When the individual significance levels of MD values for HFA and FDT were compared in early-stage glaucoma cases, the proportion of cases with a lower  $P$  value in FDT than in HFA was 10/19 (52.6%) in the POAG group and 1/11 (9.1%) in the NTG group. The proportion of cases with a lower  $P$  value in HFA than in FDT was 3/19 (15.8%) in the POAG group and 7/11 (63.6%) in the NTG group. The proportion of cases with the same  $P$  values in the testing with both perimeters was 6/19 (31.6%) in the POAG group and 3/27 (27.3%) in the NTG group (Table 3). A significant difference in the observed frequencies was found between the POAG and NTG groups ( $\chi^2$  test,  $P < .02$ ).

## Discussion

Retinal ganglion cells were divided into two major groups; large type ganglion cells derived from the two ventral layers (magnocellular layers, M-cells),

**Table 2.** Comparison of Significance Levels of Mean Deviation Values Between Frequency Doubling Technology (FDT) and Humphrey Field Analyzer (HFA)

Significance Level ( $P$ Value)	NTG Group*		POAG Group†	
	n	%	n	%
HFA = FDT	14	51.9	15	51.7
HFA < FDT	8	29.6	4	13.8
HFA > FDT	5	18.5	10	34.5
Total	27	100	29	100

\*NTG: normal-tension glaucoma.

†POAG: primary open-angle glaucoma.

and small type ganglion cells from the four dorsal layers (parvocellular layers, P-cells) of the lateral geniculate nucleus.<sup>23,24</sup> Psychophysically, M-cells are known to be sensitive to stimuli with low spatial and high temporal frequencies and P-cells are sensitive to those with high spatial and low temporal frequencies.<sup>23,24</sup> These psychophysical properties of ganglion cells were applied to the stimulus presentation method in FDT.

Kelly<sup>21,22</sup> first described the 'frequency doubling illusion' in the 1960s. This phenomenon is perceived when the low spatial frequency sine-wave sinusoidal pattern (<1 cycle per degree) is presented temporally modulated at a high frequency ( $\geq 15$  Hz). My-cells are a large-cell subset of M-cells that exhibit nonlinear response properties and are related to the perception of this illusion.<sup>3,22,25,26</sup> Because the proportion of My-cells is less than 5% of the total retinal ganglion cells and there is infrequent overlap of receptive fields compared with other ganglion cells, the functional loss (visual field deficit) of My-cells is thought to be more easily identified with a decrease in the total number of ganglion cells (reduced redundancy theory).<sup>2,3,25,26</sup>

There are few reports investigating the reproducibility of FDT perimetry. Chauhan and Johnson<sup>27</sup> performed program 30-2 of HFA and program C-20 of a prototype of FDT on the same subjects at 1-week intervals for 5 consecutive weeks, and found that the retest variability at the abnormal test locations was smaller in FDT than in HFA, and that visual field eccentricity did not increase the variability of FDT results compared with HFA.

Tamura et al<sup>28</sup> previously investigated the reproducibility of visual field results by performing FDT perimetry twice with an interval of 3 months, using the same method employed in the present study. A strong correlation in MD and PSD was found between the two tests ( $r = 0.90$  and  $0.96$ ), and no significant difference was found in the average MD and

NTG				POAG			
17.2 (11.0)	19.3 (10.2)	18.3 (10.0)	18.8 (9.9)	16.6 (11.4)	17.4 (9.7)	18.5 (9.2)	20.6 (8.2)
19.4 (10.6)	21.1 (10.9)	19.7 (10.1)	18.6 (9.1)	17.5 (12.1)	20.0 (10.6)	20.0 (9.2)	18.5 (9.0)
		27.8 (5.0)				28.2 (3.7)	
22.3 (7.5)	25.1 (6.3)	27.5 (3.1)	13.1 (2.8)	22.1 (9.6)	24.9 (8.7)	27.0 (4.1)	13.8 (4.2)
22.9 (5.3)	25.1 (4.2)	26.5 (4.4)	25.8 (5.9)	22.1 (8.8)	23.7 (8.1)	25.4 (6.0)	24.5 (7.5)

**Figure 4.** Comparison of mean retinal sensitivity at each location (Humphrey Field Analyzer). Differences in mean retinal sensitivity are not significant between primary open-angle glaucoma (POAG) and normal tension glaucoma (NTG) groups for all test locations used in Humphrey Field Analyzer.

PSD obtained by the two tests. A good correlation of retinal sensitivity was also obtained at each test location ( $r = 0.91$ ), and good reproducibility was obtained in FDT perimetry. These reports show that FDT is reliable for assessing glaucoma.

In the reports investigating the association of visual field indices between FDT and HFA in glaucoma patients, significant correlations were found in both MD and PSD, and the correlation coefficients were 0.73 to 0.86 and 0.60 to 0.79, respectively.<sup>5,29,30</sup> In this study, we investigated the correlations of visual field indices in POAG and NTG groups separately, and significant correlations in both MD and PSD were found in these two groups. This means that, in both groups, FDT demonstrates visual field defects corresponding to the degree of abnormalities detected by the HFA.

A correlation plot of MD values showed that the individual MD value in the POAG group was generally lower than that in the NTG group (Figure 2). Although no significant differences in average visual indices (MD, PSD) were found between the POAG and NTG groups when conventional perimetry (HFA) was used, the average MD was significantly lower in the POAG than in the NTG group when FDT was employed ( $P < .05$ ). In only the early-stage

glaucoma cases, the average MD in the POAG group was also significantly lower than that in the NTG group ( $P < .05$ ). No significant difference was found in the average PSD between the two groups, but the regression line shows that the PSD measured by FDT was greater than that measured by HFA for the region of small PSD in HFA, and this finding was more obvious in POAG.

We cannot directly compare the results of the two different types of perimeters because HFA measures differential light thresholds and FDT measures contrast sensitivity. In this study, we used the significance levels shown by these perimeters to compare how far the patient values deviated from the normal population. In comparisons of the significance level of MD in individual cases, a greater proportion of cases in the POAG group had a lower significance level in FDT than in HFA, and a larger proportion of cases in the NTG group had lower significance levels in HFA than in FDT. These results imply that FDT is more sensitive than HFA in detecting abnormalities of POAG, while HFA is more sensitive than FDT for NTG. This tendency was more obvious and statistically significant in early glaucoma cases ( $P < .02$ ). This implies that FDT is superior to HFA in detecting the early stage of POAG.

NTG				POAG			
14.9 (9.5)	19.1* (9.8)	19.8** (8.6)	20.8** (7.6)	10.4 (11.2)	13.9* (11.0)	13.8** (9.0)	14.9** (8.9)
17.9 (10.5)	19.5 (10.6)	24.3 (8.2)	21.9 (5.6)	17.0 (10.3)	20.0 (9.9)	23.7 (9.3)	18.9 (8.5)
		27.2 (4.9)				26.8 (5.6)	
20.2 (8.4)	24.1 (7.2)	27.9* (4.0)	26.1** (4.3)	19.7 (9.6)	23.3 (9.0)	24.6* (5.4)	21.8** (6.6)
23.4 (4.9)	25.0* (3.7)	25.8* (3.4)	25.0** (5.9)	19.3 (11.3)	20.4* (8.7)	21.4* (8.1)	19.9** (7.5)

**Figure 5.** Comparison of mean retinal sensitivity at each location (Frequency Doubling Technology). Significant differences in mean retinal sensitivities are found between primary open-angle glaucoma (POAG) and normal tension glaucoma (NTG) groups at test locations on temporal periphery in frequency doubling technology (\* $P < .05$ , \*\* $P < .01$ ).

Previous pathological research reported by Quigley et al<sup>1,31</sup> studied patients with high IOP glaucoma and monkey models of glaucoma induced by high IOP, but comparison of histopathological findings between POAG and NTG has not been reported.

Caprioli and Spaeth<sup>7</sup> reported that the optic nerve damage in POAG is caused mainly by the mechanical factor of high IOP, and that the pathogenesis of NTG is related to both mechanical and ischemic factors. Patients with NTG are more likely to have migraine or vasospastic response.<sup>8,9</sup> Clinical studies have reported that optic disc cupping in NTG is shallower and larger than in POAG, and disc hemorrhage is more frequent in NTG than in POAG.<sup>10-12</sup> In the comparison of early glaucomatous visual fields, visual field defects occur close to fixation and the degree of the slope is steep in NTG; the defects of NTG are more likely to occur at the upper paracentral lesion.<sup>13-18</sup> These findings indicate that the pathogenetic mechanisms of POAG and NTG are different.

In comparing the POAG and NTG groups in terms of mean sensitivity of FDT for each test location, the mean sensitivities in many locations on the temporal periphery were lower in the POAG group than in the NTG group (Figures 4 and 5). Large ganglion cells at the superior and inferior sectors of the

optic disc are known to be preferentially damaged by high IOP, which is explained by the structural weakness of supportive tissues at the superior and inferior poles of the optic disc.<sup>1,32,33</sup> The test locations, which differ significantly in mean sensitivity, correspond to the distribution of the optic nerve fiber from the superior and inferior poles of the optic disc.<sup>34</sup> These results might reflect the difference in pathogenesis between the two types of glaucoma; that is, mechanical damage due to high IOP is a main factor for POAG, while ischemic factors together with IOP are related to NTG.

**Table 3.** Comparison of Significance Levels of Mean Deviation (MD) Values in Early Glaucomatous Cases (MD  $\geq -5$  dB) Between Frequency Doubling Technology (FDT) and Humphrey field Analyzer (HFA)

Significance Level (P Value)	NTG Group*		POAG Group†	
	n	%	n	%
HFA = FDT	3	27.3	6	31.6
HFA < FDT	7	63.6	3	15.8
HFA > FDT	1	9.1	10	52.6
Total	11	100	19	100

\*NTG: normal-tension glaucoma.

†POAG: primary open-angle glaucoma.

Our results show that FDT perimetry detects visual field abnormalities of POAG more sensitively than those of NTG. FDT was superior in detecting early-stage POAG compared with HFA, while HFA was superior in detecting early-stage NTG compared with FDT. Because FDT specifically detects dysfunction of My-cells, this difference indicates that the pathogenesis of My-cell damage is rather different in POAG and NTG. Furthermore, the differences in mean sensitivities in the temporal peripheral test locations indicate that the pattern of visual field change is different in POAG and NTG.

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