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Possible Increase in False-Positive Results during Mass Screening for Glaucoma Using Frequency-Doubling Technology Perimetry and New Software : Comparison with Older Software

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ABSTRACT

To assess its usefulness in mass screening for glaucoma, new software (version 3.0) was compared with old software (version 2.6) for frequency-doubling technology (FDT) perimetry in 71 consecutive patients with glaucoma and 16 control subjects. Visual field abnormalities (VFA) of any grade were detected at a significantly higher frequency with the new software than with the old software in eyes with preclinical glaucoma but not in eyes with definite (clinical) glaucoma. The mean Spearman's correlation coefficient of VFA grade when the new and old software were compared at 17 test spots was 0.789/0.810 (right eye/left eye) in patients with clinical glaucoma. In contrast, Spearman's correlation coefficient of VFA grade of the total deviation measured with the Humphrey field analyzer using program 30-2 did not differ significantly between the new and old software in these patients. Testing time was significantly shorter (by 8.2 and 8.6 seconds [mean] in the right and left eyes, respectively) with the new software independent of glaucoma stage with no loss of reproducibility. In conclusion, the new software enables shorter testing times while maintaining reproducibility. However, the increased detection of VFA with the new software in subjects with preclinical glaucoma might increase the false-positive rate during mass screening for glaucoma. (Jikeikai Med J 2004 ; 51 : 43-51)

Key words : glaucoma, frequency doubling technology perimetry, screening test, version

INTRODUCTION

Because glaucoma is a common disease that causes few symptoms until an advanced stage, mass screening is an important measure for secondary prevention[1]. Unfortunately, conventional screening methods—tonometry, evaluation of the optic nerve head, and tests of peripheral vision—for normal-tension glaucoma without elevated ocular pressure are of limited effectiveness[2]. A large epidemiologic study has demonstrated that normal-tension glaucoma accounts for more than 70% of cases of glaucoma in Japan[3]. Consequently, more than 75% of cases of glaucoma in Japan may remain undiagnosed[3], despite medical checkups that commonly include glaucoma screening. Accordingly, a more effective mass-

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screening method is needed.

Recently, we attempted a new approach to mass screening based on visual field testing by frequency-doubling technology (FDT) perimetry, a promising mass screening method with sufficient accuracy to detect definite glaucomatous visual field loss[4–7]. We established a screening algorithm using FDT perimetry and demonstrated the effectiveness of this screening test in a large population-based study using the FDT screening mode C-20-1 (version 2.6)[8,9].

A new version of the FDT software (version 3.0) was released in 2001 to increase the detection of visual field abnormalities (VFA) caused by neurological diseases, but not glaucoma. According to the manufacturer, in version 3.0 of the FDT software: 1) all test patterns are offset by 2 degrees along both sides of the vertical midline axis, and the width is reduced from 10 degrees to 8 degrees for improved spatial characterization of neurological diseases that cause changes near the midline; and 2) the stimulus duration and interstimulus interval have been optimized to reduce testing time by up to 30%. No changes were made to the threshold or to the normative database.

We assumed that these changes in testing-area width and stimulus duration would influence sensitivity for VFAs in glaucomatous eyes. Therefore, to investigate how this new version of the testing software affects glaucoma mass screening, we assessed differences between the old and new versions of the testing software by performing FDT perimetry with screening mode C-20-1 with both software versions in the same subjects. We examined differences in the detection of VFA, testing time, and reproducibility after stratification of subjects by stage of glaucoma.

METHODS

Setting and patients

Glaucoma was diagnosed in patients at the Glaucoma Outpatient Clinic of The Jikei University Hospital on the basis of glaucomatous optic nerve damage and detection of VFAs with the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Inc. Dublin, CA, USA). Glaucoma was diagnosed on the basis of a vertical cup-to-disc ratio of 0.7 or more, a cup-to-disc asymmetry ratio of 0.2 or more, or typical glaucomatous disc damage, such as thinning or notching of the rim of the optic disc and nerve fiber bundle defects. Disc findings were assessed independently by 2 experienced glaucoma specialists (T.N. and G.T.). Eyes with glaucomatous VFAs were staged with the HFA according to Anderson's criteria[10], with masking of information on disc findings. The final diagnosis was determined on the basis of agreement between disc findings and HFA findings. Glaucomatous disc abnormalities and definite VFAs that met all 3 of Anderson's criteria were defined as indicating the presence of definite (clinical) glaucoma. Eyes demonstrating glaucomatous disc findings without definite VFAs were defined as having preclinical glaucoma. The severity of VFAs on HFA in definite glaucoma was further classified on the basis mean deviation values as follows: clinical-early, mean deviation > -6 dB; or clinical-late, mean deviation ≤ -6 dB. Primary open-angle glaucoma was defined by an intraocular pressure of 22 mmHg or more before treatment, where patients with normal-tension glaucoma and healthy control subject had an intraocular pressure of 21 mmHg or less. All subjects were required to have no evidence of other ocular diseases, no previous ocular surgery, and no history of diabetes or other systemic diseases. Subjects were also prohibited from taking any medications known to affect visual field sensitivity or contrast sensitivity (including miotics).

The first study involved 71 patients with glaucoma, which was diagnosed by both glaucoma specialists, and 16 healthy control subjects (48 men and 39 women; mean age, 52.2 ± 14.9 years). All subjects gave informed consent. The patients with glaucoma included 27 with primary open-angle glaucoma, 43 with normal-tension glaucoma, and 1 with pseudoexfoliation glaucoma. The control subjects showed no abnormalities of the optic disc or visual fields on ophthalmoscopy or HFA. Detailed information on the eyes studied is summarized in Table 1. The mean deviation of the HFA values was significantly lower for the left eyes than for the right eyes of subjects with clinical-early glaucoma, but no significant laterality was found in the other glaucoma stages.

Table 1. Study subjects

		Right eye			Left eye			
			mean deviation in HFA			mean deviation in HFA		
		n	median	intra quarter range	*n*	median	intra quarter range	Total
Control		19			16			35
Preclinical stage		26	−0.64	(−1.50, 0.12)	20	−0.34	(−1.29, 0.22)	46
Clinical stage								
	Early	22	−2.59	(−3.48, −1.55)	39	−3.58	(−4.46, −2.37)	61
	Late	20	−12.84	(−15.84, −7.68)	12	−11.39	(−14.70, −7.58)	32
Total		87			87			174

Observation

The FDT screening-mode tests (C-20-1, Carl Zeiss Meditec) were performed twice with the old software (version 2.6) and twice with the new software (version 3.0) on the same day according to the manufacturer's instructions ; the first run of each test was for practice and the second run was for data acquisition. FDT tests were performed by a well-trained operator under normal room illumination (500 lux) at intervals of at least 5 minutes. The version of the software used first alternated in consecutive patients.

Detection of VFA

To compare the detection of VFAs with the two versions of the FDT software, both grade scores and numerical scores were used[11]. The severity of VFAs was scored from 0 to 3 (normal [$p \geq 1\%$] = 0 ; mild loss [$p < 1\%$] = 1 ; moderate loss [$p < 0.5\%$] = 2 ; and severe loss [not seen at maximum] = 3) at each of the 17 test spots, and the sum was calculated to give the grade score. The number of VFAs of any severity detected at the 17 test spots was totaled to give the numerical score.

Location of VFAs

To investigate the locations of VFAs detected using the new and old versions of the FDT software, the presence of VFA of any severity were determined and Spearman's correlation coefficients between the severity grades were calculated for each version at each FDT test spot. In addition, to investigate the relationship between HFA and FDT results at each FDT test spot, the mean value of the total deviation at the HFA spots corresponding to the 17 FDT test spots was calculated (Fig. 1). Spearman's correlation coefficients were then calculated for the relationship between the grades (0 to 3) of VFAs obtained with and the old and new versions of the FDT software and the mean HFA total deviation at each FDT test spot ; the results were compared between the old and new versions of the software.

Reproducibility

Testing with the old and new versions of the FDT software was repeated on different days, and the results were compared to assess reproducibility. The order of initial FDT testing with the old and new versions of the software was decided as described for the first study, and the second study was done within 2 months of the first. To assess reproducibility kappa values for the presence or absence of any grade of VFA at each of the 17 test spots in the first and second tests were calculated.

Statistical analysis

All analyses were performed using SPSS 10.1J software (SPSS Japan, Inc., Tokyo). Differences between the new and old versions of the software were examined for statistical significance with the Wilcoxon matched rank sum test or the paired *t*-test. The glaucoma detection rate was evaluated with the

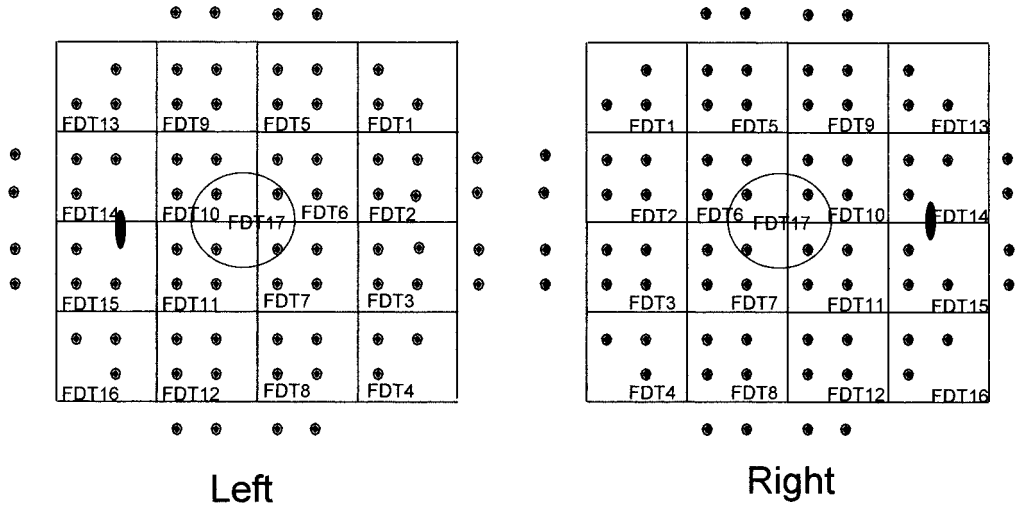


Fig. 1. This diagram indicates the stimulus locations for the 17 FDT spots (squares) corresponding to the 74 measurement locations according to the Swedish Interactive Thresholding Algorithm Standard stimulus presentation pattern on HFA (small circles).

chi-square test. Kappa values for agreement between the presence or absence of VFAs of any grade on the first and second FDT tests were calculated for each of the 17 test spots.

RESULTS

Differences in the detection of VFA with old and new FDT software

No VFAs were detected in the eyes of control subjects. Changes in grade scores and numerical scores stratified by the stage of glaucoma are shown in Fig. 2. Grade scores did not differ significantly between FDT tests with the old and new software. However, the numerical score was significantly higher with the new software than with the old software ($p=0.038$ for the right eye and $p=0.046$ for the left eye) in patients with preclinical glaucoma, although not in patients with clinical glaucoma.

No significant differences were found in subjects with preclinical glaucoma (Fig. 3A) or clinical glaucoma (Fig. 3B) in the frequency of VFAs detected with the old or new software at the 8 spots along both sides of the vertical midline axis (FDT5-FDT12) or the nasal or lateral regions (FDT1-4 and FDT13-16, respectively).

Correlation between VFAs detected with FDT perimetry and HFA

In patients with definite glaucoma the mean±SD of Spearman's correlation coefficients of the VFA grade between the old and new software at the 17 testing spots was 0.789 ± 0.091 for the right eye and 0.810 ± 0.070 for the left eye (Fig. 4A). There were no significant differences between tests with the old and new software. The correlation coefficients of total deviation of HFA and the severity of VFAs on FDT testing did not differ between the two versions of the software (Fig. 4B).

FDT testing time

Testing time was correlated with the stage of glaucoma (Fig. 5) and was significantly ($p<0.001$) shorter with the new software than with the old software. However, the reduction in testing time was not associated with the stage of glaucoma (Fig. 5). In all subjects the mean decrease in testing time with the new software was 8.2 seconds (range, 6.6 to 9.8 seconds) for the right eye and 8.6 seconds (range, 7.2 to 9.9 seconds) for the left eye.

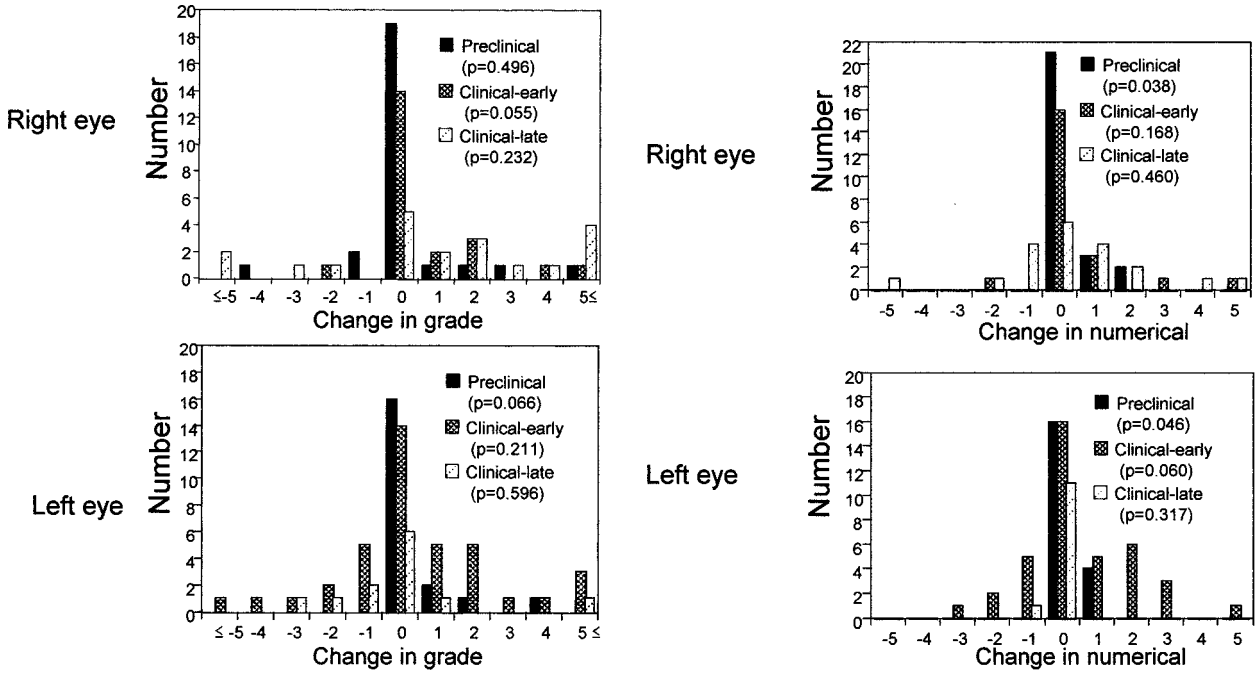


Fig. 2. Changes in grade score (A) and numerical score (B) between the old and new versions of the FDT software. The frequency of VFAs detected with FDT was evaluated with grade scores and numerical scores as described in the Methods. Changes in score represent differences between the old and new versions of the software (change in score=new software score-old software score). The p value was calculated with the Wilcoxon test.

Detection of glaucomatous VFAs

The detection rate of glaucomatous VFAs with FDT perimetry was slightly but not significantly higher with the new software, particularly in right eyes with preclinical and clinical-early glaucoma (Table 2).

Reproducibility

Twenty-one patients (11 men and 10 women aged 55.5±15.6 years) and 10 control subjects participated in this study. The stage of glaucoma was preclinical in 26 eyes, clinical-early glaucoma in 8 eyes, and clinical-late glaucoma in 8 eyes. Because VFAs were not detected with FDT in control subjects during the first or second tests, kappa values were calculated only for patients with glaucoma. The mean kappa values for the 17 test spots were 0.694±0.184 on the right and 0.793±0.118 on the left with the old software and 0.692±0.185 and 0.800±0.138 with the new software; there was no significant difference in the reproducibility of detecting VFA between the old and new versions of the FDT software.

Discussion

This study demonstrated the interchangeability of old and new FDT data in patients with glaucoma. The effects of the new software on glaucoma mass screening should be considered if FDT is used on a wide scale.

To compare the ability of the old and new versions of the FDT software to detect glaucomatous VFAs, we used the grade score and the numerical score[11]. The grade score indicates the severity of depth of field loss, whereas the numerical score indicates the numbers of areas with VFAs. With the new software we found an increase in the numerical score, but not the grade score, in eyes with preclinical glaucoma. This result suggests that the new software is better able to detect glaucomatous VFAs at an early

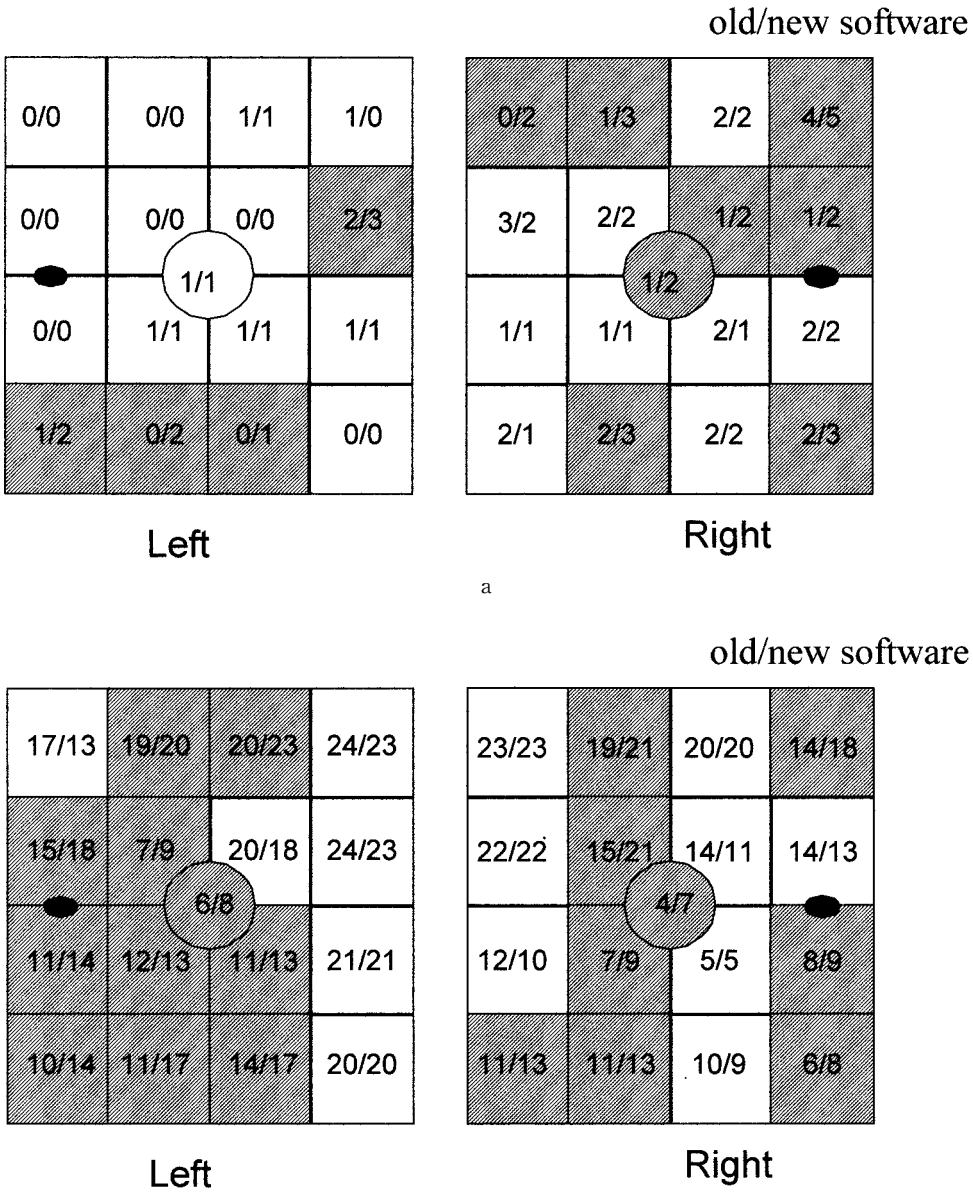
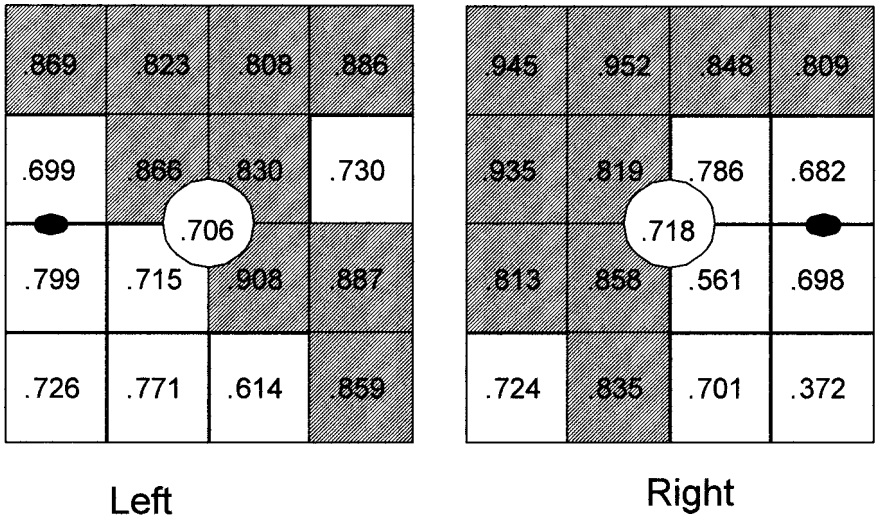
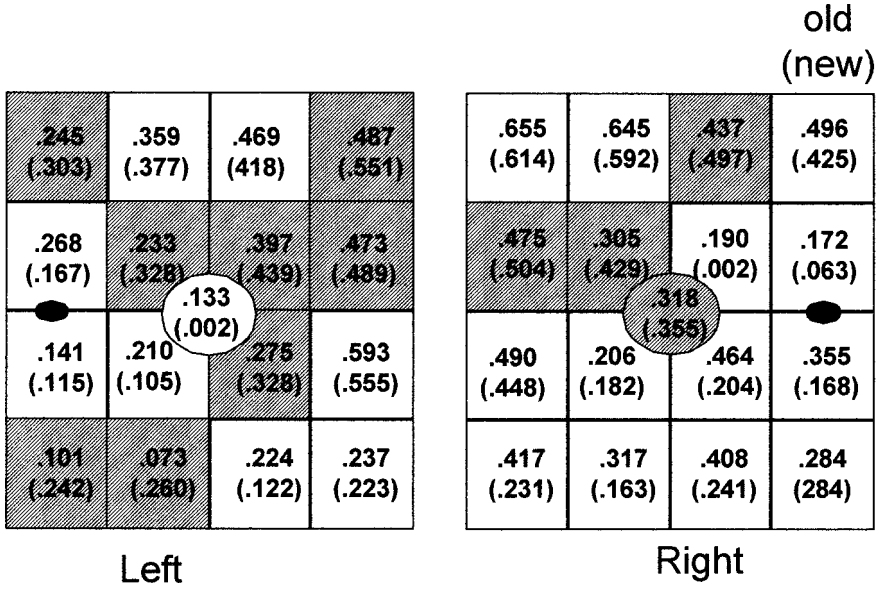


Fig. 3. Location characteristics of the frequency of VFAs detected with FDT perimetry
The frequency of VFAs of any grade of severity detected with FDT perimetry was counted at 17 testing spots in the preclinical (a) and clinical stages (b). Data show the frequency of VFAs of any grade of severity detected with FDT perimetry (old software/ new software). For preliminary comparison of differences between the old and new software, areas in which the frequency of VFA detection was increased with the new software are hatched.

stage. In addition, the rate of VFA was only increased in the right eye of patients with clinical-early glaucoma. In the eyes with clinical-early glaucoma, the mean deviation value was significantly higher in the right eye than in the left eye ; although this result suggests that in early glaucoma VFAs develop preferentially in the right eye, we could not determine whether the difference was due to selection bias or to laterality of susceptibility to glaucomatous damage, as reported previously[12,13]. The laterality in VFA frequency is consistent with the increased sensitivity for detecting VFA at an earlier stage.



a



b

Fig. 4. Correlation coefficient between the results of FDT perimetry with old and new software (a) and HFA total deviation (b). Spearman's correlation coefficient between the grades of VFAs detected with FDT perimetry with the old and new software was calculated (a). Total deviation of HFA corresponding to the FDT testing spots was calculated, and correlation coefficients between it and VFA severity grade with the old and new versions of the FDT software were calculated at 17 testing spots (b). For a preliminary comparison, hatched areas are test spots where coefficient > 0.8 of (a) or where there was an increase with the new software (b).

To investigate how the new software increases the sensitivity for detecting VFAs in earlier stages of glaucoma, we examined the effects of location because field width in the new software was changed along both sides of the vertical midline axis (FDT5–FDT12). We found no significant effect of location on the frequency of VFAs identified with the new and old versions of the FDT software or on the relationship with HFA findings ; therefore, the increase in the ability to detect VFAs was not due to changes in the width of the testing field. Another possible reason for the increased sensitivity for VFAs is that the

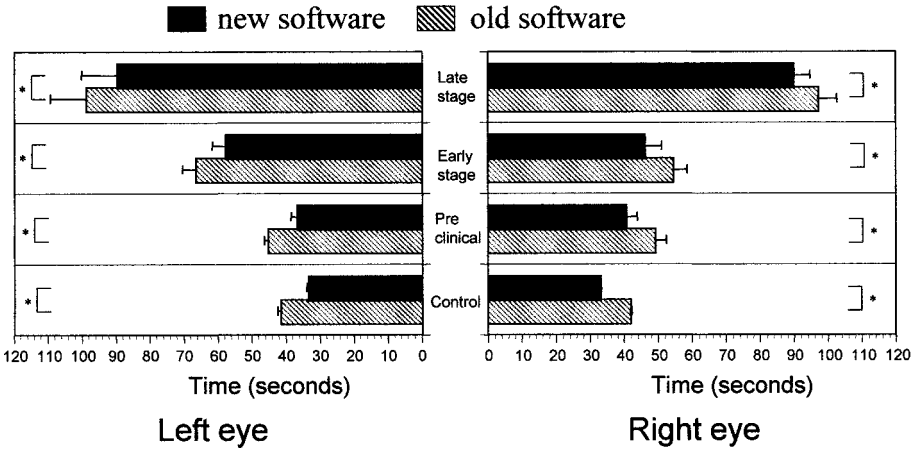


Fig. 5. FDT testing time by glaucoma stage.Mean testing time was calculated by stratification with glaucoma stage. Data are expressed as means±SE. * $p<0.01$

Table 2. Rate of VFAs of any grade of severity detected with FDT perimetry

	Left eye				Right eye			
	Version. 2.6		Version. 3.0		Version. 2.6		Version. 3.0	
	%	Positive Numbers/ Total Numbers	%	Positive Numbers/ Total Numbers	%	Positive Numbers/ Total Numbers	%	Positive Numbers/ Total Numbers
Control	0	0/19	0	0/19	0	0/16	0	0/16
Preclinical stage	23.1	6/26	26.9	7/26	25.0	5/20	30.0	6/20
Clinical stage								
Early	31.8	7/22	40.9	9/22	71.8	28/39	71.8	28/39
Late	100	20/20	100	20/20	83.3	10/12	83.3	10/12

stimulus duration and interstimulus interval are reduced in the new software. The reduction in stimulus duration might make identifying the stimulus more difficult, thereby increasing the sensitivity for VFAs at an earlier stage.

If the FDT test were used for mass screening in a large number of subjects, the new software could increase the false-positive rate (identification of patients with preclinical glaucoma is considered to be a false-positive result). Because the decision algorithm of screening is based on the numerical score[4-8], the new version of the software might increase the number of subjects in whom VFAs are detected in the preclinical stage. However, in this study, the increase in the detection rate of VFAs in eyes with preclinical glaucoma was not statistically significant, probably because of the small number of subjects.

The new FDT software reduced the testing time by almost 8 seconds independent of glaucoma stage. We recently reported on the importance of psychological factors in screening for glaucoma with FDT perimetry[9]. Fatigue and loss of concentration can decrease the accuracy of visual field testing. In population-based mass screening, most subjects have no previous experience with visual field testing. Thus, a reduction in FDT testing time by even 8 seconds may significantly decrease artifacts.

We found no changes in reproducibility because of the new software. We previously reported on the importance of reproducibility when FDT perimetry is used for glaucoma screening[8,9]. The positive predictive value was only 6% for subjects without reproducible results on FDT testing but was almost 40% for subjects with reproducible results. In terms of reproducibility, the new testing software does not affect glaucoma mass screening[8].

In conclusion, the software change from version 2.6 to 3.0 has shortened FDT testing time and in-

creased detection of VFA in the earlier stages of glaucoma. We believe these improvements will increase the usefulness of FDT perimetry for clinical use and for epidemiologic research on glaucoma. However, we must also consider the possibility that this new version could increase the false-positive rate when applied to mass screening for definite glaucoma.

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