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Temporal Modulation Transfer Function in Normal-Tension Glaucoma Patients

Kosaku Nishimura,* Aiko Iwase,†
Goji Tomita,* Tetsuya Yamamoto* and Yoshiaki Kitazawa*

*Department of Ophthalmology, Gifu University School of Medicine, Gifu;
†Department of Ophthalmology, Tajimi Municipal Hospital, Gifu, Japan

Abstract: A new screening test involving the Flicker System was used to measure temporal modulation transfer function in an effort to detect early-stage glaucoma. The study involved 64 normal-tension glaucomatous eyes and 65 normal control eyes. Patients with early-stage glaucoma (stage 0–1 of the Aulhorn-Greve classification) showed a significant modulation decrease in the 20–45 Hz range, compared to the modulation in normal eyes ($P < 0.05$). Patients with moderate stage glaucoma (stage 2–3) also exhibited significantly decreased modulation values in the 14–55 Hz range. In the 25–45 Hz range, the reduction of modulation in patients with diffuse visual defect was more profound than in those with localized or mixed defects. The results of the present study suggest the presence of diffuse visual function deficit in glaucoma. **Jpn J Ophthalmol 1998;42:146–151** © 1998 Japanese Ophthalmological Society

Key Words: Bebie curve, De Lange curve, flicker system, normal-tension glaucoma, temporal modulation transfer function.

Introduction

It is known through histopathological evaluation that retinal ganglion Y cells are damaged earlier than X cells in cases of glaucoma.[1,2] Early diagnosis of glaucoma may be possible through the early detection of Y-cell dysfunction. It has been reported that retinal nerve defect is present in the early stage of glaucoma, preceded by impairment of the visual field.[3] The feasibility of early diagnosis of glaucoma has been studied by the characterization of various visual functional disorders. This study was undertaken to evaluate temporal modulation transfer function in patients with normal-tension glaucoma (especially in its early stage) using the Flicker System (Technology & Medicine, Angers, France), a newly developed device for testing temporal modulation transfer function.

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Address correspondence and reprint requests to: Kosaku NISHIMURA, MD, Department of Ophthalmology, Gifu University School of Medicine, 40 Tsukasamachi, Gifu-shi, Gifu-ken 500, Japan

Methods

Description of the System

The Flicker System consists of a measurement unit with a yellow light-emitting diode as a light source, a response button, a computer with an analysis program, and a display monitor. Subjects are instructed to respond by pressing the button when they perceive the light in the unit is flickering, and to release it when they perceive that the light has stopped flickering. The diode emits a yellow light at a wavelength of 585 nm with an average luminance of 23 candela/m^2 uniform across the entire visual field. The background luminance is 0 candela/m^2. The test is carried out in a room illuminated by approximately 80 lux. The distance from the light source to the cornea during the test averages 25 mm and the visual angle is 32°. The test is begun after approximately 10 minutes of dark adaptation and after a preliminary test under normal pupillary conditions. Although there is no specific point of fixation required for the test, subjects are instructed to fix their gaze at the center of the visual field. The test lasts approximately 3 to 4 minutes. This apparatus generates a light with a luminance that fluctuates like a sine wave over time

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(Figure 1). The mean luminance of this light is uniform, but the amplitude and frequency are variable. The depth of amplitude is defined as modulation and is expressed as a percentage. With 100% modulation, the light consists of maximum and minimum components of luminance. With 0% modulation, the luminance is uniform. This means that brightness increases with an increase in modulation, and the light is more readily perceived as a flicker. The frequency varies at 17 predetermined levels ranging from 2–65 Hz. At each frequency, a light of 100% modulation is initially presented to the subjects. When this light is perceived as a flicker, a light of 0.1% modulation is presented next. This light is usually not perceived as a flicker, and lights of intermediate modulation are then presented to the eye one after another. The range of modulation is gradually narrowed to determine the threshold of modulation at each frequency level. A threshold curve of modulation with frequency plotted along the X axis and modulation along the Y axis is called a de Lange curve.[4] Modulation is altered drastically, but not serially, because continuous presentation of regularly changing stimuli enables the subjects to recognize pulse-to-pulse spaces. This effect seems to be preventable by drastically altering the modulation.[5] The coefficient of variations obtained by five consecutive measurements in five of the control subjects described below were 0.19–0.41 (mean 0.27) in the 2–65 Hz frequency level.

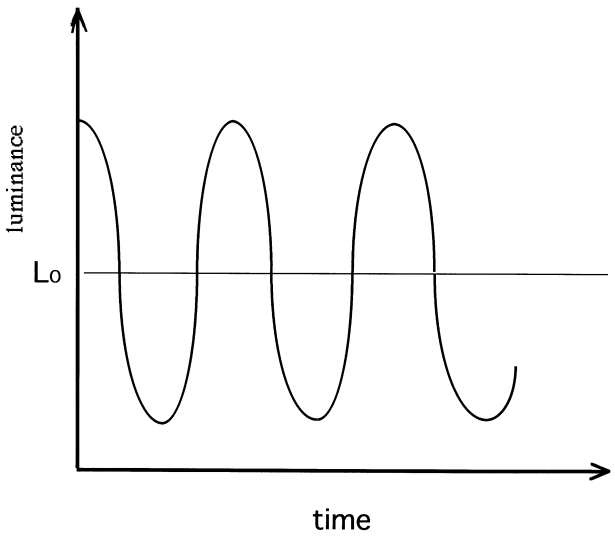

Figure 1. Luminance fluctuates like sine wave over time. $L = L_0 (1 + m \cos 2 \pi ft)$
L: luminance, L_0: luminance average level, m: modulation depth, f: flicker frequency, t: time

Table 1. Criteria for Control Subjects

Corrected visual acuity better than 20/25
Refraction within 3.0 D
Intraocular pressure less than 21 mm Hg
Normal open angle
Anterior segment, optic media normal
Normal optic disc
No history of diabetes mellitus or hypertension
No family history of glaucoma

Subjects

Control subjects were enrolled in this study after meeting the criteria shown in Table 1. Patients with normal-tension glaucoma were enrolled in this study after meeting the criteria shown in Table 2. Right eyes were subjected to the test; however, in the patient group, left eyes were used in cases where the right eyes failed to satisfy the entire criteria. The control group consisted of 65 subjects (65 eyes) who ranged in age from 22–79 years (mean ± SD, 43.2 ± 16.5). Their intraocular pressure ranged from 10–19 mm Hg (mean ± SD, 15.7 ± 3.2). The group with normal-tension glaucoma consisted of 64 patients (64 eyes) who were examined at the Department of Ophthalmology, Gifu University Hospital, between January 1993 and May 1994 and who were diagnosed with normal-tension glaucoma. The patients ranged in age from 29–80 years (mean ± SD, 49.8 ± 16.3). Their intraocular pressures ranged from 9–19 mm Hg (mean ± SD, 14.6 ± 3.9). After the visual field was examined using a Humphrey Field Analyzer central 30-2 program, the eyes in the normal-tension glaucoma group were rated by the Aulhorn-Greve classification system. Of the 64 eyes, 35 were considered in stages 0–1, 17 in stages 2–3, and 12 in stages 4–5. The 35 eyes belonging to stages 0–1 were arbitrarily classified into the following three subgroups; stage A without any scotoma below 6 dB, stage B with relative scotoma of 6–10 dB, and stage C with relative scotoma above 10 dB. Eyes with optic disc

Table 2. Criteria for Normal-Tension Glaucoma Patients

Corrected visual acuity better than 20/25
Refraction within 3.0 D
Intraocular pressure less than 21 mm Hg
Normal open angle
Visual field loss
Optic disc atrophy
No use of systemic medications that could affect intraocular pressure

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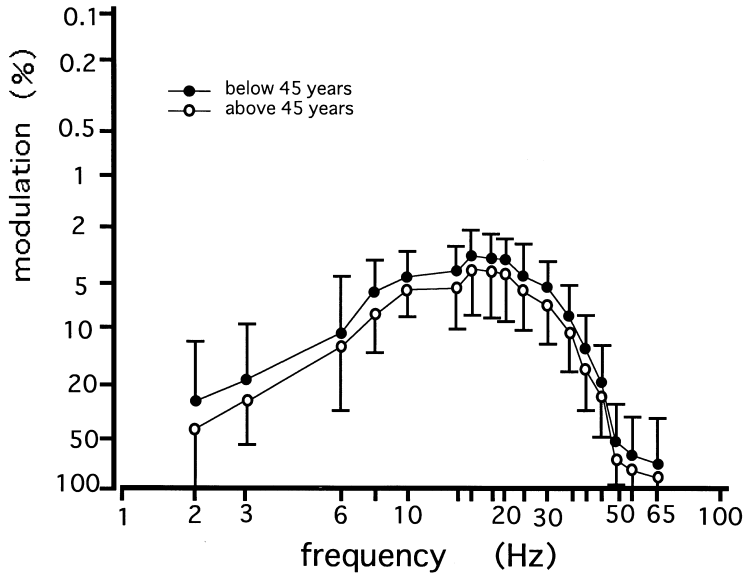

Figure 2. Lower curve (open circles) represents mean modulation in control subjects above 45 years. Upper curve (solid circles) represents mean modulation in control subjects below 45 years.

atrophy and relative scotoma above 6 dB in the contralateral eyes were assigned to the group in stage A. The number of eyes per stages A, B, and C were 15, 9, and 11, respectively. Applying the scale to the Bebie curve model[6,7] using the G1 program of the Octopus perimeter, the 17 eyes in stages 2–3 were further categorized by the degree of sensitivity variance from the normal range of the curve: 5 eyes with diffuse defects showed overall deterioration of sensitivity; 8 eyes with severe localized defects showed localized deterioration; and 4 eyes with both diffuse and localized (mixed) defects showed mixed deterioration. The control and normal-tension glaucoma patient groups were aged-matched so that the ages were evenly distributed in 10-year brackets, and the intraocular pressures were not significantly different between any two groups of subjects. The data were statistically analyzed by the Mann-Whitney *U* test.

Results

Comparing the de Lange curves of the control subjects above and below 45 years of age shows that sensitivity at all frequency levels had significantly deteriorated with age (Figure 2 and Table 3). In the stages 0–1 subgroup of patients with normal-tension glaucoma, modulation was significantly decreased in the 20–45 Hz frequency range, compared to modulation in the same frequency range in the control group. In the more advanced stages 2–3 and 4–5 subgroups, modulation was significantly decreased over the wide frequency range of 14–55 Hz, compared to modulation in the same frequency range in the control group (Table 4). Comparing stages A, B, and C subgroups with the control group shows no significant decrease in modulation at any frequency level in the stage A subgroup. In the stage B subgroup, modulation was significantly decreased at a frequency range of 25–45 Hz (Table 5). In the stage C subgroup, modulation was decreased over a wider frequency range. Comparing the stage 2–3 patients by type of visual field defect with the control group shows that modulation was significantly decreased in the 25–45 Hz frequency range in patients with diffuse defects. In patients with localized and mixed defects, however, modulation was not significantly decreased at any frequency level (Table 6).

Table 3. de Lange Curve of Control Subjects

Frequency (Hz)	2	3	6	8	10	14	16	18	20	25	30	35	40	45	50	55	65
Below 45 years																	
Mean	39.20	20.97	11.70	7.96	5.49	5.13	4.54	4.62	4.72	5.60	7.81	11.20	17.14	25.30	51.66	65.14	81.85
SD	28.71	23.74	14.14	9.16	5.79	5.90	5.17	6.70	6.52	6.02	6.67	12.83	20.83	26.09	32.12	26.82	23.05
Above 45 years																	
Mean	43.90	24.17	13.65	9.57	6.53	6.73	5.13	5.35	5.62	6.53	8.49	13.65	21.06	36.25	60.39	82.20	97.79
SD	31.55	24.47	15.75	9.93	6.62	6.25	5.33	7.13	5.71	6.53	7.87	13.13	20.87	30.20	41.25	36.75	17.87

Table 4. Comparison of Modulation in Control Subjects and Normal-Tension Glaucoma Patients in 0–1, 2–3, 4–5 Stages

Frequency (Hz)	2	3	6	8	10	14	16	18	20	25	30	35	40	45	50	55	65
Stages 0–1																	
Mean	37.23	23.46	13.69	11.28	10.41	9.07	8.89	9.41	11.85	12.36	13.59	17.53	25.31	36.50	54.38	62.18	84.25
SD	44.73	28.70	17.02	15.45	10.28	9.91	8.49	7.73	9.44	12.84	15.28	16.84	29.15	34.71	62.09	40.67	27.95
P value	0.87	0.51	0.47	0.35	0.34	0.21	0.13	0.10	0.05[a]	0.04[a]	0.05[a]	0.05[a]	0.03[a]	0.05[a]	0.18	0.52	0.79
Stages 2–3																	
Mean	40.24	28.31	16.38	13.01	15.95	13.16	12.85	13.15	13.07	16.39	15.10	21.22	35.18	45.64	68.07	72.44	100
SD	48.14	32.91	19.41	16.44	16.29	17.03	15.07	12.74	12.92	18.16	15.92	20.69	34.10	48.87	47.68	35.11	0
P value	0.55	0.41	0.30	0.19	0.09	0.05[a]	0.04[a]	0.05[a]	0.04[a]	0.02[a]	0.03[a]	0.02[a]	0.01[a]	0.01[a]	0.05[a]	0.29	0.88
Stages 4–5																	
Mean	48.75	30.95	17.04	13.92	16.20	17.10	17.47	19.59	23.60	18.93	29.13	30.96	38.75	44.32	70.80	82.26	100
SD	52.94	35.74	18.21	15.82	18.81	16.17	17.43	20.96	25.72	22.32	28.95	31.52	32.75	42.88	54.48	52.67	0
P value	0.41	0.34	0.28	0.21	0.10	0.04[a]	0.03[a]	0.02[a]	0.01[a]	0.01[a]	0.01[a]	0.01[a]	0.01[a]	0.01[a]	0.03[a]	0.04[a]	0.85

[a] $P < 0.05$; Mann-Whitney *U* test

Table 5. Comparison Between Control Subjects and Normal-Tension Glaucoma Patients in A, B, and C Stages

Frequency (Hz)	2	3	6	8	10	14	16	18	20	25	30	35	40	45	50	55	65
A stage																	
Mean	31.02	21.19	12.69	8.90	7.14	7.12	5.28	5.19	8.82	8.21	9.87	13.14	18.28	24.85	43.71	51.44	65.00
SD	38.81	24.16	14.34	9.51	8.27	9.03	7.19	6.82	8.36	9.21	11.06	12.21	20.14	18.86	50.35	34.57	25.50
P value	0.75	0.61	0.42	0.54	0.39	0.25	0.30	0.28	0.21	0.18	0.21	0.15	0.21	0.13	0.22	0.44	0.52
B stage																	
Mean	39.24	25.86	15.09	10.24	9.65	7.39	6.96	6.27	9.04	10.83	12.19	17.21	26.95	38.37	51.16	60.69	81.15
SD	47.57	29.78	17.53	10.8	11.34	9.18	8.11	7.93	9.41	9.26	15.23	18.38	27.70	30.63	48.07	52.72	35.75
P value	0.44	0.30	0.36	0.32	0.22	0.21	0.21	0.11	0.07	0.05[a]	0.05[a]	0.04[a]	0.03[a]	0.04[a]	0.11	0.35	0.30
C stage																	
Mean	44.35	24.12	14.81	13.17	13.57	12.92	11.96	12.21	12.94	14.07	16.42	19.30	28.53	41.64	69.21	70.07	100
SD	53.53	30.78	17.53	12.98	15.33	10.18	10.83	9.93	12.14	13.26	18.80	21.38	25.70	37.63	45.02	37.04	12.50
P value	0.42	0.35	0.31	0.19	0.10	0.05[a]	0.05[a]	0.05[a]	0.04[a]	0.03[a]	0.02[a]	0.03[a]	0.02[a]	0.02[a]	0.05	0.27	0.92

[a] $P < 0.05$; Mann-Whitney *U* test

Jpn J Ophthalmol
Vol 42: 146–151, 1998

Table 6. Comparison of Type of Damage Between Control Subjects and Normal-Tension Glaucoma Patients

Frequency (Hz)	2	3	6	8	10	14	16	18	20	25	30	35	40	45	50	55	65
Diffuse type																	
Mean	42.56	31.52	17.18	15.91	16.40	13.48	13.02	13.61	13.54	19.89	20.48	28.53	39.06	51.28	68.55	80.02	100
SD	53.97	43.99	21.64	22.20	20.95	19.67	15.15	14.36	18.04	17.95	21.75	30.11	40.90	52.86	51.63	67.01	0
P value	0.35	0.46	0.28	0.36	0.24	0.06	0.06	.07	0.06	0.01[a]	0.02[a]	0.01[a]	0.01[a]	0.01[a]	0.06	0.10	0.65
Localized type																	
Mean	37.89	24.52	14.45	11.40	14.82	12.50	12.38	12.14	12.51	10.77	11.59	14.14	24.87	29.09	64.45	74.21	100
SD	43.02	27.33	16.56	14.39	17.04	14.67	14.58	11.79	10.42	9.34	12.91	14.23	22.94	37.12	44.92	57.10	0
P value	0.54	0.60	0.30	0.51	0.38	0.10	0.11	0.10	0.07	0.06	0.13	0.15	0.18	0.13	0.09	0.25	0.68
Mixed type																	
Mean	39.65	28.48	16.72	14.64	14.90	12.94	12.79	13.08	12.89	10.20	11.04	16.29	26.06	31.86	67.11	68.11	100
SD	40.22	33.29	17.02	13.39	16.08	18.37	18.05	16.79	10.40	11.47	15.91	18.23	23.94	40.12	54.92	45.93	0
P value	0.42	0.52	0.27	0.43	0.32	0.07	0.08	0.07	0.07	0.08	0.12	0.09	0.10	0.12	0.07	0.06	0.72

[a] $P < 0.05$; Mann-Whitney *U* test

Discussion

The current study demonstrated that the decrease in modulation occurred in a narrow range of frequency in the early stage of normal-tension glaucoma and it spread to wider ranges of frequency as the disease progressed. Additionally, significant deterioration in modulation was found only in eyes with the diffuse type in the stage 2–3 eyes although the number of cases was small. This finding may suggest that the Flicker System may detect diffuse damage earlier than localized damage because the testing deals with the visual field as a whole.

Optic nerve damage in glaucoma results from a selective nerve fiber bundle defect which is apparent in the early stage of the disease.[8] Whether or not extensive diffuse defects of retinal optic nerve fibers occur in the early stage of glaucoma is still unclear. This is largely attributable to two reasons: a method for the accurate quantitation of retinal nerve fibers is not available; and it remains uncertain whether diffuse sensitivity deterioration, which ought to reflect the diffuse loss of nerve fibers, is truly represented in perimetry (a typical method for the diagnosis of glaucomatous visual dysfunction) as the diffuse loss of retinal nerve fibers. Histopathological examination of glaucomatous eyes[1,2] has shown that, of the retinal ganglion cells, the larger M cells are affected earlier than the smaller P cells. These M cells are believed to correlate to physiologically known Y cells, while P cells are thought to correlate to X cells. Y cells are characterized by a wider receptive area than X cells and by a responsiveness to intensity changes during photostimulation.[9,10] Selective and early diagnosis of Y-cell dysfunction may be possible by presenting the retina with a photostimulus matching one which evokes the photosensitive characteristics of Y cells. Pattern electroretinograms, visual evoked cortical potential, and temporal modulation transfer function in glaucoma have been studied in an attempt at early detection of glaucoma from the response characteristic of Y cells to different photostimuli. The results of these studies have shown that abnormality is detectable in advanced glaucoma, but not in the initial stage. If the visual field is defective peripherally, abnormality is still not detected unless sensitivity also deteriorates in the center of the visual field. Thus, the clinical usefulness of these Y cell studies has not yet been established.[11–14] Using the Flicker System, Von Van Toi et al.[15] noted the correlation between flicker sensitivity and intraocular pressure. They compressed palpebrae on the eyeballs of 10 control subjects to artificially induce pressure changes and measured the change of modulation. They found

a significant decrease in modulation at an intraocular pressure of 27.2 ± 2.1 mm Hg. They confirmed that the inhibition of psychophysical responses caused by high intraocular pressure could be acutely detected by means of a de Lange curve and that the flicker sensitivity was dependent on intraocular pressure and flicker frequency. The temporal modulation transfer function test is regarded as reflecting the function of the inner retinal nerve layer containing amacrine and ganglion cells.[16] The test is expected to allow for detection of a very early glaucomatous change that might be present before abnormality is detected by perimetry. In the present experiment, it was found that the decrease in modulation varied with frequency. In the early stage of glaucoma, a significant decrease in modulation occurred within only a narrow frequency range; the frequency range widened with the advance of the disease. In the stage 2–3 subgroups, evaluating the changes in visual field by the pathological type of glaucoma defects showed that modulation was not significantly decreased at any frequency level in the localized and mixed types. In the diffuse type, on the other hand, modulation was decreased at some frequency levels although the number of eyes was relatively small. These findings may suggest that because the entire visual field is covered in the temporal modulation transfer function test, detection is easier for the type of glaucoma defect in which whole retinal nerve fibers are diffusely involved than for the type of glaucoma defect in which the visual defect is determined perimetrically to be localized with many other retinal nerve fibers remaining intact. In the present study, changes in modulation were detected even in early stage glaucoma (stage 0–1), and it seems likely that of all types of visual defects occurring in mild glaucoma (stage 2–3), the diffuse loss of nerve fibers is primarily detected by this test.

The results of this study, therefore, support the existence of diffuse visual dysfunction in glaucomatous eyes, previously considered controversial.[17,18] It is considered significant that abnormality could be detected in patients with early glaucoma by the Flicker System, a method which is far less time-consuming than conventional perimetry.

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