Glaucoma Detection Is Facilitated by Luminance Modulation of the Global Flash Multifocal Electroretinogram

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PURPOSE. To investigate the variation of retinal electrophysiological function in glaucoma by using the global flash multifocal electroretinogram (mfERG) stimulation with altered differences in the stimulus luminance of the multifocal flashes, in an attempt to alter the levels of inner retinal contributions.

METHODS. The mfERG was assessed with a visual stimulus in steps of four video frames, which consisted of 103 scaled hexagonal elements followed by a dark frame, global flash, and dark frame. The localized luminance difference was set at 96%, 65%, 49%, or 29% stimulus contrast. Thirty subjects with glaucoma and 30 age-matched normal subjects were recruited for visual field and mfERG measurements.

RESULTS. This stimulus induces complex local first-order responses with an early direct component (DC) and a later induced component (IC). The luminance-modulated response functions of the DC and IC responses showed markedly different behavior. The peripheral IC showed a linear dependence on luminance difference, whereas the peripheral DC was saturated for higher luminance differences. This saturation became less obvious in subjects with glaucoma, mostly because of greater reduction of the response amplitude in the mid luminance-difference level. An "adaptive index" was calculated from the luminance-difference dependence of the peripheral DC, and it showed a sensitivity of 95%, with a specificity of 95% for differentiating normal from glaucomatous eyes, and also had a significant correlation ($r = 0.58$) with the glaucomatous visual field defect.

CONCLUSIONS. The peripheral DC luminance-modulated response function is altered by the adaptive mechanism that is induced by the global flash; the reduction of the adaptive index may thus relate to an abnormal adaptive mechanism, presumably due to inner retinal damage. Glaucoma appears to produce large reductions of the adaptive index which correlate with field defects. (Invest Ophthalmol Vis Sci. 2006;47:929–937) DOI:10.1167/iovs.05-0891

The multifocal electroretinogram (mfERG) has been developed to study and diagnose diseases of the human retina1 and to investigate retinal processing mechanisms.2 Recent studies have found that human first-order mfERG responses with the conventional m-sequence protocol are mainly generated from distal retinal layers (photoreceptors and bipolar cells).3 Kretschmann et al.4,5 suggested that functional disorders of the outer retinal layers can be described by this technique and that defective patterns of mfERG responses may be similar to patterns of visual field (VF) defects.

For retinal diseases restricted to the inner retinal layers, there appears to be no simple correlation between the mfERG and VF defects.3 There are conflicts in the literature regarding the early detection of glaucoma.6–8 Findings in some studies support,9–11 whereas those in other studies fail to support,12 the use of the mfERG to detect glaucoma. Changes in the mfERG are not easily detected in all patients with glaucoma, whereas in others, these changes are not related directly to the VF losses.13 Different stimulation and analysis techniques in mfERG measurement probably contribute to this disagreement.

However, evidence has been presented for a response generated from the ganglion cell fibers near the optic nerve head, and it has been shown that glaucoma can reduce this optic nerve head component (ONHC).14 Hood et al.15 essentially replicated this in the monkey. Unfortunately, the commonly used mfERG m-sequence stimulus elicits an ONHC response with a relatively poor signal-to-noise ratio, and the ONHC must be extracted from mfERG signals by the use of complex processing.

To enhance the contribution of the ONHC to the mfERG, an alternative stimulus mode has been developed that is thought to elicit a relatively larger inner retinal response. A paradigm including global flashes has been introduced to evoke a large nonlinear component.16–21 Fortune et al.20 showed that the loss of the ONHC in glaucoma was more apparent, even by use of the simple global flash stimulation sequence (multifocal flash, dark frame, global flash, dark frame, and so forth).

There are two response components (a direct component and an indirect component) in the mfERG waveform from this global flash paradigm. The induced component (IC) is the change in the response to the global flash produced by the prior local flash. It appears to be a nonlinear response, which is thought to originate predominantly from the inner retina.16 However, the large intersubject variability of the IC and the poor correlation between the localized IC responses and the VF defect20 has prevented so far the localized assessment of glaucomatous damage in individual patients.

Only a few studies have been conducted to investigate the characteristics of the direct component (DC), although it has been suggested to be sensitive to early changes in diabetic retinopathy,18 and it may show certain optic nerve head response contributions.16 The global flash paradigm actually provides an interaction between the multifocal flashes and the periodic global flash. Although it has been pointed out that the DC is analogous to a standard mfERG response (with conventional flickering protocol),16 the DC is also believed to reflect
a certain level of light adaptation produced by the periodic global flashes.\textsuperscript{22} In addition, because the shape of the DC is different from that obtained with a conventional mfERG stimulation,\textsuperscript{20} it may also contain a nonlinear response component.

The magnitude of the ONHC response saturates at approximately 60\% contrast\textsuperscript{23} and a reduction in stimulus contrast to 50\% has been attempted to increase the relative contribution of ONHC to the mfERG response.\textsuperscript{13,24} Hence, in this study, we examined patients with glaucoma and age-matched control subjects and applied the global flash mfERG stimulation with an altered stimulus luminance difference in the multifocal flashes, in an attempt to measure the inner retinal signals at different luminance adaptation levels.

\section*{Methods}

\subsection*{Subjects}

Thirty normal subjects (age range, 23–56 years; mean, 36.9 \pm 12.2 [SD]), without any reported systemic or ocular diseases were recruited. All had best corrected visual acuity (VA) of logMAR (logarithm of the minimum angle of resolution) 0.0 or better. An eye examination was performed to exclude ocular abnormalities. All subjects had cup-to-disc ratios <0.4 with normal neural rim appearance and similar optic discs in both eyes. Intraocular pressures were less than 21 mm Hg. All subjects had open anterior angles, no family history of any eye diseases, and no VF defects detected by the central 30-2 threshold test of the VF analyzer (Humphrey; Carl Zeiss Meditec, Inc., Dublin, CA). One eye of each subject was randomly selected for testing.

Thirty patients with primary open-angle glaucoma (POAG), aged from 19 to 53 years (mean, 39.4 \pm 11.5 years), without any systemic diseases were also recruited. All had diagnosed glaucoma of more than 2 years’ duration. An eye examination was performed to exclude ocular abnormalities in addition to glaucoma. One eye of each patient was randomly selected for testing. Patients had long-standing binocular glaucomatous VF loss as measured by the central 30-2 threshold test (Humphrey Visual Field Analyzer; Carl Zeiss Meditec, Inc.), and one or more quadrants of the field of the tested eye was involved in the defect (mean defect [MD] = -7.79 \pm 5.76 dB). The best corrected VA of the tested eye was 0.1 logMAR or better. The cup-to-disc ratios of the tested eyes were greater than 0.65.

All research procedures adhered to the tenets of the Declaration of Helsinki and were approved by the ethics committee of The Hong Kong Polytechnic University. All subjects were fully informed of the possible risks and gave written, voluntary consent.

\subsection*{Multifocal ERG Stimulation}

\textbf{Experiment 1.} Ten normal subjects participated in this experiment. The stimulus pattern was presented on an RGB 19-in. monitor (model GDM-500PS; Sony, Tokyo, Japan), and a computer (Macintosh G3; Apple Computer, Cupertino, CA) was used to run an mfERG program (VERIS 4.1; EDI, San Mateo, CA). The working distance was 30 cm, where the hexagonal stimulus pattern subtended 42 ° vertically and 48 ° horizontally. The mfERG was measured using the global flash paradigm of Fortune et al.,\textsuperscript{20} with modification. The pattern consisted of 103 hexagons, scaled with eccentricity and each m-sequence of the stimulus contained four video frames (each frame lasts 13.3 ms with a 75-Hz frame rate). During the stimulation with multifocal flashes, each hexagon was either bright or dark, according to the binary m-sequence (one element of the m-sequence) contains four frames. The stimulus sequence (one element of the m-sequence) contains four frames. The initial frame (multifocal flashes) alternates between white and black according to a pseudorandom binary m-sequence with a preset contrast level. After each initial frame of the four-frame set, a global flash (2.16 cd \cdot s/m²; frame 3) was applied, separated by a pre- and postdark frame (0.04 cd \cdot s/m²; frames 2 and 4). As the number of flashing elements in frame 1 involved half of the total number of hexagons, the average luminance in the global flash (frame 3) is twice as bright as frame 1. (b) The luminance difference between the brighter luminance hexagons and the dimmer luminance hexagons ($L_{\text{max}}$ − $L_{\text{min}}$) of the multifocal flashes in four stimulus contrast settings are denoted 2.12, 1.42, 1.08, and 0.62 cd \cdot s/m².

\textbf{Figure 1.} (a) The stimulus sequence (one element of the m-sequence) contains four frames. The initial frame (multifocal flashes) alternates between white and black according to a pseudorandom binary m-sequence with a preset contrast level. After each initial frame of the four-frame set, a global flash (2.16 cd \cdot s/m²; frame 3) was applied, separated by a pre- and postdark frame (0.04 cd \cdot s/m²; frames 2 and 4). As the number of flashing elements in frame 1 involved half of the total number of hexagons, the average luminance in the global flash (frame 3) is twice as bright as frame 1. (b) The luminance difference between the brighter luminance hexagons and the dimmer luminance hexagons ($L_{\text{max}}$ − $L_{\text{min}}$) of the multifocal flashes in four stimulus contrast settings are denoted 2.12, 1.42, 1.08, and 0.62 cd \cdot s/m².

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equally across the conditions, we randomized the order of the six stimulus conditions across subjects.

**Experiment 2.** Thirty normal subjects and 30 subjects with glaucoma participated in this modified experiment. The stimulus was the same scaled 103-hexagon pattern that was displayed on the same monitor as in experiment 1. Viewing parameters and luminance of the stimuli were as for Experiment 1. According to the result from Experiment 1, mfERG responses were recorded with four stimulus luminance-difference conditions of the multifocal flashes set at 2.12, 1.42, 1.08, and 0.62 cd·s/m². The recording time for each stimulation cycle was approximately 8 minutes and a $2^{15}$ binary m-sequence was also used. In other respects, the recording process was the same as for Experiment 1.

**mfERG Recording**

Before testing, the pupil of the tested eye was fully dilated, to at least 7 mm diameter, with 1% tropicamide (Alcon, Fort Worth, TX). Dawson-Trick-Litzkow (DTL) electrodes were used as the active electrode and gold-cup surface electrodes were used for both reference (located 10 mm lateral to the outer canthus of the test eye) and ground (located at the central forehead). During the mfERG recording, the untested eye was occluded. The refractive error of the tested eye was fully corrected for the viewing distance. The signal was amplified using a amplifier (band pass: 10 to 300 Hz; gain: $\times100,000$; model PS11K; Grass/Telefactor, West Warwick, RI). The measurement was monitored using the signal shown online by mfERG program (VERIS; EDI); any recording segments contaminated with blinks or small eye movements were rejected and immediately rerecorded.

**Data Analysis**

First-order kernels were analyzed using with the system software (VERIS 4.1; EDI). In experiment 1, the mfERG findings were presented by using a peak-to-peak response amplitude measurement. The responses from different stimulus conditions were plotted as a function of luminance difference. In experiment 2, the way in which these functions varied from the normal response in subjects with glaucoma was observed. These response functions were also compared with the VF defect by quadrants.

**RESULTS**

**Responses from Six Concentric Rings**

The traces in Figure 2a are typical normal ring responses grouped according to retinal eccentricity. To facilitate the comparison of waveforms, normalized responses with equal root-mean-square amplitudes were used. The DC in the central region contained a main trough at 15 ms and a main peak at 35 ms, with a very small peak at $\sim45$ ms, similar to the photopic full-field flash ERG responses. In the periphery, the DC still shows a double-peak with faster latency, P1 at 30 ms and P2 at 40 ms. The IC waveforms from central to peripheral regions are similar and contain two peaks (P3 at 55 ms and P4 at 65 ms; faster latencies are seen in the periphery) with a triphasic shape, which is quite similar to the second-order kernel response recorded from the conventional mfERG stimulation.

There is an obvious difference in the P1 waveform between central and peripheral regions. A delayed N1 seems to be observed in the peripheral region and this happens even in localized responses (Fig. 2b). All the responses from the various luminance-difference stimulus conditions, either from normal subjects or those with glaucoma show similar wave patterns and have a good signal-to-noise ratio.

The luminance-modulated response functions of the amplitude of the DC and IC response (measured as N1-P1 and P3-N4, as shown in Fig. 2a) from ring analysis showed markedly different behavior (Fig. 3). The DC responses from the central two rings show a linear function with increasing luminance difference, whereas the DC responses from the peripheral three rings seem independent of the luminance difference beyond 1.1 cd·s/m² luminance difference and become relatively steady in their responses. Ring 3 appears to be a region of transition between the central and peripheral regions. In contrast to the independence of the luminance difference shown in the peripheral DC response, the IC responses increase linearly with increased luminance difference for all six rings.

**Summed Peripheral Responses**

Because the glaucomatous VF defects occurred in the Bjerrum area, the peripheral mfERG responses were analyzed in this
study. The responses from the three peripheral rings were grouped due to their similarities in waveform and latency, as well as their similar characteristics in the luminance-modulated response function. Figure 4 shows the modified luminance-modulated response function obtained from both normal and subjects with glaucoma. Subjects with glaucoma showed a statistically significant decrease in peripheral DC response amplitude at all luminance-difference levels compared with the control subjects (Fig. 4a; Table 1). The largest decreases in response amplitudes are at the mid luminance-difference levels that make the response function show a loss of the luminance-difference independence characteristic seen in normal subjects.

Subjects with glaucoma also show a statistically significant decrease in peripheral IC responses at all luminance-difference levels compared with the control subjects. The largest differences are at the high luminance-difference levels. The luminance-modulated response function in subjects with glaucoma increases linearly with increasing luminance-difference level but with a lower slope than does the control subject group (Fig. 4b; Table 1).

**Peripheral Quadrant Responses**

The relationship between the peripheral mfERG response amplitude and the VF defect was evaluated by comparing the measurements averaged within each quadrant. The peripheral mfERG response amplitudes were averaged into four quadrants, and the MD of the VF thresholds were also averaged by corresponding quadrants, but only the points beyond 10° were included to provide similar field dimension for comparison (Fig. 5a). Figure 5 shows the response amplitudes for the
ever subjects with glaucoma showed a specific change in the DC luminance-modulated response function. We have developed an adaptive index, by calculating the area indicating the degree of saturation of the DC luminance-modulated response. This index is calculated by subtracting the responses from 0.62 to 2.12 cd·s/m² luminance difference from the area under the luminance-modulated response function fitted with a second-order best-fit line in this region (Fig. 6a). The loss of dependence on the luminance difference in the luminance-modulated response function in those subjects with glaucoma is shown in a reduction of the adaptive index. Figure 6b shows a plot of the adaptive index against the MD of the VF defect in every quadrant. The normal values of the adaptive indices for all four quadrants were similar (one-way repeated-measures ANOVA; P = 0.19); the normal range is shown by a box plot at the right of the graph. The adaptive indices among quadrants from the subjects with glaucoma show statistically significant reductions (unpaired t-test; P < 0.0001) from the normal values.

The adaptive index shows good differentiation between the two groups. Figure 7 shows the receiver operating characteristic (ROC) curve based on different cutoff values of the adaptive index. This ROC curve illustrates the balance between sensitivity and specificity for the discrimination of subjects with glaucoma from normal subjects. The area under the ROC curve provides an index for quantifying the accuracy of the test (where 1.0 is a perfect result). The area under this ROC curve is 0.986, which is close to a perfect test. The sensitivity would be 93% with a specificity of 95% using the best cutoff adaptive index value of 1.5 based on this ROC curve. Correlation of the adaptive index with the VF defect is statistically significant (r = 0.58, P < 0.0001), whereas the mERG amplitude measures do not correlate with the VF measures. Differentiation of glaucoma from normal subjects using the adaptive index is shown in Figure 6b, where the horizontal dotted line shows an adaptive index of 1.5.

**DISCUSSION**

This modified global flash paradigm with luminance modulation is designed to measure the adaptive changes in the retina. Inserting a global flash in the m-sequence stimulus adjusts the overall adaptation level, so that these adaptation effects add to the higher-order kernels of the m-sequence response. The DC is the response of the local flashes influenced to a degree by

**Table 1.** Response (Peak-to-Peak) Amplitudes of DC and IC in the Retinal Periphery

<table>
<thead>
<tr>
<th>Luminance-Difference Level</th>
<th>2.12 cd · s/m²</th>
<th>1.42 cd · s/m²</th>
<th>1.08 cd · s/m²</th>
<th>0.62 cd · s/m²</th>
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<tbody>
<tr>
<td>Direct component</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal (nV/deg²)</td>
<td>11.44 ± 2.79</td>
<td>10.90 ± 2.52</td>
<td>10.46 ± 2.63</td>
<td>6.31 ± 2.02</td>
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<tr>
<td>Glaucoma (nV/deg²)</td>
<td>8.88 ± 3.53</td>
<td>6.29 ± 2.98</td>
<td>5.25 ± 2.87</td>
<td>4.02 ± 3.04</td>
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<td>One-way repeated-measures ANOVA</td>
<td>F = 33.321</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>df = (7,239)</td>
<td></td>
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<td></td>
<td>P &lt; 0.0001</td>
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<tr>
<td>Posthoc test (Bonferroni)</td>
<td>t = 3.679</td>
<td>t = 6.643</td>
<td>t = 7.498</td>
<td>t = 3.290</td>
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<td></td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.01</td>
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<tr>
<td>Induced component</td>
<td></td>
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<tr>
<td>Normal (nV/deg²)</td>
<td>16.31 ± 3.63</td>
<td>12.36 ± 3.29</td>
<td>10.19 ± 3.30</td>
<td>6.20 ± 3.25</td>
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<tr>
<td>Glaucoma (nV/deg²)</td>
<td>7.96 ± 3.15</td>
<td>6.06 ± 1.88</td>
<td>4.82 ± 2.27</td>
<td>3.85 ± 1.74</td>
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<td>One-way repeated-measures ANOVA</td>
<td>F = 67.330</td>
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<td></td>
<td>df = (7,239)</td>
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<td>P &lt; 0.0001</td>
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<tr>
<td>Posthoc test (Bonferroni)</td>
<td>t = 11.447</td>
<td>t = 8.642</td>
<td>t = 7.353</td>
<td>t = 3.226</td>
</tr>
<tr>
<td></td>
<td>P &lt; 0.001</td>
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<td>P &lt; 0.001</td>
<td>P &lt; 0.01</td>
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the global flash in the prior m-sequence stimulation, and the IC is the change to the response of the global flash produced by the current m-sequence stimulation. Both components reflect interaction between the m-sequence stimulus and the global flash and are likely to be affected by the luminance modulation of the multifocal flashes.

**FIGURE 5.** (a) The peripheral mfERG response amplitudes were averaged into four spatial quadrants in corresponding VF quadrants. The central 10° region was omitted. The response amplitudes of (b) DC and (c) IC are plotted against the visual field mean defect according to the VF quadrants. The box plots at the right of each graph show normal values: middle line, the mean; top and bottom box edges, one SD; top and bottom bars, the range; solid lines, the best-fit line of the points showing the relationship between the mfERG amplitude and the visual field mean defect. *Correlation coefficients are statistically significant, but both are negative and of little clinical significance.
For high luminance-difference m-sequence stimulation, we have shown the different characteristics of the DC in the central (to 10°) and peripheral (beyond 19°) regions of the retina. The difference of the central response seems to be made by the overlapping of a component that is relatively larger and later than that in the periphery, just before P1 (Fig. 2a). The ascending edge of the central P1 waveforms appears to have been combined by this component, whereas separation of this component from the P1 seems to have occurred in the peripheral responses. The variations of the DC waveform with eccentricity may reflect different adaptive mechanisms across the retina, and this phenomenon is not shown in the first-order response with conventional flickering stimulation,1 where there is no constant adaptive flash. This regional change in responsiveness may be caused by variation in the rod/cone mix with eccentricity, change in the ways in which receptors and receptive fields are connected, and different responsiveness to changes in overall luminance.

The first-order response of the conventional m-sequence stimulation appears to be linearly dependent on the changes of luminance difference in the response.25 However, in a more complex interaction with the global flash stimulus, only the peripheral DC response appears to be independent of the changes of luminance difference, where the DC response seems to remain steady at high luminance-difference levels. This implies that this nonlinear response function curve is altered by the adaptive mechanism that was induced by the global flash. The different nature of the luminance-modulated response function between the central and peripheral retina suggests that the global flash adaptive effect may have different cellular bases in these regions, as a relatively pure P1 without an overlapped prior component can be obtained in the peripheral regions.

In this study, the IC response was also influenced by the luminance modulation of the multifocal flashes. The response decreased with decreasing luminance difference of the multifocal flashes, even though the mean luminance was constant. This result is not surprising, because each local flash of the multifocal frame not only elicited a particular response, it also
affected the next global flash response at the same location. The IC response thus depends on the adaptive effect elicited by the luminance intensity of the local flashes,22 but not the mean focal luminance.

The fast-adapting mechanisms that induce the IC are thought to be located predominantly in the inner retinal layers because of its nonlinear characteristics,16, 18, 20, 22 and probably have contributions from the ONHC (Bearse MA, et al. IOVS 2000;41:ARVO Abstract 536).16 Impaired adaptive effects due to inner retinal damage may affect the DC response, but the changes of the DC have been reported only in diabetic patients.18 No previous study has shown any relationship between the DC response and glaucoma. We speculate that this may be related to the different characteristics between the luminance-modulated response function of the DC and IC. The normal DC responses remain steady at high luminance-difference levels, but in subjects with glaucoma, the DC responses show less reduction in amplitude at high stimulus luminance-difference conditions than at mid stimulus luminance-difference conditions. In contrast, the IC responses show a larger reduction in amplitude under high stimulus luminance-difference conditions. Because most previous studies have only used a high stimulus luminance-difference condition for global flash stimulation (Bearse MA, et al. IOVS 2000;41:ARVO Abstract 536), this may explain why the amplitude changes of the DC responses from subjects with glaucoma were difficult to observe when compared with the IC response.

In this study, the reduction of the DC amplitude at the mid luminance-difference level enhances the loss of the luminance-difference saturation of the DC luminance-modulated response function in subjects with glaucoma. To enhance differentiation between normal and glaucomatous eyes, previous studies have suggested that the reduction in the IC in subjects with glaucoma seems indicative of impaired adaptive effects due to inner retinal damage,23 even though the variations of the IC amplitudes do not show any spatial correspondence to VF sensitivity.24 Similar results have been shown for all luminance-difference levels in our study. However, as mentioned earlier, the DC should still show an adaptive effect while it contains contribution(s) from the ONHC.16

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In this study, the reduction of the DC amplitude at the mid luminance-difference level enhances the loss of the luminance-difference saturation of the DC luminance-modulated response function in subjects with glaucoma. To enhance differentiation between normal and glaucomatous eyes, previous studies have suggested that decreased stimulus contrast increases the relative contribution of the inner retina to the mERG signal,23 and stimuli of reduced stimulus contrast have been used in an attempt to detect glaucoma.15, 26 However, in this study, the DC response amplitudes even at the mid luminance-difference level still did not demonstrate any good correlation with VF defect; hence, the mERG response amplitude alone is not likely to be a useful measure.

Alternatively, the mERG response is a measurement related to rapid adaptive processing, and any dysfunction of this processing can provide an early indication of disease.27 The inner retinal layer is believed to be damaged early in glaucoma.2, 28–30 Moreover,14 it also showed that macular cells undergo shrinkage before cell death. The widespread morphologic changes affect the physiological behavior of these neurons and thus may affect short-term retinal adaptive mechanisms.17, 19–21 Besides mERG amplitude reduction, subjects with glaucoma in this study also showed a loss of luminance-difference saturation in the DC luminance-modulated response function. This feature most likely depends on the short-term fast-adaptation mechanism due to the interaction of global flashes. However, the loss of this feature may also be due to a generalized loss of function of the neurons that respond to these input signals; thus, the abnormal changes that occur in glaucoma probably reflect a combination of factors.

Nevertheless, it is intriguing that these patients showed a specific loss of the luminance-modulated response function across a wide range of luminance-difference levels. Quantifying this loss by calculating the adaptive index showed good differentiation between the normal subjects and those with glaucoma and also showed a good correlation to the glaucomatous VF defect.

The ROC curve shows that this method provides good sensitivity and specificity in differentiating normal subjects and those with suspected glaucoma. The adaptive index in some normal field quadrants from subjects with glaucoma shows an apparent reduction in value, and this may be due to the loss of nerve fibers or neural activity before the appearance of VF defects.25 This raises the possibility that electrophysiological measurements with special stimulation protocols may detect early functional changes. Because this functional change can be tested objectively and localized, development of this test together with appropriate norms could form the basis of a new test for glaucoma and other retinal dysfunctions with abnormal adaptive mechanisms.

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