Luminance-Modulated Adaptation of Global Flash mfERG: Fellow Eye Losses in Asymmetric Glaucoma

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PURPOSE. To use the global flash multifocal electroretinogram (mfERG) in patients with asymmetric glaucoma to determine whether retinal function is affected in fellow eyes that have no glaucomatous visual field defects.

METHODS. Forty normal subjects and 12 patients with asymmetric glaucoma were recruited for visual field and mfERG measurement. The mfERG was assessed by using a global-flash stimulation paradigm with four video frames: 103 scaled hexagonal elements followed by a dark frame, a global-flash frame, and a dark frame. The localized luminance difference was set at 96%, 65%, 49%, and 29% display contrast during the four different test conditions, respectively. The first-order kernel response was measured, and the “adaptive index” which has been used previously was calculated.

RESULTS. In fellow eyes with normal visual fields, the amplitude of the induced component (IC) was significantly reduced, and the adaptive index was reduced by a factor of almost 10 (P < 0.0001), as it was in the glaucomatous eyes. Although the adaptive index in the better (fellow) eye of the patients with glaucoma was slightly higher than in the eyes with diagnosed glaucoma, these differences were not statistically significant.

CONCLUSIONS. The significant reduction of the adaptive index in the better eyes in subjects with asymmetric glaucoma shows that the fast adaptive mechanism(s) were reduced in these eyes. This implies that eyes that have functionally normal visual acuity and visual fields have abnormal fast-adaptive mechanisms. (Invest Ophthalmol Vis Sci. 2007;48:2626–2633) DOI:10.1167/ios.06-0962

Primary open-angle glaucoma (POAG) is the second leading cause of blindness worldwide.1 It primarily affects the inner retina2–4 and has unremarkable symptoms in the early stages, but damage to the inner retina results in visual field constriction and ultimately in loss of central vision.5 POAG is generally a bilateral disease, although its severity is not necessarily symmetrical, and patients with unilateral glaucomatous visual field loss are believed to constitute a group at high risk for the development of glaucomatous visual field abnormalities in the fellow eye.5–9

Standard perimetry (white-on-white automated threshold testing) is essential for diagnosis and evaluation of glaucoma. However, the relationship between losses in visual sensitivity and loss of retinal ganglion cells has been considered to lack precision.5,10,11 because a large amount of ganglion cell loss may occur before standard perimetry detects significant visual field defects. The development of the glaucoma hemifield test (GHT) for the evaluation of visual field test results in glaucoma has been based on the symmetry of sensitivity across the horizontal meridian and on the anatomic arrangement of the retinal nerve fibers.12 Incorporation of the GHT into the automated perimeter has allowed significant improvement in differentiation of normal subjects from those with glaucoma.13 Interest in the functional capacity of the fellow eye in patients with asymmetric glaucoma has prompted the current investigation.

The multifocal electroretinogram (mfERG) allows recording of multiple local retinal responses within a short period.14 The topographical distribution of responses reflects retinal function, and the first-order kernel mfERG responses are derived predominantly from distal retinal layers (photoreceptors and bipolar cells).15,16 Higher-order responses are derived from more proximal retinal layers and primarily reflect inner retinal function.17 The mfERG has been used widely in the investigation of functional changes of the retina.18–22

The global-flash paradigm, a new stimulation mode of the mfERG, is thought to elicit a relatively enhanced inner retinal response by emphasizing retinal fast-adaptive mechanisms.23 This new paradigm consists of periodic global flashes interleaved with the pseudorandom binary m-sequence multifocal stimulation; it elicits a direct component (DC) and an induced component (IC).25,24 The global-flash paradigm has been used to study retinal adaptation in various ocular diseases. The DC is the response of local flashes influenced to a degree by the global flash in the prior stimulation sequence. It has been found to be sensitive to early changes in retinal function in diabetes25 and age-related maculopathy.26 The IC is the change in the response of the global flash produced by the current m-sequence stimulation. It is a purely nonlinear response25 and has been found to be an indicator of glaucoma.27,28 However, large intersubject variability in the IC25 has limited its usefulness in the localized assessment of glaucomatous damage in individual patients.

We used a sophisticated stimulation mode that combined the global flash and luminance modulation of the multifocal flashes (luminance-modulated global flash mfERG stimulation) for glaucoma detection in our recent study.29 We quantified the nonlinearity of the DC induced with this stimulation mode and derived an adaptive index that showed significant reduction and relatively good correlation with the visual field defect in subjects with glaucoma. We believe that the reduction of the adaptive index was related to abnormal retinal adaptive mechanisms, presumably resulting from inner retinal damage.29

In the present study, we investigated whether the fast-adaptive mechanisms are affected in the fellow eye in patients...
with asymmetric glaucoma where there is no evidence of field defects with conventional perimetry.

**METHODS**

**Subjects**

Twelve patients with POAG (age range, 23–59 years; mean, 44.8 ± 12.1), with corrected visual acuity (VA) of 0.1 logMAR (20/25) or better but with unilateral glaucomatous visual field defects were selected for the study (Table 1). All subjects had asymmetric glaucoma of more than 1 year’s duration, as diagnosed by their ophthalmologists. They were being treated with either latanoprost (Pfizer Corp., New York) or timolol maleate (Alcon, Ltd., Fort Worth, TX) in both eyes. An eye examination was performed to exclude ocular abnormalities in addition to glaucoma. Visual field measurements were conducted twice on all subjects, with the 30-2 threshold (SITA) program of the visual field perimeter (Humphrey Visual Field Analyzer; Carl Zeiss Meditec, Inc., Dublin, CA). Subjects with an abnormal glaucoma hemifield test (GHT) index in the affected eye and normal visual fields plus a normal GHT index in the fellow eye were accepted in the study. Intraocular pressure in the fellow eyes was less than 21 mm Hg, and normal appearance of the optic disc in both eyes. One eye of each control subject was randomly selected for testing.

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.

**Stimulation**

The mfERG stimulus pattern was presented on a 19-inch RGB (red-green-blue) monitor (model GDM-500PS; Sony, Tokyo, Japan), and the mfERG program (VERIS 4.1; EDI, San Mateo, CA) was run on a computer (Macintosh G3; Apple Computer, Cupertino, CA). The mfERG was measured by using the luminance-modulated global-flash mfERG paradigm. In this paradigm, each m-sequence stimulation cycle consisted of four video frames (each frame lasts 13.3 ms, with a 75-Hz frame rate). There was an initial multifocal pattern with 103 hexagons, scaled with eccentricity (scale factor, 10-46), and each hexagon was either bright or dark according to a pseudorandom binary m-sequence. After the multifocal flash, there was a dark frame (0.04 cd/m² per frame), and a second dark frame before the next m-sequence stimulation. The average luminance of the multifocal flashes was approximately 1.11 cd/m² (i.e., 83 cd/m² per frame) and the background was also set to this luminance (Fig. 1).

Recordings were divided into 16 slightly overlapping recording segments. The recording time for each stimulation cycle was approximately 8 minutes, with a 2³⁻¹ binary m-sequence. Four different stimulus–contrast conditions in the global-flash paradigm were performed, and the luminance difference of the multifocal flashes was set at 2.12, 1.42, 1.08, and 0.62 cd/m² (Fig. 1B). The order of the four stimulus conditions was randomized across subjects, to distribute the effect of fatigue across conditions.

**mfERG Recording**

A Dawson-Trick-Litzkow (DTL) electrode was used, as active and gold-cup surface electrodes were used for both the reference and the ground. Before testing, the pupil of the tested eye was fully dilated to at least 7 mm in diameter with 1% tropicamide (Alcon, Ltd.). During the mfERG recording, the untested eye was occluded. The refractive error of the tested eye was fully corrected for the viewing distance of 30 cm. The signal was amplified (Grass P511K amplifier; band-pass: 10–300 Hz; gain: x100,000). The recording was monitored using the online signals shown by the 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 the mfERG system (VERIS 4.1). The mfERG findings were represented by peak-to-peak response am-

<table>
<thead>
<tr>
<th>Subject</th>
<th>Eye</th>
<th>Mean Deviation</th>
<th>Pattern Standard Deviation</th>
<th>Visual Acuity</th>
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</tr>
<tr>
<td></td>
<td>OS†</td>
<td>−10</td>
<td>8.25</td>
<td>20/20</td>
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</table>

* GHT index of fellow eyes were normal except for borderline indices found in fellow eyes of subjects 1 and 3.
† Glaucomaticus eyes with abnormal GHT indices.
plitude measurement (Fig. 2A) and the responses from different stimulus conditions were plotted as a function of the luminance difference of the stimulus. The way in which these functions varied from the normal response in subjects with asymmetric glaucoma were observed, and the adaptive index was calculated for comparison (Fig. 2B).

RESULTS

The traces in Figure 3 are typical grouped responses from three normal subjects and three with asymmetric glaucoma (both affected and fellow eyes). The waveforms were similar in appearance in control subjects and those with glaucoma; the DC amplitudes from both the affected and fellow eyes were reduced to a similar degree, but the reduction of IC amplitude was greater in the glaucomatous eyes. Peripheral mfERG responses were of interest in this study because glaucomatous visual field defects first occur in the Bjerrum area. Based on our recent study, responses from the four peripheral rings of the mfERG responses were grouped as shown in Figure 2C, because of their similarities in waveform and latency and their similar characteristics in the luminance-modulated response function.

Figure 4 shows the luminance-modulated response function obtained from control, affected, and fellow eyes. In the control

FIGURE 1. (A) Each stimulus sequence contained four frames. The initial frame (multifocal flash) alternated between bright and dark, according to a pseudorandom binary m-sequence with a preset stimulus-contrast level, followed by a dark frame (0.04 cd·s/m²). A global flash (2.16 cd·s/m²; frame 3) was then presented, followed by a second dark frame (0.04 cd·s/m²). As the number of flashing elements in frame 1 involved half the total number of hexagons, the average luminance in the global flash (frame 3) was twice as bright as frame 1. (B) The luminance difference between the brighter and the dimmer hexagons (Lmax - Lmin) of the multifocal flashes in the four stimulus-contrast settings are denoted 2.12, 1.42, 1.08, and 0.62 cd·s/m².

FIGURE 2. (A) The typical peripheral global flash mfERG response contains two components: the DC and the IC. The measurement of peak-to-peak amplitudes of the two components is illustrated. (B) Shaded area: the adaptive index of the DC response. It is calculated as the difference between the area under the curve (plotted using the second-order, best-fitting curve of the responses) and the area under the line (plotted joining the two values at the 2.12- and 0.62-cd·s/m² luminance difference). (C) The global flash mfERG responses from the four peripheral rings were grouped as the peripheral responses, which were further averaged into visual field quadrants shown for analysis.
group, the grouped peripheral DC responses are independent of the luminance difference beyond 1.1 cd·s/m² and became relatively unchanged in their responses. In affected and fellow eyes, however, the grouped peripheral DC amplitudes were reduced overall, but continued to increase as luminance difference levels increased. The response functions for both affected and fellow eyes maintained dependence of response amplitude on the luminance-difference characteristic, mainly because of the reduction in response amplitudes at the midluminance difference levels. The DC amplitudes of the control group were significantly larger than those of both eyes of the subjects with asymmetric glaucoma in all stimulus–contrast conditions, except at the lowest luminance difference (Table 2). Slightly larger DC amplitudes at all luminance difference levels were observed in fellow eyes compared with affected eyes, but there was no statistically significant difference between these two groups at any luminance difference.

We calculated the adaptive index, indicating the degree of saturation of the DC luminance-modulated response, by subtracting the area under the line joining 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. 2B). There is a reduction of the adaptive index in glaucoma. The mean adaptive index decreased by a factor of nearly 10 in the fellow eyes of subjects with asymmetric glaucoma (Fig. 5). The control group had the largest adaptive index, with a mean of 3.28 ± 1.61, but the fellow eyes from glaucoma subjects showed a significant reduction, with a mean of 0.36 ± 1.45 (unpaired t-test; P < 0.0001), and the affected eyes show a further reduction with a mean of 0.11 ± 1.21 (unpaired t-test; P < 0.0001). There was no significant difference between the affected and fellow eyes (paired t-test; P > 0.05).

The peripheral mfERG response amplitudes in fellow and affected eyes were averaged in corresponding visual field quadrants (Fig. 2C), to calculate the adaptive index to compare with visual field data. The mean value of the adaptive index was 0.37 ± 1.59 and −0.07 ± 1.65 across all four quadrants in the fellow eyes and affected eyes, respectively. There are no significant differences between the mean quadrantal peripheral adaptive index and the grouped peripheral adaptive index (paired t-test; P > 0.05) in fellow or affected eyes. Figure 6 shows the plots of the adaptive index against the mean deviation (MD) of the visual field in all quadrants. Because there was no glaucomatous field defect with a normal GHT index in the
fellow eyes, the mean MD for all field quadrants was $-1.56$ dB. The correlation of the adaptive index with the MD is statistically significant ($r = 0.37; P < 0.01$). However, there is a higher correlation of the adaptive index with the MD in the affected eye of the subjects with asymmetric glaucoma ($r = 0.44; P < 0.01$), and the mean MD is approximately $-10.15$ dB.

IC amplitude has also been reported to be a sensitive indicator of glaucoma.\(^2\) Grouped central IC amplitudes from the highest luminance difference stimulation level in the fellow eyes were evaluated, and the mean amplitude was $19.50 \pm 7.10$ nV/deg\(^2\); Fig. 7A; unpaired \(t\)-test; \(P > 0.05\). The mean amplitude of the grouped peripheral IC amplitudes from the highest luminance difference stimulation level in the fellow eyes was $10.28 \pm 4.25$ (nV/deg\(^2\)), which is significantly lower than the grouped peripheral IC amplitudes ($15.86 \pm 3.74$ nV/deg\(^2\)) of the control group (Fig. 7B; unpaired \(t\)-test; \(P < 0.001\)).

Figure 4 suggests that the rate of change of the luminance-modulated response function may be another indicator of variation of retinal adaptation. In addition, this may offer a way to reduce the testing time for this paradigm, allowing only two luminance modulation levels to be tested, rather than four. Therefore, the slope of the DC response between the two lowest luminance difference levels (1.08 and 0.62 cd ⋅ s/m\(^2\)) was calculated. The grouped central and peripheral regions were compared. The control group had the highest slope values, whether from the central or from the peripheral region, with mean slopes of $11.10 \pm 5.58$ and $8.21 \pm 5.58$, respectively. The central region of the fellow eyes of subjects with asymmetric glaucoma had a mean slope of $7.97 \pm 5.96$, a small, nonsignificant reduction (unpaired \(t\)-test; \(P > 0.05\)). However

**TABLE 2.** Grouped Peripheral Response (Peak-to-Peak) Amplitudes of DC for the Three Groups at Four Luminance Difference Levels, with Statistical Comparisons

<table>
<thead>
<tr>
<th>Luminance Difference Level</th>
<th>Control group (nV/deg(^2))</th>
<th>Affected eyes (nV/deg(^2))</th>
<th>Fellow eyes (nV/deg(^2))</th>
<th>One-way ANOVA F (\text{df} = (11, 244); P &lt; 0.0001)</th>
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<td>2.12 cd ⋅ s/m(^2)</td>
<td>$10.85 \pm 2.78$</td>
<td>$6.55 \pm 2.58$</td>
<td>$7.39 \pm 2.98$</td>
<td>Post hoc test (Bonferroni corrected)</td>
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<td>1.42 cd ⋅ s/m(^2)</td>
<td>$10.53 \pm 2.93$</td>
<td>$5.57 \pm 2.90$</td>
<td>$6.26 \pm 3.55$</td>
<td>Control vs. affected eyes</td>
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<tr>
<td>1.08 cd ⋅ s/m(^2)</td>
<td>$9.95 \pm 2.74$</td>
<td>$4.93 \pm 2.33$</td>
<td>$5.63 \pm 3.35$</td>
<td>Control vs. fellow eyes</td>
</tr>
<tr>
<td>0.62 cd ⋅ s/m(^2)</td>
<td>$6.18 \pm 2.21$</td>
<td>$4.14 \pm 1.99$</td>
<td>$4.33 \pm 2.14$</td>
<td>Affected vs. fellow eyes</td>
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</tbody>
</table>

**FIGURE 5.** Statistical results of the adaptive index from the three groups shown as box plots. There was a statistically significant reduction (*) of the adaptive index in both the affected and fellow eyes of the subjects with glaucoma when compared with the control group (\(P < 0.05\)). Dotted line: best cutoff point of the adaptive index for glaucoma differentiation; middle line: the mean; top and bottom box edges: ±1 SD; top and bottom bars: the range. (♀) Individual values from fellow and affected eyes of subjects with asymmetric glaucoma.

**FIGURE 6.** The adaptive indices from all quadrants from fellow (A) and affected (B) eyes of the subjects with asymmetric glaucoma plotted against visual field mean deviation (MD) values in corresponding visual field quadrants. Vertical dotted lines: mean MD for each group. Solid line: the best-fitting line of the points showing a statistically significant correlation (\(r = 0.37 \) and \(r = 0.44\)) between adaptive index and visual field MD of fellow eyes (top) and affected eyes (bottom).
affected eyes show a significant reduction of the slope value (mean, 4.57 ± 4.18; unpaired t-test; \( P = 0.00005 \)).

In the peripheral region, there was a significant reduction of the slope in both eyes of subjects with asymmetric glaucoma. Slopes in affected and fellow eyes were 1.72 ± 2.84 (unpaired t-test; \( P = 0.0005 \)) and 2.84 ± 3.67 (unpaired t-test; \( P = 0.0003 \)), respectively (Fig. 8).

Figure 9 (top) shows the receiver operating characteristic (ROC) curve based on different cutoff values of the peripheral slope for the discrimination of subjects with glaucoma from normal subjects. These data are derived from all eyes in the present study. The area under this ROC curve is 0.822; the sensitivity is 75% with a specificity of 80% when the best slope cutoff value of 4.7 is used. However, four fellow eyes and two affected eyes were considered normal, based on this cutoff value. When the ROC was based on the luminance-modulated response (adaptive index) in these eyes and derived from quadrant responses as in our previous report, the area under the curve increased to 0.922 (Fig. 9, bottom), and sensitivity and specificity increased to 82% and 91%, respectively. The cutoff for the adaptive index in this case is 1.5, confirming our previous findings. As expected, better discrimination between the control subjects and those with glaucoma was obtained when more information was used.

DISCUSSION

Our findings with the global-flash paradigm with luminance modulation in this study have shown that fellow eyes of patients with asymmetric glaucoma are similar to glaucomatous eyes that have impaired retinal adaptive changes.

We used patients with POAG who had unilateral glaucomatous visual field defects in the present study because Harbin et al. reported that 43% of fellow eyes of patients with POAG with monocular field loss developed visual field losses within 4-4 years.

Previous studies have reported that there may be retinal changes before any defined visual field loss is present in the fellow eyes of patients with asymmetric glaucoma. Neuroretinal rim thinning has been reported after tomography analysis (Heidelberg Retina Tomograph; Heidelberg Engineering, Heidelberg, Germany). A report of a study in which OCT was used suggested that retinal nerve fiber layer changes can be detected before any reduction in visual field sensitivity. The pattern-reversal electroretinogram (PERG) in patients with asymmetric glaucoma has shown significant differences between eyes, but these early amplitude reductions in fellow eyes were not compared with a normal control group. The PERG has been reported to be an early indicator of dysfunction preceding glaucoma and can help to predict stability or progression to ocular hypertension glaucoma at least 1 year ahead of conversion.

The mfERG provides an objective measurement of retinal function, and the second-order kernel is believed to be effective in assessing nonlinear retinal responses, mainly reflecting the adaptation activity of inner retinal layers. However, Sakemi et al. found that the second-order kernel of the mfERG does not correlate with glaucomatous visual field abnormalities, and they questioned its relationship with inner retinal responses. In fact, outer retinal activity also makes a contribution to second-order responses, and this contribution may complicate interpretation of any retinal changes in patients with glaucoma. Sakemi et al. also reported a nonsignificant difference in the second-order kernel of the mfERG between eyes in the same subject with glaucoma who had unilateral visual field abnormalities. Their result is not surprising if inner retinal function of eyes with normal visual fields from subjects with asymmetric glaucoma is compromised. It suggests that the retinal function of the fellow eye in patients with asymmetric glaucoma should be further investigated.
coma and that reduction of the IC seems indicative of impaired fast-adaptive effects in the periphery of the fellow eyes of patients with asymmetric glaucoma further confirms that an impaired fast-adaptive mechanism occurs before observed visual field abnormalities in patients at high risk for glaucoma. Caution must be exercised in interpreting our data because the samples were not precisely age-matched (44.8 ± 12.1 years for the subjects with asymmetric glaucoma and 41.5 ± 13.2 years for the control subjects), and the DC may be age dependent.

The adaptive index, however, can only be used for responses obtained outside the macular region. A simple comparison of DC response amplitude at the two lowest luminance difference levels may be another important parameter to allow monitoring of macular and peripheral retinal function. Although the correlation of the DC slope with the MD of the visual field results in glaucoma subjects is not as good as that with the adaptive index (data not shown), it provides similar information to that provided by the adaptive index. The reduction of the slope value is likely to represent directly the depression of responses at the midluminance difference level caused by glaucomatous damage. Therefore, both central IC amplitude and central DC slope showing the nonsignificant differences between the control and the fellow eyes indicate that the central retinal function may not be obviously affected in the early stage. This conclusion agrees with the progression of glaucomatous damage that initially affects the Bjerrum area.

The significant reduction of both the adaptive index and the DC slope in asymmetric glaucoma shows that the fast adaptive mechanism of both eyes is compromised. Our previous study demonstrated that the best cutoff point of the adaptive index for glaucoma differentiation is 1.5 (Fig. 4). This value works well in the present study, since only 8.7% of field quadrants from the normal subjects were classified as abnormal based on this level, and the mean level, even in fellow eyes, was still below the cutoff point. Thus, even eyes that were functionally normal in visual acuity or visual field had abnormal changes in the fast-adaptive mechanism, which allows us to differentiate them from normal by preestablished criteria. The ROC curve for the peripheral DC slope shows that this method provides reasonable sensitivity and specificity in differentiating the normal subjects from those with suspected glaucoma, although it does not work as well as the adaptive index. However, care must be exercised in interpreting the ROC data derived herein, and the values obtained should be used only as a rough guide; both eyes from the subjects with asymmetric glaucoma have been included (and these cannot be regarded as independent), and the number of glaucomatous eyes included is small.

The measurement of the adaptive index or DC slope using this luminance-modulated global-flash mfERG stimulation can provide additional information for diagnosis. The DC slope can be used as a screening tool for detection of glaucomatous damage, but for more detailed monitoring of regional changes of retinal function, we suggest use of the adaptive index because of its relatively lower variability which gives better differentiation between the normal subjects and those with glaucoma.

**References**


