Mapping of Glaucomatous Visual Field Defects by Multifocal VEPs

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PURPOSE. To objectively measure a visual field and to sensitively detect glaucomatous visual field defects by measuring the contrast sensitivity function (CSF), using multifocal visual evoked cortical potentials (MVEPs).

METHODS. MVEPs of normal subjects (n = 28) and of patients with glaucoma (n = 12) or ocular hypertension (OH, n = 1) were recorded. A multi-input procedure was used to obtain 37 local VEP responses to each scaled hexagon, composed of 24 triangular patterns, reversing in a counterphase manner. Two pattern contrasts of 32% and 8% were used for measuring the contrast threshold. To improve the signal-to-noise ratio, 37 MVEPs were averaged into 20 groups. The root-mean-square (RMS) measures at both contrasts were calculated. Contrast thresholds were estimated by extrapolating the regression line of the amplitude versus contrast to the mean noise levels.

RESULTS. RMS amplitudes of each local MVEP decreased as the eccentricity increased and as the pattern contrast decreased in normal subjects. It was also revealed that the amplitudes were smaller in the upper-half field than those in the lower-half field. Compared with the RMS amplitudes, CSFs estimated by MVEPs were relatively constant without being strongly influenced by retinal eccentricity. In patients with glaucoma, the CSFs, even from the locations where the mean perimetric sensitivities ranged to more than 30 dB, were significantly smaller than those in the normal control subjects (P < 0.001, Mann-Whitney test). CSFs in the 20- to 30-dB and 100 to 20-dB groups were also significantly smaller than those in the more-than-30-dB or 20- to 30-dB groups, respectively (P < 0.001, Mann-Whitney test). A significant correlation was found between the logarithmic function of the CSF and perimetric sensitivity (r = 0.57, P < 0.001, n = 216). The CSFs were evaluated on the basis of normal SD. Mappings of the CSFs agreed well with those of the perimetric sensitivity in all patients with glaucoma and was even more sensitive in detecting slight optic nerve damage by glaucoma than was perimetry.

CONCLUSIONS. Local optic nerve damage caused by glaucoma can be sensitively detected by measuring contrast sensitivity using the MVEP. (Invest Ophthalmol Vis Sci. 2001;42:3341–3348)

Although extensive efforts1,2 have been made so far to evaluate a visual field objectively by using visual evoked cortical potentials (VEPs) none of the methods has achieved great clinical success.

Recently, Baseler et al.3 reported that many local responses of the VEPs could be obtained by using the multi-input method originally developed for electroretinograms (ERGs) by Sutter and Tran,4 but they concluded that large intersubject variability is one of the obstacles to clinical use. However, Klistorner et al.5 reported that MVEP responses could be obtained from a wider field area by appropriate positioning of the electrodes. Large interindividual variability and sharp amplitude reduction with an increase in retinal eccentricity in the MVEPs remain as two major problems. Hood et al.6 reported that local optic nerve damage could be quantitatively measured by interocular comparison of the MVEP. This technique solved the problem of intersubject variability to some degree and enabled substantial progress to be made in objective visual field measurements. This method works well in patients in whom the visual field defects are not symmetrical. However, the majority of patients with glaucoma, for example, have visual field defects in both eyes. In such a case, it may be difficult to detect local optic nerve dysfunction by a method of interocular comparison.

Thus, a method for evaluating the MVEP from only one eye to detect optic nerve dysfunction is needed. A method that enables detection of optic nerve dysfunction in the early stage of the disease is also needed. In the present study, we tried to find a solution to these problems.

METHODS

Subjects

MVEPs were recorded from 28 eyes of 28 normal subjects whose ages ranged from 20 to 71 years (mean age, 45.2 years) and from patients with primary open-angle glaucoma (POAG, n = 5) or normal tension glaucoma (NTG, n = 7) whose ages ranged from 20 to 71 years (mean age, 50.9 years). One patient with ocular hypertension (OH) also participated in this study (MD = +1.6; see P13 in Fig. 6C). Mean deviations of Humphrey static perimetry (Humphrey-Zeiss, San Leandro, CA) in patients with glaucoma ranged from −2.3 to −17.0 dB (9.6 ± 6.0 [SD]). The sensitivity mapping and mean deviation (MD) for each are shown in Figure 4. All the patients had clear media and no eye diseases, apart from those mentioned. All the subjects had good corrected visual acuity of more than 20/20. Intraocular pressure in the patients with glaucoma was maintained at less than 18 mm Hg. Our investigation followed the tenets of the Declaration of Helsinki, and informed consent was obtained from all participants once the nature of the study had been clearly explained.

Visual Stimulus

The stimulus array of 37 hexagons with a triangular pattern was displayed on a 21-inch black-and-white monitor at a frame rate of 75 Hz, produced with visual evoked response imaging system software (Figure 1; VERIS Science 3.1; Electro-Diagnostic Imaging, San Mateo, CA). The stimulus consisted of 37 scaled hexagons, each with 24 triangles, 12 black (<0 candelas [cd]/m²) and 12 white (<200 cd/m²). The entire stimulus was subtended 42° × 42° in diameter. Four pattern contrasts (32%, 16%, 8%, and 4%) were used to confirm a linear function between the root-mean-square (RMS) amplitude and pattern contrast in three normal subjects. Two contrasts, 32% and 8%, were used to measure contrast thresholds in 12 patients with glaucoma. The mean luminance of the pattern was equally set at 102 cd/m². Each stimulus pattern and its MVEP response were numbered from 1 to 37.
in order from nasal to temporal and from top to bottom (Fig. 1A). The stimuli were reversed independently, according to a pseudorandom m-sequence.4,5

Recordings
To obtain an MVEP, signals were fed into an amplifier with band-pass filtering from 5 to 100 Hz (model 12 amplifier; Grass, Quincy, MA). The m-sequence had 2^{15}–1 elements. The recording was divided into eight segments with a resting time, and 10 minutes were needed for a single recording session. Fixations of the eyes were well maintained during each recording segment. The next recording session viewing different contrast was performed after a resting time of 10 minutes or more. The MVEPs were recorded with a needle electrode placed at 4 cm above the inion. A reference electrode was placed on the inion, and an electrode was placed on the forehead as a ground.

Analysis
The first slice of second-order kernel was extracted using VERIS 3.1. static perimetry (program 30-2; Humphrey), which was also performed for comparison with the MVEP (Fig. 1C). In the present study, procedures such as artifact removal that may affect the original MVEP waveforms were not used. To evaluate response magnitude, the RMS measure was calculated.

$$RMS_{i–j}(C) = \sqrt{\frac{\sum_{t = i}^{j} [(R(t) - A_{i,j})^2]}{(j-i+1)}}$$

where $R(t)$ is the response at time $t$, $C$ is contrast of a pattern, and $A_{i,j}$ is the average of the amplitude from $i$ to $j$ msec. $RMS_{0–49}(C)$ is the signal amplitude, and $RMS_{0–49}(32)$ and $RMS_{0–49}(8)$ for each location.

A contrast (supra-) threshold was determined as the point at which the extrapolating regression line intersected the line of mean noise level calculated from $RMS_{0–49}(32)$ and $RMS_{0–49}(8)$ for each location.

To increase the signal-to-noise ratio, the local MVEP responses were grouped and averaged (Fig. 1B) based on the response magnitudes in normal subjects. The upper two groups (Fig. 1B, upper [U]1 and U2)
were averaged from four responses. The upper middle group (U3) and lower two groups (lower [L]5 and L9) were averaged from three responses. The upper two groups (U4 and U5), middle two groups (central [C] 1 and C5), and a lower group (L10) were averaged from two responses.

Figure 1C shows the two-dimensional relationship between the field location of the MVEPs and testing points of the Humphrey 30-2 visual field. To compare with the MVEPs, perimetric sensitivities of two testing points (Fig. 1; first, third, fifth, and seventh rows; dotted arrow and black ellipse) or four testing points (second, fourth, and sixth rows; black arrow and black circle) that were within or near the corresponding hexagon of the MVEP were averaged.

RESULTS

Waveform Changes of Local MVEPs to Different Pattern Contrasts

Figures 1D and 1E show trace arrays of the 37 MVEPs and 20 grouped MVEPs from a normal subject at contrasts of 32% and...
8%. By averaging, substantial MVEPs that could not be distinguished from noise before averaging (Fig. 1D) became clearly perceivable even in the peripheral locations (Fig. 1E). Although the response magnitudes at 8% contrast were smaller than those at 32%, waveforms at the same location were almost identical.

Figure 2A shows an example of MVEPs from a normal subject at four contrasts. The five locations were selected from 20 grouped locations (U3, U5, C3, L3, and L8). In each location, the peak-to-trough amplitude gradually decreased as the pattern contrast decreased. No substantial response that was distinguishable from noise was found at the initial part of the MVEP from 0 to 49 msec at each location. However, substantial responses were perceived from 50 to 180 msec. MVEPs in the upper area were inverted in waveform compared with those in the horizontal and lower areas. Although the MVEP waveforms varied considerably with location, those at the same location were almost identical, irrespective of the contrast.

Means of RMS amplitudes of the 20 grouped MVEPs from three normal subjects were calculated between 50 and 150 msec and were plotted to logarithmic function of the contrast (Fig. 2B). The MVEP responses gradually decreased as the pattern contrast decreased from 32% to 4% at each location. Although there was a tendency for the slope of the regression line to decrease as the retinal eccentricity increased, a linear function was found between the RMS amplitude and logarithmic function of contrast.

Figure 2C shows the contrast (supra-) threshold measurements in a normal subject, by using the regression line of the RMS amplitude versus the logarithmic function of contrast. In the figure, mean noise of $0.5 \times (RMS_{50–150(32)} + RMS_{50–150(8)})$ have been subtracted from the RMS amplitudes for each location. A contrast (supra-) threshold was determined as the point at which the extrapolating regression line intersected the x-axis at each location.

**Mean and SDs of RMS$_{50–150(32)}$, RMS$_{50–150(8)}$ in Normal Subjects**

Approximately 1 hour was needed to record a single session of the MVEPs at four pattern contrasts. This is too long for a patient with glaucoma to maintain a good fixation during recordings. Thus, only pattern contrasts of 32% and 8% were used to evaluate contrast thresholds in patients with glaucoma. The mean ± 1 SD of RMS$_{50–150(32)}$ and RMS$_{50–150(8)}$ in 28 normal control subjects are plotted against location in Figures 3A and 3B, respectively. Three peaks of means were found at C3, L3, and L7 (Figs. 3A, 3B). All these locations were near the vertical meridian intersecting the center point of the viewing map. The largest peak was at C3, which is located in the central area, and the next largest peak was at L3, which is located in the lower area. The mean amplitudes of RMS$_{50–150(8)}$ were smaller than those of RMS$_{50–150(32)}$. The means of the coefficient of variation were 0.53 for RMS$_{50–150(32)}$ and 0.63 for RMS$_{50–150(8)}$ at all 20 locations. Thus, the intersubject variability was so large for both RMS$_{50–150(32)}$ and RMS$_{50–150(8)}$ that it was difficult to detect slight changes in the MVEP in the patients with glaucoma.

**Signal-to-Noise Ratio of Local MVEPs as a Function of Field Location in Normal Subjects**

Thus, signal-to-noise ratios were calculated at each of the 37 locations in the 28 normal subjects. If the local MVEP response met the criterion of the formula $|RMS_{50–150(8)}(C)|/RMS_{50–150(8)}(C)| > 1.1$, where $C$ is 8% or 32%, the response was regarded as a significant signal. Although an ideal criterion for differentiating a significant signal from noise would differ from subject to subject and from location to location, the criterion of more than 1.1 was used arbitrarily in the present study. In the normal subjects, if the number was replaced with a larger number, more data would be missing as noise. In the group of 37 MVEPs without averaging, rates of significant response obtained from the 28 normal subjects were 82% to 96% in the central and lower areas and 39% to 67% in the peripheral and upper areas, respectively. In contrast, by grouping the MVEPs into 20

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**Figure 2.** RMS$_{50–150(32)}$ and RMS$_{50–150(8)}$ in 28 normal subjects. (A) MVEP amplitudes (RMS) at contrast of 32%. Mean and standard deviation (N=28). (B) MVEP amplitudes (RMS) at contrast of 8%. Mean and standard deviation (N=28). (C) Mean and SD of CSF by MVEP (N=28).
groups, the rates of significant response obtained were increased to 100% at 32% contrast and more than 93% at 8% contrast at all locations in the 28 normal subjects (data not shown).

**CSF Measured by MVEPs in 28 Normal Control Subjects**

The contrast (supra-) threshold was calculated at each of the 20 locations in the 28 normal subjects. The data were obtained by extrapolating the regression line (RMS amplitudes of the MVEP versus logarithmic function of the pattern contrast) to the mean noise level. The CSF is a reciprocal of the contrast threshold. In the present study, we could not determine a threshold higher than 0.32 (32%), because MVEPs were not measured at contrasts higher than 32%. Thus, in calculating the contrast threshold, if neither $RMS_{50-150}(32)$ nor $RMS_{50-150}(8)$ was significant, the threshold was estimated to be 0.32 (32%, CSF, 3.1) as the maximum threshold.

Figure 3C shows a graph of the means ± 1 SD of CSFs (plotted in logarithmic function 10) to the location. The distribution of the mean CSFs to the location was quite different from that of the RMS amplitudes. The mean CSF was not highest in the central area, unlike that of the RMS amplitude. The mean CSFs were relatively constant throughout the locations. The mean coefficient of variation was 0.37 for CSF at all 20 locations.

**Detection of Local Optic Nerve Dysfunction by the MVEP-CSF Method**

Figure 4 shows maps of the CSFs measured by the MVEP from the 12 patients with glaucoma. CSFs in the patients with glaucoma were scaled for each of the 20 locations based on the normal SD from the 28 normal control subjects. Gray-scale maps of the perimetric sensitivity within 25° of visual field angle are also shown in the figure. Each of the 20 grouped locations was scaled from black to white. The black shading indicates the decrease over 2 SD from the normal mean. The white shading indicates the decrease within mean ± 1 SD. The shadings of the fine and coarse dots indicate the decreases of over 1 and 1.5 SD from the normal mean, respectively. These mappings of the CSFs agreed well with those of the perimetric sensitivity in the patients with lower field loss (P5 and P6),
upper field loss (P7 and P8) and severe field loss (P10–P13). It was noted that the CSF was more sensitive to local damage to the optic nerve than was perimetry in some areas of the map. Thus, slight optic nerve dysfunction even in cases in which perimetric sensitivity loss was slight could be sensitively detected by using the MVEP-CSF method. This method may also enable detection of local optic nerve dysfunction that could not be detected by perimetry in patients with early-stage glaucoma (P1–P3).

CSF and Perimetric Sensitivity in Patients with Glaucoma

CSFs evaluated by MVEPs were compared with perimetric sensitivities for all patients with glaucoma. CSFs at C1 and C5, located on the horizontal line, were excluded from the comparison, because of the low response and because of the low signal-to-noise ratio at C5 and large intersubject variability at C1. Moreover, the mean of the perimetric sensitivity was not reliable because C5 contained a blind spot. Thus, 18 CSFs were compared with the mean sensitivities of the corresponding spots (Fig. 1C) for each of the 18 locations in all patients. The CSF decreased as the perimetric sensitivity decreased in patients with glaucoma. Figure 5A shows that the CSFs were significantly decreased, even in the area where the perimetric sensitivity was over 30 dB, compared with normal data ($P < 0.001, n = 62$, Mann-Whitney test). The CSFs from the locations where the mean perimetric sensitivities ranged from 20 to 30 dB were significantly decreased compared with those of the more-than-30-dB group ($P < 0.002, n = 68$, Mann-Whitney test). There was also a significant difference between the mean CSFs in the 20- to 30-dB and 10- to 20-dB groups ($P < 0.001$, Mann-Whitney test). The relation is expressed in an exponential function ($y = 12.4e^{0.06x}$).

MVEP Changes in Early Stages of Glaucoma

Figure 6 shows four sets of MVEPs from a normal subject and from three patients with different stages of glaucoma. The uppermost row shows MERGs from a normal subject of 63 years of age. There was no decrease in the CSF over 1 SD from the normal mean. P7 was selected as an example of moderately progressed glaucoma (NTG) and had visual field defects in the upper-half field. As shown in the total deviation of the perimetry in Figure 6, the perimetric sensitivity was decreased significantly only in the upper-half field. However, although both $RMS_{50-150}(32)$ and $RMS_{50-150}(8)$ decreased under the noise levels in the locations of U1 to U4, C1, C5, and L5 (**); a decrease over 2 SD), CSFs were also reduced in the lower field of L1, L2 (*; a decrease over 1 SD) and L7 (**; a decrease over 1.5 SD). CSFs were also decreased in the locations of C3 (*) and L7 (**).

P2 was selected as an example of early-stage glaucoma (POAG). Local optic nerve dysfunction in the lower field was detected by both MVEPs and perimetry. The mapping of CSF loss agreed well with that of the total deviation. OH was diagnosed in the right eye of P13. There was no significant decrease in the indices of the static perimetry (Humphrey), but there were a few locations where the CSFs decreased over 1 or 1.5 SD from the normal means (* or **).

DISCUSSION

Objective evaluation of a visual field has been thought to be difficult due to variability in the response distribution related to the structure of the visual cortex. It has generally been considered that most of the VEP responses are from the central retina within 5° to 8° of the visual field and that responses from more peripheral areas are difficult to measure. Recently, possibilities for detection of visual field defects in patients with optic neuropathy in the VEPs, using a multifocal technique, have been suggested. The technique enables measurement of VEPs from the more peripheral retina with a high signal-to-noise ratio. Moreover, interocular comparison of the MVEPs enables...
This method is sensitive and useful for detecting local optic nerve dysfunction in unilateral ophthalmic disorders. However, there are some problems with this technique. The local MVEP responses decrease with retinal eccentricity, as was shown by the results of the present study (Figs. 1, 2, 3). The coefficient of variation of the RMS amplitude also increases with eccentricity (Figs. 3A, 3B). Thus, the signal-to-noise ratio of the local MVEP varies with eccentricity. In the present study, we used a retinally scaled-stimulus of 37 hexagons rather than a cortically scaled stimulus. Although the stimulus conditions used are not optimal for recording peripheral responses, we managed to achieve a reasonable signal response by averaging over areas. It may be possible to further improve these signals in the periphery by optimizing the stimulus and recording conditions. RMS measure can easily be affected by noise, particularly in noisy traces with low signals. To overcome this problem, local MVEP responses were grouped and averaged to increase the signal-to-noise ratio, significant responses were differentiated from noise using the formula:

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\text{RMS}_{C} = \frac{\text{RMS}_{32} - \text{RMS}_{8}}{\text{RMS}_{0-49}}
\]

where \( C \) is 8% or 32%, and a contrast (supra-) threshold was determined as the point at which the extrapolating regression line intersected the line of mean noise level calculated from \( \text{RMS}_{0-49}(32) \) and \( \text{RMS}_{0-49}(8) \) for each location.

Interocular comparison could be effective for detecting local optic nerve damage if the MVEPs from the affected area were compared with those from the corresponding normal area of the opposite eye. However, the precise degree of optic nerve dysfunction can be quantitatively determined by the method described.

**Figure 6.** Waveform changes in different stages of glaucoma. *Normal:* Normal subject of 63 years of age. MD = +1.13 D. P13: OH. MD = +1.6. P2: Early-stage glaucoma (POAG, MD = −3.81). P7: Moderately progressed glaucoma (NTG, MD = −11.6). *Gray wave:* MVEP at contrast of 32%; *black wave:* MVEP at contrast of 8%. ***CSF < (mean − 2SD); **CSF < (mean − 1.5 SD); *CSF < (mean − 1 SD).
nerve damage could not be determined if both corresponding areas were affected.

Estimation of the absolute amplitudes of MVEPs is not an optimal method for detecting a local visual field loss because of its dependence on electrode placement and anatomic variations in the visual cortex. The VEP amplitude and polarity vary with the location and orientation of the underlying cortical sources relative to the electrodes. There is also a large intersubject variability in anatomy. In contrast, coefficients of variance in the ratio of CSF were greatly reduced compared with the RMS amplitudes over all locations (Fig. 3C). Thus, the contrast threshold, which is a relative value determined from the regression line, is more applicable for evaluation of the visual field, because its variability can be reduced much more than that of the absolute value of the MVEP amplitude itself.

The absence of a substantial response does not necessarily imply an actual perimetric sensitivity loss. It is important to know whether the local MVEP is significant. If the signal-to-noise ratio of the response is not sufficiently high to determine the CSF, the data will be impossible to evaluate. In the group of 37 MVEPs without averaging, the rates of significant response obtained from the 28 normal subjects decreased as the retinal eccentricity increased, especially in the upper areas. However, substantial MVEP responses from normal subjects could be recorded from most field locations by averaging and grouping MVEPs into 20 groups. Thus, we can partially overcome these major problems by evaluating the CSF and by averaging the responses. Further study on recording conditions is needed to improve the signal-to-noise ratio of the responses in the periphery. Klistorner et al.5 and Klistorner and Graham7 reported that improved and larger signals could be derived when two additional electrodes were placed horizontally on either side of the inion. If these multiple-channel recordings were applied to the MVEP-CSF method, local optic nerve dysfunction would be more sensitively detected.

CSFs have generally been measured from VEP recordings by extrapolating the regression line (VEP RMS amplitude versus log pattern contrast) to zero amplitude. The technique was originally introduced by Campbell and Maffei.8 In a strict sense, sinusoidal grating should be used for CSF evaluation when using VEPs. However, the triangular pattern used in the present study was effective for deriving relatively clear MVEP amplitudes. This distribution is related to those of parallel pathways of parvocellular (P) and magnocellular layers (M). The M system is tuned to low spatial frequencies and high temporal frequencies. M neurons have high-contrast gain but are saturated at fairly low contrasts, whereas the P system has lower contrast gain but is saturated at much higher contrasts. Although the 75-Hz frame rate used in this study is thought to be suitable for an M system, 32% contrast may also stimulate P system because MVEP amplitudes tend to saturate at 32% contrast. Thus, if a contrast lower than 16% was used to derive MVEPs, a more linear function between the amplitude and contrast might be obtained. Baseler and Sutter10 suggested that contributions to the VEP from the M pathway preclude those from the P pathway and that the ratio of P-to-M contributions decreases with eccentricity. The stimulus used in this study was effective for deriving responses from these two systems. In the present study, there were discrepancies between the MVEP and visual field, as shown in Figure 5B. Hood et al.6 gave four possible explanations for such discrepancies in their study: reliability of the tests (false negative-positive or artifacts) varied from subject to subject, data from some field locations were less reliable than data from other locations, there was a difference in the sensitivities of MVEP and perimetry to pathologic changes, and there were differences in the testing stimulus—pattern in MVEP and spot in the visual field. These also seem to be reasonable explanations for the discrepancies in the present study. We think that the fourth explanation is the best explanation for the difference between the objective and subjective test results.

To overcome intersubject variability and to sensitively detect local optic nerve dysfunction, we compared, within an eye, two sets of MVEPs at different pattern contrasts. In conclusion, evaluation of contrast sensitivity using multifocal VEPs is a novel sensitive technique for detection of local optic nerve dysfunction that can be used clinically in patients with glaucoma.

References