Visual Field Defects and Multifocal Visual Evoked Potentials

Evidence of a Linear Relationship

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**Objective:** To determine the relationship between spatially localized multifocal visual evoked potentials (mfVEPs) and Humphrey visual fields (HVFs) in patients with unilateral field defects.

**Methods:** Humphrey visual fields and mfVEPs were obtained from 20 patients with unilateral field losses due to either ischemic optic neuropathy or glaucoma. Monocular mfVEPs were obtained for each eye. The amplitude of the mfVEP responses was calculated using root-mean-square and signal-noise ratio measures. Estimates of the HVF loss in the same regions of the field used for the mfVEP were obtained by interpolating the 24-2 HVF data.

**Results:** Monocular mfVEP amplitude decreased with HVF loss, although small mfVEP signals were not uniquely associated with poor fields. On average, the monocular mfVEP was indistinguishable from noise for field losses between –5 and –10 dB, and good monocular mfVEP amplitudes were never associated with extensive visual field loss. The interocular ratio of the mfVEP amplitudes correlated well with the difference between the HVF values of the 2 eyes, and this correlation improved with increased signal-noise ratio.

**Conclusions:** The monocular and interocular results were consistent with a linear relationship between the amplitude of the signal portion of the mfVEP response and linear HVF loss. One way to produce this relationship would be if both the signal in the mfVEP and linear HVF loss were linearly related to the percentage of local ganglion cells lost. The clinical limitations of the mfVEP technique can be understood by taking the signal-noise ratio, and the linear model proposed herein, into consideration.

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Although Humphrey automated perimetry is generally accepted as the gold standard for detecting glaucomatous damage, the technique is not without its problems. Some patients are unable to perform the task adequately. In addition, significant loss of ganglion cells can occur before the development of visual field loss.1-3 Because of these problems, more sensitive tests are needed.

One recently proposed candidate is the multifocal visual evoked potential (mfVEP) technique,4 which is based on Sutter’s general multifocal electroretinogram technique, described by Sutter5 and Sutter and Tran.6 With the mfVEP technique, many (typically 60) mfVEP responses, each associated with a local region of the visual field (or retina), are recorded simultaneously. Klistorner and colleagues7 found that the monocular mfVEP was reduced in patients with optic atrophy, including those with glaucoma. They pointed to a qualitative agreement between regions of decreased mfVEP amplitude and regions showing Humphrey visual field (HVF) defects. Because the local mfVEP responses can be very small in some healthy control subjects, interocular comparison techniques have been proposed as a better way to quantify and detect damage.8-12 As the mfVEP responses from monocular stimulation of the 2 eyes are essentially identical, an interocular comparison method has the potential to detect local damage as long as one eye is locally more affected than the other. Interocular comparisons of mfVEPs have been used to identify local damage in patients with glaucoma.8,10,11 Ischemic optic neuropathy (ION),8,10,11 optic neuritis,12,13

Using their interocular technique, Graham et al10 concluded that it may be possible to detect glaucomatous changes before HVF losses occur. A similar claim has recently been made for a test based strictly on monocular mfVEPs.15 In our ex-
experience, the mfVEP can sometimes detect damage in an apparently normal HVF.16,17 However, the HVF can also detect damage when the mfVEP is within the normal range.16,17 To determine the conditions under which one or the other test may be more sensitive to glaucomatous damage requires a better understanding of the relationship between the amplitude of the mfVEP and the depth of the HVF defect. To examine this relationship, we studied 20 patients with unilateral field loss. To see whether different mechanisms of ganglion cell damage would lead to similar results, we included patients with ION as well as patients with glaucoma.

METHODS

SUBJECTS

We tested 20 patients, 10 with ION and 10 with glaucoma, with unilateral damage. Nine of the patients with ION and 8 of the patients with glaucoma were selected from a larger group of patients who were tested with the mfVEP during the past 3 years. The selection criteria were independent of their mfVEP results and included a better eye with a normal HVF and a more affected eye with a visual acuity of 20/50 or better. Three additional patients (1 with ION and 2 with glaucoma) were recruited on the basis of the same field and acuity criteria. The Table contains the patients’ ages and visual acuity and the mean deviation of their HVFs. The visual acuity in 19 of the better eyes and in 15 of the more affected eyes was 20/20. The visual acuity in 1 of the better eyes was 20/25 and in 5 of the more affected eyes was less than 20/20 (range, 20/50 to 20/20−). All patients had “reliable” fields in both eyes, as determined by the HVF statistics. For the better eye, 19 of 20 patients showed no indication of HVF abnormalities; for 1 patient (patient 3 of those with glaucoma) the mean deviation, although small (−2.0 dB), was marginally significant (P<.05). The affected eyes had a range of field defects from −3.9 to −17.5 dB (in patients with ION) and from −1.5 to −13.4 dB (in patients with glaucoma). The patients served as their own controls. Procedures followed the tenets of the Declaration of Helsinki, and the protocol was approved by the committee of the Institutional Board of Research Associates of Columbia University, New York, NY.

mfVEP PROCEDURES

Display

The display was a 60-sector dartboard, with each sector containing 16 checks: 8 white (200 candela [cd]/m²) and 8 black (<1 cd/m²). The display is a standard option produced by the VERIS software (Dart Board 60 With Pattern; Electro-Diagnostic Imaging, Inc, San Mateo, Calif). The entire display had a diameter of 44.5°. The sectors were scaled; the central 12 sectors fell within 2.6° of the foveal center (Figure 1A). The stimulus array was produced with a black-and-white monitor that was driven at a frame rate of 75 Hz. The 16-element checkerboard of each sector had a probability of 0.5 for reversing on any pair of frame changes, and the pattern of reversals for each sector followed a pseudorandom (m-) sequence. (For a more detailed description of the general multifocal technique, see Sutter,5 Sutter and Tran,6 and Hood10o; of the mfVEP technique, see Baseler et al,4 Klistorner et al,7 Hood et al,8 and Hood and Zhang.12)

Recording

During the presentation of the display, 3 channels of signals were obtained by means of gold cup electrodes. The electrodes for the primary channel (channel 1) were placed 4 cm above the inion (active), at the inion (reference), and on the forehead (ground). For the other 2 channels, the same ground

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<th>Visual Field, MD (dB)</th>
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∗P<.01.
†P<.05.
and reference were used, and the active electrode was placed 1 cm up and 4 cm lateral to the inion on either side. By configuring the electrodes with a common reference, the 3 recording channels allowed for 3 additional “derived” channels representing the 3 pairwise combinations of the 3 active electrodes. (See Hood et al19 for details and a discussion of the choice of electrode positions, and Klistorner and Graham11 for the benefits of laterally placed electrodes.)

For all 3 channels, the continuous visual evoked potential (VEP) (electroencephalography) record was amplified, with the low- and high-frequency cutoffs set at 3 and 100 Hz, respectively (half amplitude; Grass preamplifier P511J; Grass Instruments, Quincy, Mass) and was sampled at 1200 Hz (every 0.83 milliseconds). The m-sequence had \([12^{11}-1]\) elements and required about 7 minutes for a single record. In a single session, two 7-minute recordings were obtained for monocular stimulation of each eye, using an A-B-B-A design. The records illustrated in the figures are the average of 2 of these recordings. To improve the subject’s ability to maintain fixation, the recording was divided into overlapping segments, each lasting about 27 seconds. The responses were extracted using VERIS 4.x software (Electro-Diagnostic Imaging, Inc). (Technically, these are second-order components.4) All other analyses were performed with programs written in MATLAB (The MathWorks, Inc, Natick, Mass). The signals were low-pass filtered with a sharp cutoff at 35 Hz and a fast Fourier transform technique.

**QUANTITATIVE MEASURES**

Figure 1B illustrates records from monocular stimulation of the left (red) and right (blue) eyes of patient 8 with glaucoma. RMS indicates root mean square. C, Mean record of 14 healthy control subjects showing the “signal window” and “noise-only window” that were used for the signal-noise ratio (SNR) analysis. D, Sample records from patient 8 with glaucoma (B), illustrating different SNR values. The calibration bars indicate 100 V (y-axis) and 100 ms (x-axis). E, Schematic showing the spatial relationship between the sectors of the multifocal VEP display (A) and the locations (dots) of the Humphrey visual field test spots.
To measure the magnitude (hereafter called amplitude) of these responses, the root mean square (RMS) was calculated across the interval from 45 to 150 milliseconds. Root mean square is commonly used because it requires only the specification of a time interval rather than the identification of a particular aspect of the response waveform. In addition to measuring the RMS of each of the 60 responses for each eye, an SNR measure was obtained as previously described. Briefly, to obtain the SNR, a signal window (45-150 milliseconds) and a “noise-only” window (325-430 milliseconds) are specified. Figure 1C shows the average responses from a group of 14 healthy controls to illustrate that the signal has terminated before the noise-only window begins. The SNR of a given response is obtained by dividing the RMS of the signal window by the average of the 60 RMS values of the noise-only window.

The SNR has the advantage of normalizing the responses from patients with different levels of noise. Figure 1D shows sample records from Figure 1C, with SNRs ranging from less than 1 to more than 9. (A response without any signal present would have, on average, an SNR equal to 1.0.) The records are all oriented in polarity so that if a response were present, it should have a prominent negative component followed by a prominent positive component. There is little or no response present for the record with the SNR around 1.0, and the signal becomes more salient as the SNR increases.

Interocular Comparisons

To compare the mfVEP responses from the 2 eyes, the RMS of the right eye is divided by the RMS of the left, and the logarithm (log) of the ratio obtained is our measure. In particular, the log mfVEP ratio equals $10 \times \log_{10}(RMS_{OD}/RMS_{OS})$. The log is used for 2 reasons: First, it provides a scale that is symmetrical around zero. That is, if the response from the right eye is double that of the left, then the value is 0.3 log unit (3 dB), and if the left is double that of the right, the value is –0.3 log unit (–3 dB). Second, these values are compared with interpolated visual field values in decibels, which is a log scale. To facilitate these comparisons, our log mfVEP ratio value is multiplied by 10 to convert it to decibels (1 dB=0.1 log unit), the unit used in the HVF. The inset in Figure 1B shows 2 examples where the log mfVEP ratios were –8.9 and –3.6 dB.

Multichannel Recording and the Best Channel

The data presented herein are for the “best of the 6 channels.” The best of the 6 channels is the channel at each location that produces the largest SNR of the 12 responses (2 eyes × 6 channels). For both the monocular and interocular analyses, the best channel is defined on the basis of the recording from both eyes at each location, and then the pair of responses from this channel is used for subsequent analysis.

HVF PROCEDURES

Humphrey visual fields were obtained with the 24-2 program as part of the patient’s routine examination. The Swedish Interactive Threshold Algorithm standard program was used for 17 patients and the full threshold for 3 patients. The mean deviation values for the HVFs are given in the Table.

Care must be exercised when comparing HVFs with mfVEPs, because the displays for the 2 techniques, and the ways in which the fields are sampled, are very different. The spatial relationship of the test spot locations of the 24-2 HVF to the multifocal stimulus is shown in Figure 1E. Since the mfVEP display is scaled, the 60 regions are unequally sampled by the 24-2 HVF test locations. In some cases (eg, in the outer ring), 3 HVF test locations fall within an mfVEP sector, while in other cases (in the first annulus), none of the test locations fall within a sector. This makes a comparison of the HVF with the mfVEP difficult. Furthermore, there is no agreed-upon method for combining HVF values (in decibels) from different field locations. A common procedure involves averaging the decibel values. This is theoretically indefensible, at least when the objective is to compare HVF values with mfVEP responses.

To overcome these problems, we have proposed the use of the interpolated field (Figure 2). The upper row of Figure 2A contains the total deviation probability plots from the 24-2 HVFs of the patient whose mfVEPs appear in Figure 1B. The lower row of Figure 2A contains the total deviation numbers associated with these probability plots. Recall that –3 means that, at that point, the patient is –3 dB (or half) as sensitive as a group of age-matched controls who are part of the 24-2 HVF test. Figure 2B shows the interpolated fields. Each sector corresponds to 1 sector of the mfVEP display (Figure 1A and E). For ease of display, these sectors are shown as being of equal size. Here, a –3 indicates that the value interpolated from the 24-2 HVF for this region is –3 dB. To obtain a monocular interpolated field, the antilog of the total deviation value was obtained for each HVF location. These values were interpolated into a high-resolution surface and averaged within the

Figure 2. Illustration of the interpolated fields. A, Total deviation values and probability plots from the 24-2 Humphrey visual field (HVF) of patient B with glaucoma. B, Monocular interpolated field values shown for each of the 60 sectors of the multifocal visual evoked potential display (Figure 1A). The shading indicates that the interpolated HVF values exceeded the mean for a group of 100 healthy control subjects at that point by greater than 2 (light gray) or 3 (dark gray) SDs. C, Interocular interpolated field obtained by subtracting the values in B.
region of each sector of the mfVEP display. The interpolated decibel value for a given sector is the log of the average value. To obtain an interpolated field for the interocular comparison, the difference between the monocular interpolated fields is obtained, as shown in Figure 2C. In this case, −3 means that the left eye is 3 dB less sensitive than the right eye, and a 3 means the reverse. Thus, if the right eye is twice as sensitive as the left, this value is 3 dB, while if the left eye is twice as sensitive as the right, this value is −3 dB. The shading in Figure 2B and C indicates that the interpolated HVF values exceeded the mean for a group of healthy controls by greater than 2 or 3 SDs.

**RESULTS**

**Figure 3** A shows the SNR of the mfVEP responses from the midline channel (inion +4, referenced to inion) as a function of the field loss estimated from the interpolated field. The responses from the central 12 sectors have been omitted, as they are poorly sampled by the 24-2 HVF. (Only 1 point exists for all 12 sectors, and 11 of these sectors do not contain an HVF test point [red circle in Figure 1E].) The results for the more affected eye, as well as for the eye with the better visual field, are shown for the patients with ION and glaucoma. Although it is difficult to discern all the points in this figure, the general trends are clear. Nearly all the points for the better eye fall to the right of the vertical dashed line, which marks a 5-dB loss. In fact, only 2 of the 960 points from the better eyes had HVF values less than −5 dB. For the more affected eye, there is a range of field losses extending to almost 35 dB. As the field defect becomes more profound, the SNR values tend to become smaller and approach the line for an SNR equal to 1.0 (the solid horizontal line). (If no signal were present, the SNR would have an average value of 1.0.) Once the interpolated field value has reached −15 dB or more, the points tend to cluster around the dashed horizontal line in Figure 3A and fall below the dotted line. The dotted line denotes an SNR of 2.0, which is the SNR for records that have RMS amplitudes that are twice the noise level. Thus, for the regions of loss greater than −15 dB or so, the signal, if present, is very small, much smaller than the noise level.

The same data are shown in a summary form in Figure 3B. Notice that the scale on both the axes is different from that in Figure 3A. The y-axis extends only to an SNR of 5 and the x-axis only to −25 dB, to allow a clearer picture of the data. For this analysis, the data for all patients were divided into 8 bins, each with an equal number of points. The points included in the first bin were the eighth with the largest HVF loss, those in the second bin were the eighth with the next largest HVF loss, and so on. The symbols are the median of the SNR for the points in each bin plotted against the mean HVF loss for that bin. (The median SNR is plotted, as the SNR distribution is not normal.) The smooth curve is a theoretical prediction and will be discussed herein. The error bars indicate the 5% range. That is, 5% of the points fall below this range. (The 95% bars are omitted for clarity, as they extend off the graph for the lower values of HVF loss.)

The overall trends in Figure 3A are easier to see in Figure 3B. The median SNR value decreases monotonically with HVF loss for both the affected and the better eye. By the time the field has lost 10 dB, the median SNR is near the value (1.0) expected of a response without a signal. Although responses associated with region of reduced field sensitivity are small, many of the small responses are also associated with regions with little or no field loss. In particular, all the points in Figure 3A below the dotted horizontal line (SNR, 2.0) and to the right of the vertical dashed line (HVF loss of 5 dB) have very small amplitudes but fields within 5 dB of normal. Many of the points from both the affected and better eyes fall in this region. This can be seen in Figure 3B where the 5% limit is well below 2, and in some cases close to 1, for the points from the better eye. Thus, a small response does not necessarily mean that the field will be poor or that the eye is affected. Small responses, defined
as either signals with small SNR values (Figure 3A and B) or small RMS amplitude, also occur in healthy controls.8,19,21

Because the responses from a normal eye can be small in some locations, Klister and Graham11 suggested using additional electrodes that are placed lateral to the midline. As described in the “Methods” section, we recorded with additional electrodes and obtained the equivalent of 6 channels of responses. Figure 3C shows the data, illustrated as in Figure 3B, for the SNR of the best response at each location as described in the “Methods” section. (Multichannel recording was obtained for only 17 of the 20 patients, so the results for 3 of the patients will be the same as for the midline channel.) There are fewer points with small SNR values for the “best response,” as indicated by the 5% limits for the better eye. However, these limits still extend well below an SNR of 2.0. As expected from previous work,19 multichannel recording improves the SNR, but a substantial number of points still have a very small mfVEP response. This does not mean, however, that the monocular data are not useful for clinical purposes. It does mean that they must be interpreted with care17 (see “Comment” section).

Although it is hard to discern in Figure 3A, the trends for the patients with ION and glaucoma were similar. The small symbols in Figure 3C show the median SNR separately for the patients with ION and those with glaucoma. The SNR of the better eye is slightly greater for the patients with glaucoma, and the HVF for the affected eye of the patients with ION is, on average, slightly worse (Table). The general pattern of results in Figure 3C were very similar for the 2 groups.

**INTEROCULAR COMPARISONS**

Since the mfVEP response from normal regions of the field can be very small, we developed a method for comparing the responses from the 2 eyes.8,9,12 This method takes the ratio of the amplitude of the mfVEP from the 2 eyes. Figure 4 contains plots of the log of the ratio of the mfVEP (in decibels) vs the ratio of the HVF (also a log scale in decibels). As described in the “Methods” section, these are comparable scales. For example, if the mfVEP response from the right eye is 2 times larger than that of the left, this produces a log ratio of 3 dB. Likewise, if the sensitivity of the right eye is twice that of the left, the ratio of HVF sensitivities is 3 dB. As indicated in Figure 4A, if smaller mfVEP responses are associated with poorer fields, the points will fall in the upper right or lower left quadrants, depending on which eye is more affected. Figure 4B shows the results for all 20 patients for the midline channel. The responses from the central 12 sectors have been omitted for reasons detailed already. The correlation, r, is 0.68, and the points tend to fall into the quadrants, as expected from Figure 4A. However, there is considerable variability. Figure 4C shows a similar plot for the best channel. (For the 3 patients without multichannel recording, the midline channel was used.) The correlation is nearly the same (0.72), but again, considerable scatter can be seen.

There are various reasons for the variability seen in Figure 4B and C.12,10,17 One important reason will be considered here. The analysis in Figure 4B and C includes all points, even if the mfVEP response is very small in both eyes. If the mfVEP response in the better eye is very small, the ratio of the RMS amplitude of the 2 eyes will be meaningless. In the extreme, if the response from the better eye contains no signal and only noise, this response will not differ from the response of the affected eye, no matter how extreme the defect or damage. If the locations with poor responses are excluded, a clearer picture of the relationship between the mfVEP and the HVF loss emerges. Requiring one of the eyes to have an SNR better than either 3, 6, or 9 produces the results shown in Figure 4D-F, respectively. (Figure 1D shows sample responses with approximately these SNRs.) The correlation coefficients are now 0.79, 0.84, and 0.85 for Figure 4D-F, respectively. More important, the relationship between the mfVEP and HVF ratios is now clearer. The points tend to fall near the line of slope 1.0 (dotted diagonal line) for relatively small field losses and tend to asymptote at a level that depends on the SNR criterion. By considering a simple model, one can easily understand the pattern of results in Figure 4D-F.

**A SIMPLE MODEL FOR DESCRIBING THE RELATIONSHIP BETWEEN mfVEP AND HVF RESPONSES**

Assume that the mfVEP response is the sum of 2 components: signal and noise. Assume further that the amplitude of the signal, but not the noise, component is linearly related to the change in HVF sensitivity. (A formal presentation of this model can be found in an appendix that is available from the authors on request.) In particular, assume that if the HVF of one eye is half as sensitive as that of the other (−3 dB), the signal in the mfVEP response is half as large (−3 dB). If the mfVEP response contained only signal and no noise, the model would predict that the points in Figure 4 should fall along a line of slope 1.0 (diagonal line in Figure 4). The points clearly deviate from this line. One reason is obvious. The HVF can measure decreases in sensitivity as large as −30 dB or a decrease of 1/1000. The relative sizes of the signal and the noise level of the recording, on the other hand, will limit the extent to which the mfVEP amplitude can be reduced by disease. Once the signal in the record is reduced to well below that of the noise level, the signal in the record can no longer be measured. The simple linear model assumes that the signal in the mfVEP is proportional to the change in the HVF sensitivity. Taking noise into consideration produces a family of predicted curves that will differ depending on the SNR of the response in the better eye. This family of curves is shown in Figure 5A for SNRs ranging from 1.1 (ie, the response is only one-tenth larger than the average noise level) to 18.0. The predicted curve deviates from the line of slope 1.0, and this deviation occurs at smaller field losses for smaller values of the SNR. For example, if the SNR of the response is 18.0, reducing the signal in the affected eye by a factor of 4 (−6 dB) reduces the mfVEP response by a factor of nearly 4 (−5.9 dB) as well. However, reducing the signal in the affected eye by a factor of 4 will reduce the response by a factor of only 3.3 (−5.2
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Figure 4. The log of the ratio of the multifocal visual evoked potential (mfVEP) amplitudes ($10 \times \log_{10}(RMS_{ld}/RMS_{ld})$) in decibels for the 2 eyes is shown as a function of the log ratio of the Humphrey visual field (HVF) sensitivities (right eye minus left eye, in decibels). A, If the left eye is more affected, the data should fall in the upper right quadrant. If the right eye is more affected, the data should fall in the lower left quadrant. B, The data for the midline channel, shown as red if the left eye is more affected and blue if the right eye is more affected. The dotted diagonal has a slope of 1.0 and is the locus for points of equal decibel losses in mfVEP and HVF. C, As in B, for the channel with the best SNR at each field location. The solid curves are the predictions of the simple model described in “A Simple Model for Describing the Relationship Between mfVEP and HVF Responses” subsection of the “Results” section for the different SNRs of the better eye. D, As in C, but for only those data points with SNRs of 3.0 or more. E, As in C, but for only those data points with SNRs of 6.0 or more. F. As in C, but for only those data points with SNRs of 9.0 or more.

If the SNR of the response is 6.0, by a factor of only 2.4 (−4.1 dB) if the SNR is 3.0, and by a factor of only 1.09 (−0.4 dB) if the SNR is 1.1. The solid curves in Figure 4 are the predicted relationships for an SNR of 1.1 (Figure 4C), 3.0 (Figure 4D), 6.0 (Figure 4E), or 9.0 (Figure 4F). The dashed curve is the expected result if the SNR were very high; in this case, an SNR of 18.0, nearly the highest observed in our data. According to this simplified model, the points should tend to fall around a family of curves bounded by the dashed and solid curves. The agreement is reasonably good.

The simple model predicts that the loss in the amplitude of the signal in the monocular mfVEP should be linear with field loss. Because the field loss does not affect...
the noise, the predicted amplitude of the mfVEP response will be a nonlinear function of HVF loss. The family of curves in Figure 5B, plotted as in Figure 3, shows the predictions for a range of starting SNR values. On the semilog plot of Figure 5B, the model predicts an exponential decrease in SNR with increased HVF loss until an asymptotic SNR of 1.0 is reached. The scatter in the data of Figure 3A is expected on the basis of these predictions, as the responses from a healthy eye will have a range of SNRs from close to 1.0 to about 18.0. Thus, these points should scatter around and between the curves for 1.0 (horizontal line) and 18.0 (bold solid curve in Figure 3A). They basically do. (The 2 plus signs well above the line in Figure 3A represent points from a single patient.) The solid curves in Figure 3B and C show the predictions for the model. To obtain these predictions of the model, only the initial point for an HVF loss of zero needs to be specified. This value was taken from the less affected eye for HVFs near zero. The model describes the data quite well. Even the data for the better eye follow the predicted curve. There is, however, a suggestion that the mfVEP may be slightly smaller than what the model predicts for field losses of less than 1.0 dB. That is, the solid symbol plotted at around a 0-dB loss falls below the curve for both the midline and best channels.

**COMMENT**

Our objective was not to compare the relative merits of the HVF and mfVEP techniques in the detection of ganglion cell damage, but rather to determine the relationship between the mfVEP amplitude and HVF loss. The agreement between the simple model and the data suggests that the decrease in the signal portion of the mfVEP response is, to a first approximation, proportional (or linearly related) to HVF loss.

Although the agreement between the simple model and the data in Figures 3B and C and 4C-F is far from perfect, it is surprisingly good considering the following: First, each of these measurements exhibits variability. Recall that the SD of the HVF is on the order of 2.5 dB or more. In addition, the sources of variability associated with each are different. Second, 2 very different measurements are being compared: the amplitude of a gross electrical response (VEP) and a behaviorally determined threshold. Third, our comparisons involved deriving an interpolated field, which is an estimate of the visual field sensitivity in the sector producing the mfVEP. Fourth, we know that defects can be seen in the HVF that are not necessarily picked up by the mfVEP, and the reverse also can be found. Despite these caveats, the simple model does a reasonably good job of describing the nature of the relationship between the mfVEP and HVF changes.

The simple model assumes that the decrease in the mfVEP signal is proportional to the HVF loss. To the extent that the model describes the data, it implies that the same relationship exists between mfVEP amplitude reduction and ganglion cell loss, on the one hand, and visual sensitivity loss and ganglion cell loss, on the other. One simple interpretation is that each is proportional to ganglion cell loss. For example, a local loss of 50% of the ganglion cells leads to a halving of field sensitivity (a 3-dB loss) and a halving of the mfVEP response (a 3-dB decrease).

Are HVF and mfVEP losses both proportional to local ganglion cell loss? It is not hard to imagine how the local loss of ganglion cells may result in a proportional loss in the amplitude of the mfVEP. It is more difficult to explain a linear relationship between local HVF sensitivity loss and local ganglion cell loss, especially in the case of modest field losses (ie, less than 10 dB). One theoretical study argued that this relationship should not be strictly linear. However, the deviations from a linear relationship were relatively minor. In fact, a more sophisticated attempt at modeling found that this relationship was approximately linear. The only direct measures of the relationship between the local loss in field sensitivity and the local loss of human ganglion cells can be found in postmortem ganglion cell counts by Quigley and colleagues and Kerrigan-Baumrind et al. Although these studies are often taken as evidence that the relationship between local field loss and local ganglion cell loss is not simple, their results are not inconsistent with a simple linear relationship. In particular, Quigley and colleagues conclude that at least 25% to 35% of the ganglion cells are lost before defects are picked up on the 24-2 HVF test. If one assumes a linear relationship with ganglion cell loss and an SD of about 2.5 dB for the HVF, it would take, on average, a local loss of nearly 70% of the ganglion cells for a single point on the HVF to reach statistical significance (P<.05). Given the uncertainties involved in the postmortem ganglion cell counts, the es-
timate, 70%, which is based on a linear relationship, is in the same ballpark as the conclusion by Quigley and colleagues1-3 that “at least 25% to 35% of the ganglion cells are lost before defects are detected.”

Local ganglion cell counts and HVF measures are available from monkeys with experimentally induced glaucoma,24 but these do not support a linear relationship between HVF loss and ganglion cell loss. In particular, field losses of about 6 dB are noted before ganglion cell losses are detected. However, this finding appears to contradict the finding of significant ganglion cell loss before HVF loss in the human postmortem studies.1-3 Harwerth et al24 suggest that either the high-pressure model for experimentally induced glaucoma is not exactly mimicking human glaucomatous damage or the ganglion cells are damaged but have yet to die in their monkeys.23 Recent electrophysiological and anatomical evidence in the monkey support the latter conjecture.25

CLINICAL IMPLICATIONS

Monocular mVEPs

Since the response from normal regions of either patients or controls can be small (Figure 3), the efficacy of a monocular test has been questioned18,17 and interocular comparison methods have been developed.8,10 However, Goldberg et al13 recently obtained good specificity with a monocular test by defining an abnormal field as one with a cluster of 3 points at P<.05, with at least 1 at P<.02. Although the statistics behind this approach are not simple, we have confirmed their general finding.17 In any case, the results in the present study supply a theoretical basis for understanding the limits of a monocular test. Relatively modest field defects are associated with mVEP responses that are indistinguishable from noise (Figure 3). On average, the SNR in the more affected eye of the patients was reduced to less than 49% of its original size by field losses of 5 dB and to the level of noise by the time the HVF had lost 10 dB. Of course, the responses from regions that start with relatively small SNR values will be reduced to those of the noise level by even smaller HVF losses. Thus, unless the SNR of a region is very large before damage occurs, relatively modest field losses will reduce the mVEP close to the level of noise. Although the responses from healthy controls can be quite small, the 95% confidence limits, in general, exceed the noise level.17 This observation, combined with a cluster criterion, explains the apparent success of the monocular test. It also suggests its limitations.

If the SNR of a region is very large (eg, 18.0 [Figure 5B1]), the monocular test will not detect a defect until, on average, the HVF is down by more than 10 dB. Fortunately, when the SNR is large, the interocular test is very sensitive.17 A second limitation concerns the ability to detect progression. The HVF can detect a local change that extends to −30 dB. On the other hand, the mVEP, on average, cannot follow a local defect of more than approximately −6 dB.

Although a small mVEP response does not mean that the visual field will show a corresponding defect, a large response means that the visual field is relatively good. If it is not good, the field should be questioned. The clinical implication is that the monocular mVEP can be used in situations where the clinician suspects that a defect is not “real.” For example, an SNR of 2.0 falls well outside the 95% confidence limits for a monocular defect of −15 dB or more. Thus, a response with an SNR of greater than 2.0 suggests that the region should not have a decibel loss of greater than −15 dB. We have seen a number of patients with poor or questionable visual fields who have had large responses (SNR, much greater than 2.0) in regions of their fields with losses exceeding 15 dB. In these cases, the monocular mVEP indicates that the region is probably no worse than −x dB from the normal value, where x depends on the SNR of the response.

Interocular mVEP

With the use of an interocular comparison technique, the mVEP can detect localized ganglion cell damage that is sometimes missed by the HVF.10,16,17 What is less clear is how the mVEP will compare with the HVF in following progression and/or detecting early damage. Our results suggest that the mVEP, even with interocular comparisons, will not be particularly useful for following the progression of the depth of a defect over time. If a local region were to decrease in field sensitivity from −10 to −20 dB, it is unlikely that a change in the local mVEP would be detected, unless the deepening of the defect were also accompanied by a widening (ie, a wider area of ganglion cells involved).

Implications are raised for the debate as to whether the HVF or the mVEP is more sensitive. The conditions under which the mVEP will be better than the HVF in detecting the presence or the progression of glaucomatous damage have yet to be determined. In the “Introduction,” we noted that, by using an interocular comparison, Graham et al10 concluded that it may be possible to detect glaucomatous changes before HVF losses occur, while our group16,17 has found, with essentially identical techniques to theirs, that the reverse also can be true. That is, the HVF can detect damage that has been missed by the mVEP. The results of the present study suggest that the SNR of the records must be taken into consideration in any debate as to whether the HVF or the mVEP is more sensitive. On the one hand, the interocular mVEP technique will be a poor detector of damage in regions where the better eye has a small SNR. On the other, the mVEP will do well compared with the HVF when the SNR is large. The larger the SNR of the better eye, the more likely it is that the mVEP will do better than the HVF in detecting damage.

In summary, the mVEP signal appears proportional to the HVF loss. Consideration of this linear relationship, in combination with an SNR analysis, should improve the clinical usefulness of the mVEP technique.

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