Clinical Application of Objective Perimetry Using Multifocal Visual Evoked Potentials in Glaucoma Practice

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Objectives: To evaluate the role of objective perimetry using multifocal visual evoked potentials (mVEPs) in glaucoma practice, and to assess its utility in patients with inconclusive standard automated perimetry findings.

Method: A retrospective case series of 436 consecutive subjects referred for glaucoma investigation who underwent testing with the AccuMap V1.3 mVEP system (ObjectiVision Pty, Ltd, Sydney, New South Wales, Australia) within a defined 12-month period. Sensitivity was determined by comparing this testing with that of standard automated perimetry and that used in a subgroup in whom masked stereoscopic optic disc photographs were used as an alternative reference standard. Overall clinical diagnostic outcomes were assessed.

Results: The mVEP changes were correlated with the stage of disease and Humphrey mean deviation ($r = 0.78$). The overall sensitivity for detecting glaucoma with established subjective field loss was 97.5% (early glaucoma, 93.0%), whereas 92.2% of low-risk suspects had normal mVEPs. When masked disc assessment alone was used for diagnosis of abnormality, sensitivity of mVEP (80.6%) and Humphrey visual field results (81.9%) were similar, but mVEP specificity was better (89.2% vs 79.5%). The mVEP was particularly useful in assessing excessive subjective field loss (45 eyes) by showing a much closer correlation with the clinical picture.

Conclusions: Multifocal VEP is an effective method for detecting visual field loss in glaucoma. It provides a valuable aid to the clinician in categorizing patients with unreliable, variable, unconfirmed, or excessive subjective field loss.

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In the assessment of glaucoma, it is essential to evaluate visual function. The gold standard for this is subjective automated static perimetry. However, many patients have difficulty providing reliable perimetric results, which complicates the clinician's task. In a recent study of the performance of the Swedish Interactive Threshold Algorithm (SITA) vs full-threshold visual field testing, the specificity of SITA was only 38.1% at first test and 73.7% after 2 tests. In an attempt to provide an objective and clinically feasible test for glaucoma visual field assessment, the multifocal visual evoked potential (mVEP) has recently been developed. With the use of multiple recording channels, signals from all areas of the visual field can be detected to provide an objective map of visual function. Signal amplitudes are compared with values from healthy populations, and probability plots can be created. Using this technique, sensitivity has been reported to be greater than 90%, depending on the criteria used to define abnormality. Hood et al have demonstrated that mVEP amplitude correlates with the subjective visual field threshold. However, in contrast to the amplitude, mVEP latency did not demonstrate good correlation with visual field loss, despite the promise it held in earlier works based on full-field stimulation.

The multifocal method can also be useful in other optic neuropathies such as optic neuritis or ischemic optic neuropathy. Studies have described mVEPs in subjects with cortical lesions and in assessment of the visual field in children. Several reports have shown the ability of the mVEP to confirm subjective scotomas in established glaucoma, but there have not been any reports of its utility in the clinical setting, where a wide variety of subjects are encountered. In addition, all mVEP studies to date have applied selection criteria (eg, visual acuity limits, reproducible field defect, unilateral damage, and other ocular pathology) for their selection of subjects. In particular, they
usually required reliable confirmed subjective visual fields, which masks some of the limitations of standard perimetry encountered in normal clinical practice.

This report examines the results of mVEP testing in a busy glaucoma referral practice during a 12-month period to further investigate its sensitivity in glaucoma detection and to evaluate its role in the outcomes of patient assessment. All patients undergoing testing during the study period have been included, regardless of their subjective field performance or ocular status. The overall role in investigation of glaucoma, particularly in cases of poor, unreliable, or suspicious subjective test results, can then be reviewed.

A retrospective review was performed of all subjects referred for glaucoma assessment within a defined 12-month period who underwent testing with the AccuMap (ObjectiVision Pty Ltd, Sydney, New South Wales, Australia).

METHODS

A retrospective review was performed of all subjects referred for glaucoma assessment within a defined 12-month period who underwent testing with the AccuMap (ObjectiVision Pty Ltd, Sydney, New South Wales, Australia).

SUBJECTS

There were 436 subjects referred for glaucoma investigation who also underwent mVEP testing. None of these results were used in previous publications. Of the 436 patients, 83 were at low risk of glaucoma (low-risk suspects), 107 at high risk of glaucoma in at least 1 eye (high-risk suspects), and 221 with glaucoma in at least 1 eye (glaucoma patients) (2 glaucoma patients were unocular). An additional 25 patients were referred for investigation with excessive field loss or uninterpretable fields in at least 1 eye. All subjects had undergone Humphrey 24-2 (SITA or full-threshold) field testing at least once. Visual field criteria for inclusion in the different subgroups are described in the analysis section below.

The initial classification was based on the diagnosis made by the clinician. Low-risk suspects were those with ocular hypertension (intraocular pressure, >21 mm Hg) and/or a family history of glaucoma but normal optic discs and visual fields. Corneal thickness measurements were only available in a limited number of subjects; therefore, this was not used as a discriminator.

High-risk suspects had a suspicious or abnormal optic disc appearance in at least 1 eye (eg, large cup [ie, cup-disc (C/D) ratio >0.6], nerve fiber layer thinning, notch, or hemorrhage) and/or asymmetrical discs with a C/D ratio difference of more than 0.2, with or without raised intraocular pressure and family history, and still with a normal visual field. This group therefore included some preperimetric glaucoma cases.

The patients with glaucoma had (at least in 1 eye) an abnormal optic disc appearance with characteristic glaucomatous cupping and corresponding visual field defect, with or without raised intraocular pressure and family history. Patients with glaucoma whose fellow eyes still had a normal visual field were identified and analyzed as a separate group. Informed consent was obtained from all subjects before mVEP testing, and the study followed the principles of the Declaration of Helsinki.

ANALYSIS

We approached the analysis in several ways. First, the clinician’s diagnosis was used to categorize eyes as low- or high-risk suspects or glaucomatous per our definitions described in the “Subjects” subsection. The clinician’s diagnosis was based on the full clinical picture at the time of referral, including optic disc appearance (by means of slitlamp stereoscopic disc assessment in all cases) and visual fields, but before recording mVEP. Because of the heterogeneity of the group of patients with glaucoma (eg, a patient can have glaucoma in one eye and suspicious findings in the other), the data were analyzed with each eye classified separately, and data for all eyes are included. Table 1 shows the breakdown of all eyes in the study according to the level of severity. Humphrey mean deviation (MD) values were recorded and used to subgroup glaucoma into early (MD, <7 dB), moderate (MD, 7-13 dB), and advanced (MD, ≥14 dB) stages. Although it is acknowledged that some early glaucomas with focal defects may have low MDs and high pattern standard deviation values, the opposite can be true of advanced cases. At present, mVEP amplitude is evaluated in a total deviation plot (analogous to the total deviation plot of the Humphrey visual field test); a corresponding pattern standard deviation–based score has yet to be developed.

For Humphrey visual fields, the glaucoma hemifield test (GHT) was used to classify fields as normal or abnormal. A confirmed field defect was a finding of a field outside normal limits on 2 consecutive occasions, with a field defect in the same location. These subjects were used for sensitivity assessment. Reliability of the field test and, in the case of repeat tests, any variability in location of scotomas or fluctuation in GHT ratings were noted. The mVEP records were analyzed separately with the investigator masked to the clinical data and subjective visual field results.

To investigate the relationship between stage of disease and mVEP results, mean values for the new modified AccuMap Severity Index (ASI) (a proprietary technique) for each subgroup were determined. A correlation between the Humphrey MD and ASI values was performed for all glaucoma patients.

Second, for the purpose of verifying the sensitivity of mVEP in glaucoma, a subgroup of the patients with glaucoma who had more than 1 reliable Humphrey field result available and had reproducible visual field loss (same location in field) were identified. There were 286 glaucomatous eyes that met these criteria, and their ASI results were reviewed to determine sensitivity of the AccuMap. Further analysis was performed based on the detection of a scotoma on the mVEP amplitude deviation plot or the asymmetry plot. A scotoma for the amplitude deviation plot was defined as a cluster of 3 points in 1 hemifield with P<.02 and at least 1 point with P<.01. For asymmetry, the cluster was 3 points with P<.01 or 2 points with P<.005. The 4 central superior rim points were excluded from the clusters.

Because no healthy subjects underwent testing in this study, a true specificity could not be determined. Therefore, as an indirect measure of specificity, the rate of abnormality in low-

#### Table 1. Glaucoma Subgroups*

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Eyes</th>
<th>Humphrey MD, dB</th>
<th>C/D Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk suspect</td>
<td>180</td>
<td>−0.44 ± 1.33</td>
<td>0.46 ± 0.13</td>
</tr>
<tr>
<td>High-risk suspect</td>
<td>205</td>
<td>−0.64 ± 1.46</td>
<td>0.70 ± 0.08</td>
</tr>
<tr>
<td>Fellow eye with glaucoma</td>
<td>81</td>
<td>−0.94 ± 1.37</td>
<td>0.62 ± 0.15</td>
</tr>
<tr>
<td>Early glaucoma</td>
<td>211</td>
<td>−5.11 ± 1.9</td>
<td>0.76 ± 0.12</td>
</tr>
<tr>
<td>Moderate glaucoma</td>
<td>79</td>
<td>−10.0 ± 2.2</td>
<td>0.80 ± 0.14</td>
</tr>
<tr>
<td>Advanced glaucoma</td>
<td>69</td>
<td>−20.5 ± 4.7</td>
<td>0.87 ± 0.11</td>
</tr>
</tbody>
</table>

Abbreviations: C/D, cup-disc; MD, mean deviation.

*Groups are described in the “Subjects” and “Analysis” subsections of the “Methods” section. Unless otherwise indicated, data are expressed as mean ± SD.
risk suspects (180 eyes) was determined for the ASI and presence of a scotoma (as defined for sensitivity, normal GHT results on all testing occasions qualified as normal). This provides an estimate of the lower limit of mVEP specificity because it is anticipated that very few of these subjects had true glaucoma at the time of testing.

In high-risk suspects and fellow eyes (with normal visual fields) of glaucoma patients, the rate of mVEP abnormality was determined to assess its potential use as an early marker of disease. A subgroup of eyes had variable Humphrey field results. Variable fields were defined as fields classified differently by GHT results on at least 3 consecutive occasions (eg, normal/abnormal/normal or abnormal/normal/abnormal) or, alternatively, fields that had a different quadrant location of abnormal points (upper vs lower, or nasal vs temporal) on at least the last 2 tests. The situation where the visual field gradually improved (eg, abnormal/borderline/normal), which could be due to a learning effect, was not considered variable but classified as a normal field, and the eye was classified according to disc appearance. Another group of patients had unconfirmed visual field loss, with a new scotoma not yet confirmed on repeat testing. This group was not included in the sensitivity estimates, but because this is a common problem encountered in the clinical environment, outcomes based on mVEP findings were determined. Confirmation would ultimately require repeat subjective and/or mVEP testing. Furthermore, we identified subjects with excessive visual field loss, as determined by the clinician, compared with their optic disc appearance. These subjects had undetectable or mild structural disc change with greater visual field loss than expected. The role of mVEPs in these 3 groups (variable fields, unconfirmed field changes, or excessive loss) was assessed separately.

Finally, the morphology of the optic disc was used as an independent reference of disease to obtain an estimate of sensitivity and specificity. All subjects who underwent stereoscopic disc photography within the last 12 months were identified. Photographs were graded in randomized masked fashion by 2 glaucoma specialists (S.L.G. and I.G.) as normal, suspect, or glaucoma. Photographs were graded independently (masked from each other), and when classification differed, photographs were then reviewed by both clinicians and consensus was reached. Visual field and mVEP results were then evaluated based on this classification. Although older photographs could have been used in glaucoma cases, because the changes are permanent once present, the same did not apply to suspect eyes with normal or borderline discs, which could have progressed over any longer period of time. Therefore, the photographs were restricted to the prior 12 months. The sample size available was also limited by the fact that many patients now have alternative forms of disc imaging performed (mainly scanning laser with the Heidelberg retinal tomograph [Heidelberg Engineering, Heidelberg, Germany]).

Statistical analysis was performed using Statistica 4.1 (StatSoft, Tulsa, Okla [1994]).

mVEP RECORDING

The method of mVEP recording is the same as previously reported in the report by Goldberg et al and used the AccuMap perimeter (ObjectiVision Pty Ltd). The only differences were that the AccuMap had a new 4-channel amplifier, and the filtering settings were tightened from those used in the previous study. In brief, the system uses a spread-spectrum technique with families of binary sequences to drive the visual stimulus. Two opposite checkerboard pattern conditions undergo pseudorandom binary exchange at each of 38 sites in the visual field. Each input (stimulation site) is modulated in time according to a different sequence. The technique permits computation of the resulting signal by cross-correlation of the response evoked by the sequence stimulation with the sequence itself. Short sequences of 4096 elements are used, which result in 55 seconds of continuous recording time (1 run). Further runs then use different sequences for the same stimulation site to reduce the potential for cross-contamination. Results can be viewed on screen after each run, then averaged online, and the recording is terminated when stable signals are achieved.

The visual stimulus was generated on a 53-cm high-resolution display (Hitachi Ltd, Tokyo, Japan) with a stimulation rate of 75 Hz. A display of 36 closely packed segments in a dartboard configuration was used, with 2 additional segments located in the nasal step region. The segments were cortically scaled with eccentricity to stimulate approximately equal areas of cortical (striate) surface to produce a signal of similar amplitude from each stimulated segment. Each segment contains a checkerboard pattern (16 checks) with the size of individual checks proportional to the size of the segment and therefore also dependent on eccentricity. The central area of 1° was not stimulated but used as a fixation marker. Numbers of similar shape (3, 6, 8, or 9) were displayed in random sequence, and the subject was asked to respond by pressing a button when a particular number appeared. This ensured good concentration throughout the recording, and the percentage of missed and incorrect responses was calculated automatically after each run (runs with >30% missed or incorrect responses were rejected), which rarely occurred. Luminance of the white check was 146 candela (cd)/m², and luminance of the black check was 1.1 cd/m². This produced a Michelson contrast of 99%. Background luminance of the screen was maintained at a mean level of 73.5 cd/m², and a dim room light was on.

Subjects were seated comfortably in a chair with the chin slightly elevated to relax neck muscles. They were asked to fixate on the small, randomly changing number at the center of the stimulus pattern. The distance to the screen was 30 cm, corresponding to a radius of the stimulus of 24° with an additional nasal step out to 33°. All subjects underwent optimal refraction for near distance, and the pupils were not dilated. All recordings were collected using monocular stimulation. Data were recorded using a 4-channel amplifier (ObjectiVision Pty Ltd), with the bandpass filter ranging from 1 to 30 Hz. The signal was amplified 100 000 times and then digitally filtered from 1 to 20 Hz. The data-sampling rate was 450 Hz. Usually 7 to 9 runs of 35 seconds each were recorded to provide a stable signal as indicated by the trace improvement software in the Opera V1.3 program (ObjectiVision Pty Ltd).

An ObjectiVision occipital cross-shaped electrode holder predetermined the 4 electrode positions. The cross had 4 electrode plugs into which the standard gold cup electrodes were clipped. The plugs were hollow to permit electrode gel (Dracard, London, England) to be injected into the cup once it was positioned. The scalp was cleansed with electrode gel (Nuprep; D.O. Weaver & Co, Aurora, Colo) at each site before finalizing the electrode position. Four channels were used as described previously to cover different underlying dipole orientations. The lower midline electrode was negative for the vertical and oblique channels, whereas the left horizontal electrode was negative for the horizontal channel. Both eyes underwent testing and evaluation so that asymmetry analysis could be performed.

Data were analyzed using Opera V1.3 software. Raw data for each run were cross-correlated with Kasami sequences to extract the mVEP signal for each segment of the visual field stimulated and then scaled according to underlying electroencephalographic activity to reduce intersubject variability. The procedure was repeated for each run, and the results were averaged for each channel independently. Maximal peak-to-trough amplitudes for each wave within the interval of 60 to 180 milliseconds were determined and compared among channels for every stimulated seg-

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ment of the visual field. The wave of maximal amplitude from each segment in the field was selected and a combined topographic map was created by the software.

The mVEP amplitudes for each individual zone in the combined trace array were compared with those found in the normal database, and probability of abnormality plots were constructed. The intereye asymmetry was also calculated for every segment of the tested visual field. A probability plot for asymmetry was constructed based on the normal database distribution of asymmetry between the 2 eyes.

Finally, a new, modified ASI (ASI version 2) was calculated by the Opera software for each subject. The ASI assigns scores to individual abnormal points and clusters of points with a weighting for location and whether they are present on the asymmetry plot. The ASI provides an overall index of whether the mVEP amplitude results are within normal limits (score, 0-11), borderline (score, 11-19), or outside the normal range (score, ≥20).

Unless otherwise indicated, data results are expressed as mean ± SD.

### RESULTS

#### CORRELATION WITH GLAUCOMA SEVERITY

The patients with glaucoma showed substantial changes in their mVEP results, dependent on the severity of the disease. Figure 1 shows the mean ASI values for all groups. There was a statistically significant difference between all groups except for the group of fellow eyes of patients with glaucoma, which was not statistically different from the low- and high-risk suspect groups (Table 2) (1-way analysis of variance and Tukey honest significant difference test). The fellow eye group might have been expected to show a higher rate, but it included a broad mix of disc appearances.

A strong correlation (linear regression coefficient, \( r = 0.78 \)) was demonstrated between ASI and Humphrey MD fields for all patients with glaucoma, as shown in Figure 2. This is similar to previously reported studies.

Because the ASI increased through all stages of the disease process, this suggests that it reflects the severity of disease. It also correlated with the severity of visual field loss as detected by the Humphrey MD global index.

#### SENSITIVITY AND SPECIFICITY

Two hundred eighty-six glaucomatous eyes had more than 1 reliable Humphrey field available and had reproducible visual field loss (same location in field). For these subjects, the sensitivity of the mVEP ASI in detection of visual field defects was calculated as 279 (97.6%) of the 286 eyes. When analyzed by disease severity, all eyes with advanced (69 eyes) and moderate (79 eyes) stages of glaucoma were identified (100% sensitivity), whereas in the early glaucoma group, the sensitivity was 131 (95.0%) of 138 eyes. Figure 3 shows examples of early, moderate, and advanced glaucoma, with Humphrey printouts and AccuMap trace arrays and amplitude and asymmetry (for early glaucoma only) deviation plots.

Of the 7 cases of early glaucoma in which the mVEP did not detect abnormality, 3 had shallow defects (Humphrey MD range, −1.26 to −1.86 dB), and the other 4 had more significant defects (Humphrey MD range, −1.9 to −5.1 dB) but advanced disease in the second eye, thereby reducing the relative contribution of asymmetry to the ASI. Examples are presented in Figure 4.

An estimate of the lower limit of mVEP specificity was determined based on the group of low-risk suspects. Of the 180 low-risk suspect eyes, 13 had variable Humphrey field (standard automated perimetry [SAP]) results and another 13 had an unconfirmed defect and underwent separate analysis as was done for the glaucoma group. Of the remaining 154 eyes, 142 (92.2%) had a normal mVEP result. In 12 eyes, the mVEP result was borderline or abnormal. However, in 8 of these eyes, there was a moderate to high refractive error, which is a known cause of reduction of mVEP central amplitude and may explain the abnormal result in at least some cases.

When our scotoma criteria were used as the basis for abnormality on the monocular amplitude deviation plot or the asymmetry plot, the sensitivity was slightly lower than for ASI. In the eyes of patients with glaucoma, the asymmetry plot in an additional 6 cases did not register an appropriate cluster, whereas only 1 additional case was detected that was not flagged by the ASI (sensitivity, 95.5%). For the monocular plot, a cluster was missed in a further 18 cases, revealing that it is not as sensitive as asymmetry in early disease (sensitivity, 88.8%). Specificity (using low-risk suspects), however, remained the same as when ASI was used. There were 7 eyes with abnormal findings on monocular and asymmetry plots and an additional 3 with abnormal findings on asymmetry only and 2 with abnormal findings on monocular amplitude only. If the criterion of either being abnormal is used, this gives a specificity of 92.2%, which is the same as that determined using ASI.

#### DISC ANALYSIS AS REFERENCE GOLD STANDARD

Instead of the usual gold standard of subjective visual fields, the morphology of the optic disc was used as an independent reference of disease. One hundred eleven subjects (218 eyes) had undergone stereoscopic disc photography within the last 12 months that was of sufficient quality to grade.

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Figure 1. Mean ± SD AccuMap Severity Index (ASI) values for different glaucoma groups. Limit lines indicate standard deviations. Groups are described in the “Subjects” and “Analysis” subsections of the “Methods” section.
Disc photographs were graded as normal in 83 eyes, suspect in 63, and glaucoma in 72. In 86.7% of eyes, the observers were in agreement as to the disc grade with their first view. In the remaining 13.3%, a consensus was reached after conferring and second viewing. Subjective visual field and mVEP results were then evaluated based on this classification to determine sensitivity and specificity.

For those eyes graded as having normal discs, 74 (89.2%) had normal mVEP results and 66 (79.5%) had normal Humphrey field results. Therefore, the specificity was better for mVEP than for subjective visual fields (SAP) when an independent reference standard was used. Within this group, there were no true normal subjects because they consisted mainly of low-risk suspects, and it is possible that some of them may have had early glaucoma despite the normal disc findings.

Sensitivity, however, was very similar for the mVEP and SAP tests. In the 72 eyes with discs graded as glaucoma, 58 (80.6%) had abnormal mVEPs, and 59 (81.9%) had abnormal Humphrey field results.

For those 63 eyes graded as suspect, 7 (11.1%) had abnormal mVEP results and 13 (20.6%) had abnormal Humphrey fields. All eyes with normal mVEP results had normal SAP results. However, of 5 eyes with abnormal SAP and normal mVEP results, 4 had unreliable subjective fields, suggesting they were probably false-positive findings.

In summary, the performance (sensitivity) of the mVEP was equivalent to that of the subjective Humphrey fields for detection of glaucoma based on masked classification of optic discs, with a better specificity. The structural changes in the disc that can be detected by a trained observer are known to occur in advance of functional losses. Therefore, it is not surprising that the sensitivity of the 2 functional tests was less than 100% when relying on disc appearance only.

**HIGH-RISK SUSPECTS**

High-risk suspects are of particular interest because glaucoma is more likely to develop in these eyes. In fact, some preperimetric eyes already have early stages of the disease, despite the subjective field finding remaining normal.

The high-risk suspect group consisted of 205 eyes. Of those, 163 eyes (79.5%) had normal SAP results, 16 (7.8%) had unconfirmed SAP defects on their most recent field, and 26 (12.7%) had variable SAP results. High-risk eyes with a variable or unconfirmed SAP defect underwent separate analysis (described in the “Analysis of Eyes With Variable Fields” subsection).

From the 163 eyes with a normal SAP result, 133 (81.6%) had a normal mVEP, thereby reassuring normal function. However, 30 eyes (18.4%) demonstrated various degrees of abnormality in mVEP, with 16 eyes classified as borderline and 14 eyes as abnormal based on the ASI. Further analysis revealed that 22 (73.3%) of these 30 eyes had other indications of early glaucoma (had been classified as having preperimetric glaucoma or had asymmetric discs). Therefore, it is possible that in at least 22 cases, the mVEP detected changes of early glaucoma before change on the subjective field test result. If the results from the low-risk suspects are accepted as an estimate of the lower limit of test specificity (92.2%), then these cases are more likely to be definite glaucoma and not false-positive results (as we would expect no more than 3 cases [around 10%] to produce false-positive results).

**ANALYSIS OF FELLOW EYES IN PATIENTS WITH GLAUCOMA**

In patients with glaucoma, 81 fellow eyes still had normal visual fields on SAP results. Of these, results in 14 (17.3%) were classified as abnormal or borderline by mVEP. Of this 14, 7 eyes were considered preperimetric owing to the appearance of the optic disc. It was expected that the fellow eyes might have a higher rate of abnormality than in high-risk suspects, but this was not the case. One possible explanation is that in high-risk suspects, the mVEP abnormality is mainly revealed by intereye asymmetry, whereas

| Table 2. Probability Values for Statistical Comparison of ASI Between Different Glaucoma Groups* |
|-----------------------------|-------------------|-----------------|-----------------|-----------------|-----------------|
| Groups                      | High Risk         | Fellow Eye      | Early Glaucoma  | Moderate Glaucoma| Advanced Glaucoma|
| Low-risk suspect            | .021              | .42*            | <.001           | <.001           | <.001           |
| High-risk suspect           | <.001             | .32*            | <.001           | <.001           | <.001           |
| Fellow eye with glaucoma    | <.001             | <.001           | <.001           | <.001           | <.001           |
| Early glaucoma              | <.001             | <.001           | .003            | <.001           | <.001           |
| Moderate glaucoma           | <.001             | <.001           | <.001           | <.001           | <.001           |

Abbreviation: ASI, AccuMap Severity Index.
*Groups are described in the "Subjects" and "Analysis" subsections of the "Methods" section.

**Figure 2.** Correlation between Humphrey 24-2 field mean deviation (MD) and multifocal visual evoked potential (mVEP) AccuMap Severity Index (ASI). Line indicates best linear regression fit.
IN THE FELLOW (NORMAL) EYE OF PATIENTS WITH GLAUCOMA, ASYMMETRY OFTEN DOES NOT PRODUCE DETECTABLE CHANGES WHEN THE SECOND EYE IS SIGNIFICANTLY DAMAGED OR THE SCOTOMA ARISES IN THE SAME PART OF THE VISUAL FIELD. IN THESE CASES, WE HAVE TO RELY ON THE MONOCULAR AMPLITUDE DEVIATION PLOT. WHEN USING THE DEFINITION OF A SCOTOMA RATHER THAN THE ASI, THE RATE OF ABNORMALITY WAS SLIGHTLY HIGHER AT 21%.

ANALYSIS OF EYES WITH VARIABLE FIELDS

Assessment of variable fields (in terms of severity and/or localization of the defect) commonly presents a clinical challenge. The rate of variable fields in the study was similar for all groups. Variable fields were found in 16 low-risk suspect eyes (8.9%), 26 high-risk suspect eyes (12.7%), and 28 eyes with early glaucoma (13.2%). Figure 5 shows the distribution of mVEP results in these 3 subsets. Moderate to advanced glaucoma with variable fields was not analyzed separately, since mVEP results did not change clinical outcomes.

Low-Risk Suspects

As can be seen from Figure 5, all eyes with variable SAP findings that were clinically classified as low-risk suspects had a normal mVEP, thereby confirming the nor-
mal status of those eyes. This serves to reinforce the clinical impression that the eye is still normal.

**High-Risk Suspects**

Only a small proportion of results of variable high-risk suspect eyes (4 of 26) were borderline or abnormal on mVEP ASI. Of the 22 remaining eyes, none were considered clinically preperimetric, and in 7 cases the abnormal SAP finding was thought to be caused by rim artifacts. Therefore, the normal mVEP result in these subjects reveals that the variability in the subjective field is less likely to be progression of glaucoma.

**Subjects With Early Glaucoma**

In the 28 eyes classified as early glaucoma with variable fields, 13 eyes had normal mVEP results. All 13 of these eyes had been classified as early glaucoma based on the fellow eye having a definite glaucomatous field defect (they could not, however, be classified into the group of fellow eyes of patients with glaucoma, because this group by our definition had to have a normal field finding, and they had an abnormal SAP finding at some stage). These eyes mostly had only mild disc changes, but our definition placed them into the early glaucoma group. The mVEP results did not detect any definite functional change in these 13 eyes.

In comparison, the other 15 eyes with variable fields and classified as early glaucoma had borderline or abnormal mVEP results. There was a statistically significant difference between the C/D ratio and Humphrey MD (P = .02 and P = .01, respectively) for the group of patients who had an abnormal mVEP result (mean C/D ratio, 0.77; MD, −4.3 ± 1.4 dB) and those who still had a normal mVEP result (mean C/D ratio, 0.67; MD, −2.6 ± 1.1 dB). In 7 of 10 eyes with variable field and a definitely abnormal mVEP result (ASI, >20), there were additional indications of abnormality such as notched or asymmetrical disc or nerve fiber layer defect. Therefore, in these patients, the mVEP result confirms what is suspected by the disc appearance and the fluctuating fields, ie, that there is evidence of early glaucoma.

**UNCONFIRMED FIELD DEFECTS**

Evaluation of unconfirmed or newly diagnosed visual field defects is another area of uncertainty in diagnosis because the specificity of first-time subjective perimetry is low, and even experienced observers can show large fluctuations between tests. Figure 6 shows the distribution of mVEP results in low-risk suspects, high-risk suspects, and glaucoma patients whose last (or only) subjective field result was abnormal.

**Low-Risk Suspects**

In the low-risk suspect group, of the 13 eyes with an unconfirmed SAP defect (10 eyes with borderline GHT results and 2 with results outside normal limits; MD, −0.4 ± 1.1 dB) all had a normal mVEP result. Because the optic disc was normal in these eyes, the mVEP result shows better correlation with disc appearance.

**High-Risk Suspects**

Sixteen high-risk eyes had unconfirmed SAP defects. None of these 16 eyes was considered truly glaucomatous clinically by the reviewing clinician. Of these, 13 (81%) had a normal mVEP result, suggestive of still normal function. In 3 cases, the mVEP result was classified as abnormal, which may represent early glaucoma. Follow-up with mVEP and subjective field testing would be required to confirm this.

**Patients With Early Glaucoma**

Forty-five eyes had an unconfirmed scotoma in the last (or the only) SAP result, and in most cases this was a first attempted visual field. In 26 (58%) of these eyes (SAP MD, −4.2 ± 4.1 dB), an abnormal mVEP finding corresponded to the defect, thereby supporting the abnormality found on Humphrey field testing.
Based on disc appearance, 8 of these eyes were classified as early glaucoma (mean ± SD C/D ratio, 0.73 ± 0.08). All underwent subjective visual field testing on 2 or more occasions, and if SAP criteria were used, all would have been inappropriately classified as moderate or advanced glaucoma (MD, −13.1 ± 6.7 dB; range, −7.15 to −23.88 dB). Although the mVEP result was abnormal in 7 of 8 cases, the abnormality was very mild, with the ASI ranging from 23 to 46 (Figure 7). This finding was in keeping with the clinical picture and the expected severity of field loss based on the structural changes in the disc and nerve fiber layer.

The remaining 37 eyes were classified as glaucoma suspects (C/D ratio, 0.59 ± 0.1), with an SAP MD range of −1.57 to −27.8 dB (MD, −10.6 ± 7.9 dB). Based on optic disc and nerve fiber layer appearance, these eyes should not have had a significant visual field defect. However, some individuals may not show a structural change before field loss, or structural change might be present but not detectable by means of routine clinical examination. The mVEP ASI identified 34 (92%) of these 37 eyes as being within normal range, with the 3 remaining only as borderline cases. Two of those borderline eyes had mild central depression of mVEP amplitude due to cataract, whereas in contrast, the SAP result demonstrated very advanced reduction of sensitivity all across the field (MD, −29.1 and −23.8 dB) that was not consistent with the clinical status.

Of the same 37 eyes, the fields of 18 were rated as unreliable by means of Humphrey MD (Figure 9), and many were variable in their severity (Figure 9). However, the remaining 19 eyes demonstrated substantial, consistent, and reliable subjective visual fields (Figure 10). Some of these were rim- or upper eyelid–type SAP artifacts, but some had marked constrictions. An experienced clinician may be able to exclude some of these as artifacts at a glance, or by repeating subjective testing with closer supervision of the patient. However, in most cases the test had already been repeated with the same result, so the objective results help to interpret the changes as not significant.

CLINICAL OUTCOMES

The clinical outcomes of mVEP objective perimetry in assessing glaucoma are summarized in the glaucoma investigation model patient flowchart (Figure 11). In a large proportion of subjects, the mVEP result supported suspected defects or excluded defects where the SAP result was unreliable, variable, or excessive. The total numbers of eyes falling into each category are included. The breakdown does not report the numbers of unreliable fields within each category, but many of these fell within the variable and excessive loss groups. In these subjects, the mVEP appears to have a particularly important role.

COMMENT

In this retrospective study, we evaluated the mVEP recorded with the AccuMap objective perimeter across a wide range of clinical presentations in the investigation of glaucoma. It was closely correlated with the severity of the disease in diagnostic category and directly with the Humphrey MD. It achieved a high level of sensitivity in

Figure 7. Example of early glaucoma with mild disc cupping (inferior notch) but advanced subjective field loss. The multifocal visual evoked potential (mVEP) confirms a superior arcuate defect that is consistent with the structural findings. ASI indicates AccuMap Severity Index.

Figure 8. Example of unreliable subjective field (66% false positive) with advanced losses. The subject had a normal disc confirmed functionally by multifocal visual evoked potentials (mVEPs). ASI indicates AccuMap Severity Index.

However, the remaining 19 eyes (SAP MD, −2.8 ± 2.2 dB) demonstrated a normal mVEP result. In 10 of these, the SAP finding was unreliable and likely false positive. In 2 cases, the fellow eye had advanced glaucoma, which reduced the relative contribution of asymmetry analysis (and therefore the ability to detect early glaucoma). These 2 cases have probable false-negative mVEP results. In the remaining 7 cases, the mVEP result tends to suggest that the eye is still functionally intact, and again repeat testing is needed to confirm this.

EYES WITH EXCESSIVE VISUAL FIELD LOSS COMPARED WITH DISC

A group of 24 patients (45 eyes) had loss of the subjective visual field that was much more excessive than expected from the optic disc appearance. The referring clinician highlighted this fact in the assessment.
detecting abnormal visual fields when compared with the Humphrey (SAP) gold standard. The sensitivity was 97.3%, with the only cases missed being in the early glaucoma category. In addition, a significant proportion of high-risk suspects (18.4%) and fellow eyes of glaucoma patients with normal visual fields (16.0%) had abnormal mVEP results. This is supportive of earlier detection of defects, especially when it is considered that in the low-risk suspect group, only 7.8% of the results were abnormal, providing an estimate of the lower limit of specificity. Some of these could actually be early glaucoma that is not showing a structural change as yet, with follow-up being required to determine true status.

The new ASI performs better than setting criteria for the identification of clusters on the monocular amplitude deviation or asymmetry deviation plots. The asymmetry plot is limited when the fellow eye has significant glaucoma. However, because the ASI also relies to a significant extent on asymmetry, it will also be less sensitive in these cases.

The rate of abnormal results in fellow eyes (17%-21%) is lower than in the previously published study.7 We believe this is due not only to a higher proportion of fellow eyes that were actually at relatively lower risk but also to the fact that we have tightened our diagnostic criteria for a scotoma on the deviation plots and in the ASI to improve specificity.

When masked assessment of disc photographs was used as the comparator, mVEP and SAP performed similarly; however, mVEP demonstrated a significantly higher specificity (89.2% vs 79.5%). The lower sensitivity (81.6% for mVEP and 82.9% for SAP) for both types of functional test is expected, because structural changes are known to precede functional changes. In addition, suspect discs can also be misinterpreted as glaucoma, even by trained observers. Therefore, it is not surprising that the sensitivity of the 2 functional tests was less than 100% when relying on disc appearance only. Based on the changes seen in some high-risk suspects, we had expected to see a higher sensitivity for mVEP than for SAP, but we may have been limited by the small sample size of those with photographs available.

The study limitations include the retrospective data and the wide variations between subjects of the data available for patients (eg, number of SAP fields). However, because all consecutive cases were included for analysis, with no entry criteria exclusions, the results are representative of a large clinical practice where all levels of disease and experience are encountered and typical patients who perform poorly or variably on subjective testing need to undergo evaluation. Clinical decisions hinge on visual field data, which is often flawed. In the cases described with variable field loss, excessive field loss compared with the disc appearance, and new but unconfirmed defects, the mVEP result was very helpful in determining the functional status.

The GHT was used because it is a simple method for evaluating fields and is used by clinicians regularly in clinical practice. We acknowledge that many other factors should be considered when interpreting fields (such as pattern standard deviation), and many definitions exist in the literature, but no agreement as to which is the ideal exists. In addition, because we were comparing the GHT with a 3-way classification of normal, borderline, and abnormal ASI, the results were more easily compared.

Both eyes were included for the analysis despite the known association of statistical problems because in the clinical setting there is frequently different performance on SAP between eyes, and a selection criteria that chose only the better eye or the eye with the more reliable field would not give us an overall view of how patients are performing. Random selection of an eye would exclude a substan-
subjective perimetry that complicates interpretation in former conditions. There is also a learning curve associated with test to test, and patients may be repeatedly poor per-field test with an abnormal or an unreliable result, as clinically from normal to abnormal. Where their subjective field results fluctuated considerably from normal to abnormal, clinicians classified as low-risk suspects had normal mVEP results, functional status. In particular, all subjects clinically classified as high-risk suspects had abnormal mVEP results, whereas their subjective field results fluctuated considerably from normal to abnormal.

In the glaucoma cases where the SAP result showed excessive loss compared with disc appearance, most had more appropriate levels of change on the mVEP result that matched the degree of structural change. In the eyes with normal or suspect discs but advanced field changes, the mVEP result was nearly always normal. It is possible that some individuals may not show a structural change before field loss, or that some structural change was present but not detectable on clinical examination. We believe it is unlikely that those cases with advanced losses, however, would still have a normal-appearing disc.

Across all diagnostic groups of the study, 12% to 16% of subjects showed variable SAP results during their last 3 tests. In these subjects, the mVEP result clarified their functional status. In particular, all subjects clinically classified as low-risk suspects had normal mVEP results, whereas their subjective field results fluctuated considerably from normal to abnormal.

In many cases, it is not enough to repeat a subjective field test with an abnormal or an unreliable result, as clinical trials have shown large fluctuations in defects from test to test, and patients may be repeatedly poor performers. There is also a learning curve associated with subjective perimetry that complicates interpretation in new patients, such that 2 to 3 field tests need to be performed before a reliable result is achieved. In a recent study of the performance of SITA vs full-threshold visual field testing, the specificity of SITA was only 73.7% after 2 tests, which confirms that in many cases the clinician will be faced with results that cannot be interpreted or will be misleading as to the extent of disease. However, SAP is now the accepted gold standard with which we investigate glaucoma and is used in most major clinical trials, despite its known limitations.

Alternative subjective tests have been shown to detect glaucomatous change early in the disease, in particular methods such as short-wavelength automated perimetry and frequency-doubling perimetry. Being subjective in nature, they are still subject to the same limitations relating to patient cooperation and understanding of the test technique.

Finally, in terms of patient outcomes, the roles of objective perimetry in assessing glaucoma are summarized in the glaucoma investigation model patient flowchart (Figure 11). The mVEP supports or helps rule out glaucomatous change early in the disease, in particular methods such as short-wavelength automated perimetry and frequency-doubling perimetry. Being subjective in nature, they are still subject to the same limitations relating to patient cooperation and understanding of the test technique.

Figure 11. Glaucoma investigation model patient flowchart. SAP indicates standard automated perimetry; mVEP, multifocal visual evoked potential.
out of proportion to disc changes (not seen in this study sample), then further pathology should be suspected (eg, intracranial tumor), and computed tomography/magnetic resonance imaging should be considered.

The mVEP provides some significant advantages over subjective testing of the visual field. It presents objective results, removing the effects of patient indecision. It does not seem to have a learning curve, and it has a high level of patient acceptance. Unlike other electrophysiological tests such as pattern electroretinography, the setup is noninvasive. Its main limitation remains cases of noisy recording, which can lead to false-positive findings and increased variability.

Further developments in mVEP technology should be directed toward improving signal-to-noise ratios and thereby increasing sensitivity and reducing variability. Reproducibility studies with AccuMap V2.0 are underway to determine if reproducibility is good enough to enable application to glaucoma progression analysis. The ultimate goal is to provide an objective measure of functional change over time. At present, the mVEP provides a valuable diagnostic aid in many different clinical settings involving the assessment of the patient with glaucoma.

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