

Dichoptic Stimulation Improves Detection of Glaucoma with Multifocal Visual Evoked Potentials

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PURPOSE. To determine whether simultaneous binocular (dichoptic) stimulation for multifocal visual evoked potentials (mfVEP) detects glaucomatous defects and decreases intereye variability.

METHODS. Twenty-eight patients with glaucoma and 30 healthy subjects underwent mfVEP on monocular and dichoptic stimulation. Dichoptic stimulation was presented with the use of virtual reality goggles (recording time, 7 minutes). Monocular mfVEPs were recorded sequentially for each eye (recording time, 10 minutes).

RESULTS. Comparison of mean relative asymmetry coefficient (RAC; calculated as difference in amplitudes between eyes/sum of amplitudes of both eyes at each segment) on monocular and dichoptic mfVEP revealed significantly lower RAC on dichoptic (0.003 ± 0.03) compared with monocular testing (-0.02 ± 0.04 ; $P = 0.002$). In all 28 patients, dichoptic mfVEP identified defects with excellent topographic correspondence. Of 56 hemifields (28 eyes), 33 had Humphrey visual field (HFA) scotomas, all of which were detected by dichoptic mfVEP. Among 23 hemifields with normal HFA, two were abnormal on monocular and dichoptic mfVEP. Five hemifields (five patients) normal on HFA and monocular mfVEP were abnormal on dichoptic mfVEP. In all five patients, corresponding rim changes were observed on disc photographs. Mean RAC of glaucomatous eyes was significantly higher on dichoptic (0.283 ± 0.18) compared with monocular (0.199 ± 0.12) tests ($P = 0.0006$).

CONCLUSIONS. Dichoptic mfVEP not only detects HFA losses, it may identify early defects in areas unaffected on HFA and monocular mfVEP while reducing testing time by 30%. Asymmetry was tighter among healthy subjects but wider in patients with glaucoma on simultaneous binocular stimulation, which is potentially a new tool in the early detection of glaucoma. (*Invest Ophthalmol Vis Sci.* 2007;48:4590-4596) DOI: 10.1167/iovs.07-0318

Early detection of glaucomatous damage remains a challenge. Although structural changes often precede functional loss as detected by subjective perimetry,¹ the demon-

stration of functional field defects lends more confidence to the diagnosis of this disease, a diagnosis that often leads to permanent lifestyle changes for the patient.

Multifocal visual evoked potential (mfVEP) recording is a sensitive objective perimetric technique for the detection of glaucomatous visual field loss; reported sensitivity is 80% to 95% in early glaucoma with the conventional black-white pattern-reversal stimulus.²⁻⁴ Since it was first described in 1994,⁵ several advances have made the technique less variable and more clinically applicable. Four-channel recording made it possible to reliably record VEPs from multiple stimulated areas of the visual field.^{6,7} Asymmetry analysis improved consistency and sensitivity by overcoming variability caused by differences in cortical anatomy between patients.^{8,9} Electroencephalogram (EEG)-based scaling of amplitudes used in multifocal objective perimetry greatly reduced intersubject variability by accounting for external factors (skull thickness, underlying tissue conductivity), possibly resulting in considerably better sensitivity.¹⁰ Recently, 100% sensitivity in early glaucoma has been reported with a newly developed blue-on-yellow pattern-onset stimulus.¹¹

However, the technique as typically applied is relatively time consuming and requires 20 to 30 minutes per patient, primarily because recordings are conducted monocularly. Another disadvantage of sequential monocular recording is unequal psychophysical conditions during recordings of each eye. As was reported previously, asymmetry analysis of mfVEP amplitude is the most sensitive way to detect early changes.^{8,9} However, toward the end of the test, the patient may become fatigued or lose attention, which may negatively affect recording of the second eye, producing artificial asymmetry and therefore false-positive results. Simultaneous recording of both eyes would, therefore, be beneficial for decreasing recording time and improving asymmetry analysis.

Recording of binocular (dichoptic) mfVEPs has been recently reported by James et al.¹²⁻¹⁵ using a liquid crystal polarizing shutter with associated polarizing spectacles. Although it did permit simultaneous recording from multiple visual field areas of both eyes, this stimulation technique caused considerable reduction in the level of luminance contrast, resulting in lower amplitude of responses and, consequently, smaller dynamic range of the response, limiting clinical applicability.

We recently reported successful simultaneous binocular (dichoptic) recording of mfVEP using virtual reality goggles for stimulus display.¹⁶ This stimulation technique does not require the patient to wear polarizing glasses, and it presents true simultaneous recordings with both eyes continuously receiving stimuli as opposed to alternating ferro-electric shutters. To record dichoptic mfVEP using virtual reality goggles, different pseudorandom binary sequences were used to stimulate test locations in both eyes, and responses for multiple visual field areas in both eyes were derived from a single cortical signal. It yielded amplitude comparable to monocular stimulation and accurate topographic representation of the visual field.

The aims of the present study were to determine the ability of dichoptic mfVEP using virtual reality goggles to detect glaucomatous visual field loss and to test whether the potential

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Supported by a National Health and Medical Research Council Development grant. AK is a Sydney Medical Foundation Research Fellow.

Submitted for publication March 15, 2007; revised April 29, 2007; accepted July 30, 2007.

Disclosure: **H. Arvind**, None; **A. Klistorner**, ObjectiVision Pty. Ltd. (R, P, C); **S. Graham**, ObjectiVision Pty. Ltd. (R, P, C); **J. Grigg**, None; **I. Goldberg**, None; **A. Klistorner**, None; **F.A. Billson**, None

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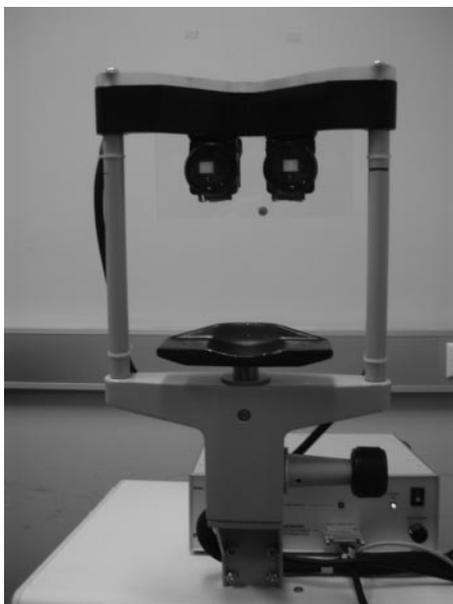


FIGURE 1. Set-up used for simultaneous binocular display.

advantages hypothesized earlier—namely, decreased testing time and lower intereye variability—can be demonstrated.

METHODS

Twenty-eight patients with glaucoma were recruited from a glaucoma practice. Approval was obtained from the institutional review board, written informed consent was obtained from all participants, and the study was conducted in accordance with the tenets of the Declaration of Helsinki.¹⁷

The diagnosis of glaucoma was made on the basis of glaucomatous cupping of the optic disc, as judged by stereoscopic ophthalmoscopy with a corresponding visual field defect on Humphrey visual field analysis (HFA). All patients fulfilled the following inclusion criteria: best-corrected visual acuity greater than 6/18 in the worse eye; reliable and repeatable visual field defects on Swedish Interactive Threshold Algorithm (SITA) standard 24-2 perimetry, which corresponded to disc excavation; and absence of other ocular abnormalities (except glaucoma). A scotoma on Humphrey field examination was defined as a set of three contiguous abnormal points in the same hemifield at $P < 5\%$, with at least two points at $P < 2\%$ on the pattern deviation plot. Points immediately above and below the blind spot could not qualify as

part of the scotoma. Peripheral rim points could qualify as part of the overall scotoma, but at least two of the points qualifying as the scotoma nucleus had to be non-rim. Patients with significant cataract or other media opacities, anisometropia greater than 1.5 D, and inconsistent or nonrepeatable visual field defects were excluded. Significant cataract was defined as cataract causing visual acuity to drop below 6/12 after best correction.

In addition, 30 healthy subjects were recruited to construct normative databases for monocular and binocular tests. All had best-corrected visual acuity of 6/6 or better in both eyes, anisometropia (if any) less than 1.5 D, stereoacuity of 40 seconds of arc on Titmus fly stereogram, and normal ophthalmic examination results. All subjects underwent mfVEP testing on monocular and dichoptic stimulation, and the order of tests was randomized.

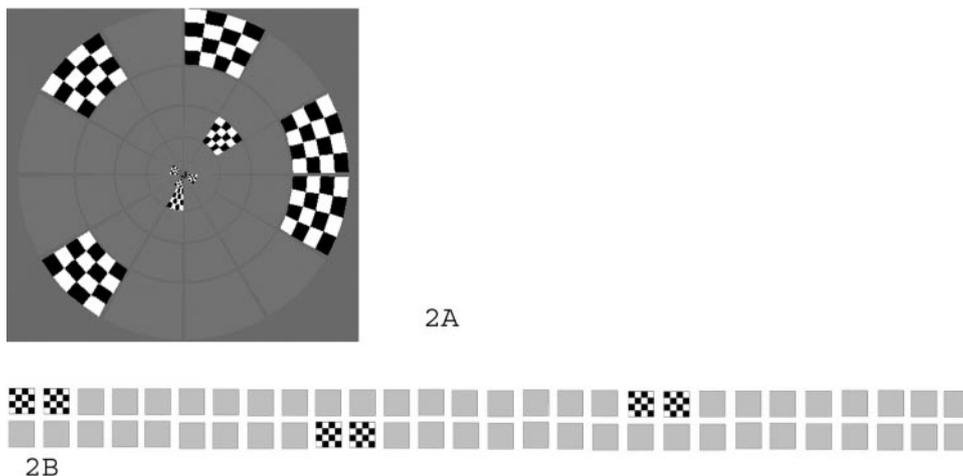
Dichoptic Testing

Instrument Set-up. Stimuli were presented simultaneously to both eyes using virtual reality goggles (nVisor SX; NVIS, Reston, VA), which are based on liquid crystal on silicon (LCOS) technology and have a 60-Hz display refresh rate for each screen, driven by separate video boards. The goggles' screens were removed from their head mounts (provided by the manufacturer) and mounted on a chin-rest set-up to facilitate placement of the recording electrode cross on the occipital region. Figure 1 shows the instrument set-up used. The subject was seated comfortably in front of the machine, with chin placed on the chinrest, forehead against the forehead support, and full refractive correction in place for distance. The patient viewed the binocular display through two separate eyepieces. Vertical bars were marked to indicate the level of lateral canthus used to align the eyes vertically with the goggles' screens. The distance between eyepieces was adjusted to match each person's interpupillary distance.

The display to each eye consisted of a cortically scaled dartboard (Fig. 2A) with 56 segments arranged in five concentric rings (0.5° - 1° , 2° - 3° , 3° - 6° , 6° - 11° , 11° - 18°) and a central fixation target extending up to 0.5° . The stimulus in any segment consisted of a 4×4 black-and-white check pattern. Segment size was scaled according to the cortical magnification factor.¹⁸ Corresponding to the size of the segments, the size of the individual checks also increased with eccentricity. Luminance of the white check was 85 cd/m^2 , luminance of the black check was 2.4 cd/m^2 , and luminance of the background was 44 cd/m^2 . A central fixation target was provided that consisted of rotating and slowly changing letters. These features—the ring arrangement and the fixation target—were identical with displays for both eyes. The patient perceived a single binocular image of the dartboard.

Stimulus. Sparse pattern onset or "pattern-pulse" stimulation was used because it yields larger amplitudes and shows lower interocular suppression on dichoptic testing.¹² These attributes were reproduced

FIGURE 2. (A) Cortically scaled dartboard with sparse stimulation. Fifty-six segments are arranged in five concentric rings. Gray segments indicate the pattern-off state, and segments with black-and-white checks indicate the pattern-on state. (B) Schematic representation of stimulation sequence at each segment for dichoptic testing. Upper and lower rows represent stimulus presentation to corresponding segments of the left and right eyes, respectively. Eighteen frames (16.67 ms/frame) constituted one recording sequence. Presentation of the stimulus to the second eye was shifted by nine frames, and the minimum separation between stimuli of corresponding areas of the visual fields of both eyes was seven frames.



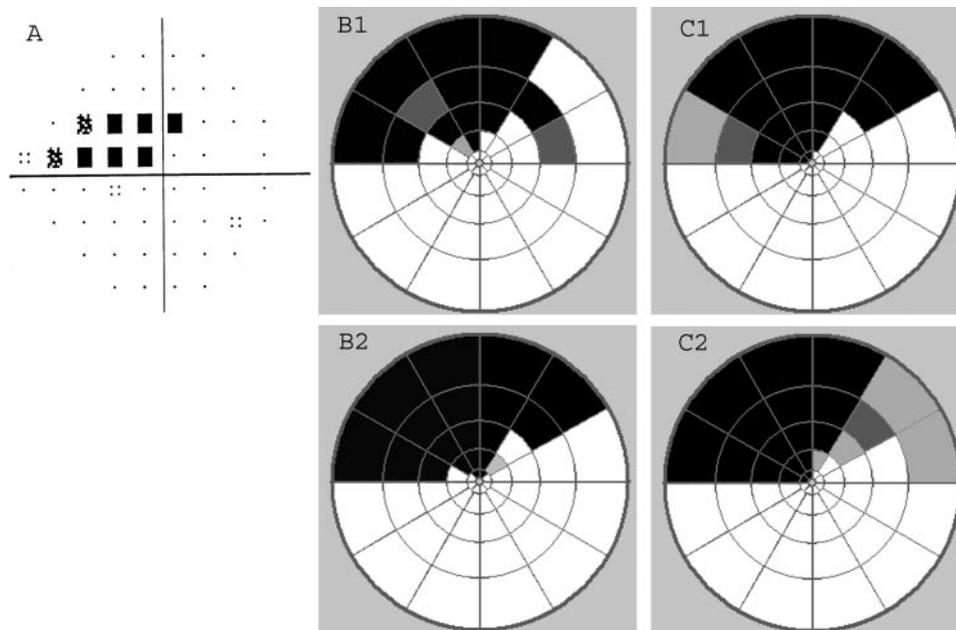


FIGURE 3. (A) Total deviation plot of Humphrey field analysis. (B1) Amplitude deviation plot of monocular mfVEP. (B2) Amplitude asymmetry plot of monocular mfVEP. (C1) Amplitude deviation plot of dichoptic mfVEP. (C2) Amplitude asymmetry plot of dichoptic mfVEP, recorded from the right eye of the same patient, demonstrating excellent topographic correspondence.

by us in pilot runs. Pseudorandom binary sequences (PRBS) were used to drive stimuli at each test location, so that the presentation at each location was random and independent of other locations. Each binary sequence had a 50% probability of being 1 or 0 at any point of time. Element 1 was represented by two consecutive states: state *pattern on* lasting two frames of the screen (33.3 ms), when the stimulus pattern was displayed, and state *pattern off* lasting 16 frames (266.4 ms), when the whole segment was diffusely illuminated with an intensity of the mean luminance. Element 0 consisted of a pattern off state for 18 frames. The average rate of presentation at each segment was 1.66 times/s. Presentation of the stimulus to the corresponding segment of the second eye was always shifted by nine frames; therefore, the minimum separation between stimuli to corresponding areas of the visual fields of both eyes was seven frames (116.7 ms; Fig. 2B). Three runs were recorded, each lasting 139 seconds.

Monocular Testing

Instrument Set-up. Monocular black-white multifocal VEPs were recorded for each eye (right eye first) using multifocal objective perimetry (Accumap, version 2.0; ObjectiVision Pty. Ltd., Sydney, Australia), described in detail elsewhere.² Sparse stimulus presentation was also used for monocular stimulation. The dartboard stimulus was the same as that used for each eye of the dichoptic tests. The stimulus was generated on a 21-inch high-resolution display (Hitachi Ltd., Tokyo, Japan) with stimulation rate of 75 Hz. All subjects were given optimal refraction for near and were seated 30 cm from the screen.

Stimulus. For monocular recording, each recording sequence had a duration of nine frames of the monitor (13.3×9 ms = 119.7 ms). Each element "1" of the binary sequence was represented by a pattern on state that lasted for two frames and a pattern off state that lasted for seven frames. For element "0" of the stimulating sequence, the pattern off state was active for 9 frames. Five runs were recorded for each eye, each run lasting 56 seconds.

Recording

For monocular and dichoptic tests, four gold cup electrodes (Grass, West Warwick, RI) mounted in an occipital cross-electrode holder were used for bipolar recording. Two electrodes were positioned 4 cm on either side of theinion: one electrode was in the midline 2.5 cm above theinion, and one electrode was 4.5 cm below theinion. Electrical signals were recorded along four channels as the difference between superior and inferior, left and right, and obliquely between

left and inferior and right and inferior electrodes. A ground electrode was placed on one ear lobe. Cortical responses were amplified 100,000 times and band-pass filtered (1–20 Hz). Software (Opera; ObjectiVision Pty. Ltd.) correlated the responses with the stimulating PRBS and attributed the calculated signals to the respective segments of the visual field. This software also scaled the responses to the background EEG to reduce the interindividual variability, described elsewhere.¹⁰ For every segment, the largest peak-to-trough amplitude for each wave within the interval of 60 to 200 ms was determined for each channel. The wave of maximal amplitude from each segment in the field from the four channels was automatically selected, and the software created a combined topographic map.²

Statistical Analysis

For monocular and dichoptic mfVEP, this map was compared with a normal database of 30 healthy subjects, and the visual field defects were documented by constructing amplitude probability plots. The difference in intereye amplitude at each segment was also calculated, and this was compared with the expected difference in the normal population. Areas of visual asymmetry (or visual loss) were documented by constructing an asymmetry probability plot.⁸ A scotoma on the amplitude deviation plot was defined as a cluster of three abnormal points in the same hemifield at $P < 0.02$, with at least one of them at $P < 0.01$. For the asymmetry plot, a cluster of three contiguous points at $P < 0.01$ or two points at $P < 0.005$ was considered a scotoma. The four central superior rim points were excluded from the clusters.

TABLE 1. Hemifield Analysis of Defects Identified by HFA, Monocular mfVEP, and Dichoptic mfVEP

Hemifields	Number	Abnormal Hemifields on mfVEP		
		Monocular	Binocular	<i>P</i>
Abnormal on HFA	33	31	33	0.16
Normal on HFA	23	2	7*	0.03
Total	56	33	40	0.008

P values were calculated using the McNemar test.

* Includes two hemifields normal on HFA and abnormal on monocular mfVEP and five hemifields normal on HFA and monocular mfVEP.

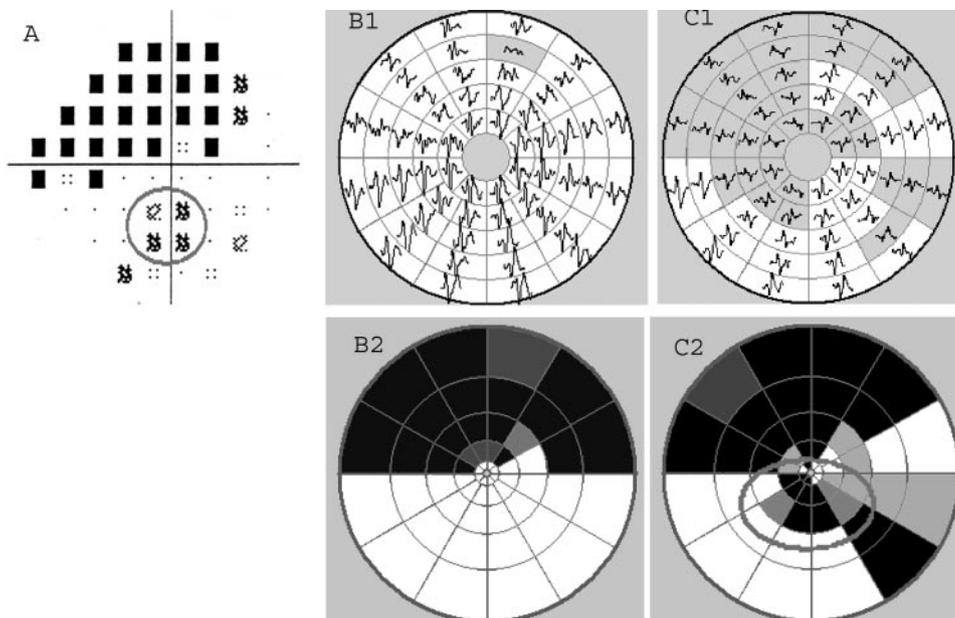


FIGURE 4. Total deviation plot of Humphrey field analysis (A), monocular mfVEP results (B1, traces; B2, asymmetry deviation plot), and dichoptic mfVEP results (C1, traces; C2, asymmetry deviation plot) recorded from the right eye of the same patient, demonstrating a visual field defect in the second (inferior) hemifield detected on HFA (A) missed by monocular mfVEP (B1, B2) and detected by dichoptic mfVEP (C1, C2). In addition, note the suppression of traces in most segments on dichoptic, compared with monocular, testing. The other eye was normal (not shown).

Analysis was based on detection of scotomas by HFA, monocular and dichoptic mfVEP, and topographic correspondence between scotomas. To compare asymmetry obtained with monocular and dichoptic recording, the degree of asymmetry expressed as the RAC between the eyes of each subject was calculated as the difference in amplitude between the left eye and the right eye divided by the sum of amplitudes at each segment.

RESULTS

Healthy Controls

Thirty healthy persons (15 men, 15 women) were examined, and the mean age was 44.43 ± 19.7 years (21–77 years). As described earlier for monocular mfVEP,¹⁰ the amplitude of dichoptically recorded mfVEP (and scaled for EEG activity) did not correlate with age ($r = 0.1$) or sex ($P = 0.8$; t -test). Similarly, there was no correlation between the magnitude of response asymmetry and either age ($r = 0.1$) or sex ($P = 0.36$; t -test). Comparison of mean RAC on monocular and binocular testing revealed significantly lower interocular asymmetry on dichoptic testing (RAC, 0.003 ± 0.03) compared with monocular testing (RAC, -0.02 ± 0.04 ; $P = 0.002$; t -test). According to our definition of scotoma, the rate of abnormality among healthy controls was 3.33% (1 of 30 persons).

Glaucoma

Twenty-eight persons with glaucoma were examined. Eighteen were men and 10 were women, and the mean age was 67.4 ± 8.03 years (52–80 years). Three of 28 patients had bilateral visual field defects on HFA; the rest had unilateral defects. The affected eye was chosen for patients with unilateral glaucoma, and one eye was chosen at random for patients with bilateral field defects. Fourteen patients had mean deviation (MD) less than 7 dB on HFA, 12 had MD 7 to 14 dB, and two had MD 14 to 16 dB. Therefore, most patients had early or moderate glaucoma, 24 patients had best-corrected visual acuity 6/9 or better in the worse eye, and the remaining four had vision of 6/12 to 6/18 in the worse eye. All patients had stereoacuity better than 200 seconds of arc.

In all 28 eyes with glaucomatous defects, monocular and dichoptic mfVEP identified defects, all which corresponded

topographically to the scotomas on HFA. An example is shown in Figure 3.

A hemifield-wise analysis of visual field defects (Table 1) showed that while all abnormal hemifields on HFA ($n = 33$) were identified by dichoptic recording, two HFA defects were missed by monocular recording (Fig. 4).

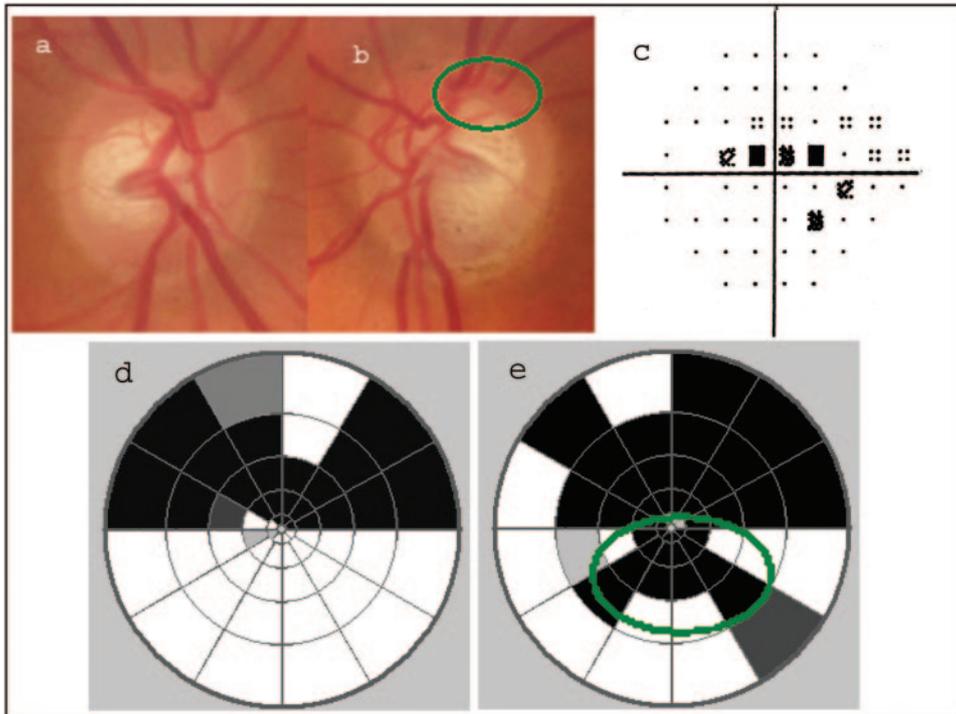
Among 23 hemifields (of 23 eyes) that had no defects on HFA, two were considered abnormal on monocular and binocular mfVEP testing. In addition, five hemifields (of 5 patients; 17.9% of patients tested) considered normal on HFA and monocular mfVEP were identified as abnormal by binocular mfVEP. To clarify whether the second hemifield involvement in these five patients represented false-positive results or true defects, stereo disc photographs of these five patients were reviewed by two independent observers. The examiners were masked to the mfVEP results and were asked to identify all areas of rim thinning. In four patients, rim notching corresponding to the second scotoma detected on binocular mfVEP was observed by both observers (Fig. 5). In the fifth patient, the corresponding rim was considered definitely thinner in the affected eye compared with the other eye but was not focally notched. The second scotoma in four of these patients was identified by asymmetry analysis and by amplitude deviation in one.

To quantify the differences between monocular and dichoptic tests in glaucoma patients, RAC values were compared. Mean RAC of all segments of the affected eye was significantly higher on dichoptic (0.283 ± 0.18) compared with monocular (0.199 ± 0.12) tests ($P = 0.0006$; paired t -test). When hemifields with HFA defects ($n = 33$) and hemifields without HFA defects ($n = 23$) were examined separately, the difference in mean hemifield RAC between tests was significant for affected (mean dichoptic RAC, 0.443 ± 0.20 ; mean monocular RAC, 0.328 ± 0.16 ; $P < 0.0001$, paired t -test) but not for unaffected hemifields (mean dichoptic RAC, 0.09 ± 0.08 ; mean monocular RAC, 0.075 ± 0.06 ; $P = 0.5$, paired t -test; Fig. 6).

DISCUSSION

Attempts to simultaneously record VEPs from both eyes were made as early as 1978 by Lennerstrand,¹⁹ who recorded full-field VEPs during dichoptic pattern-reversal viewing by using different frequencies of stimulation to each eye and phase-

5A



5B

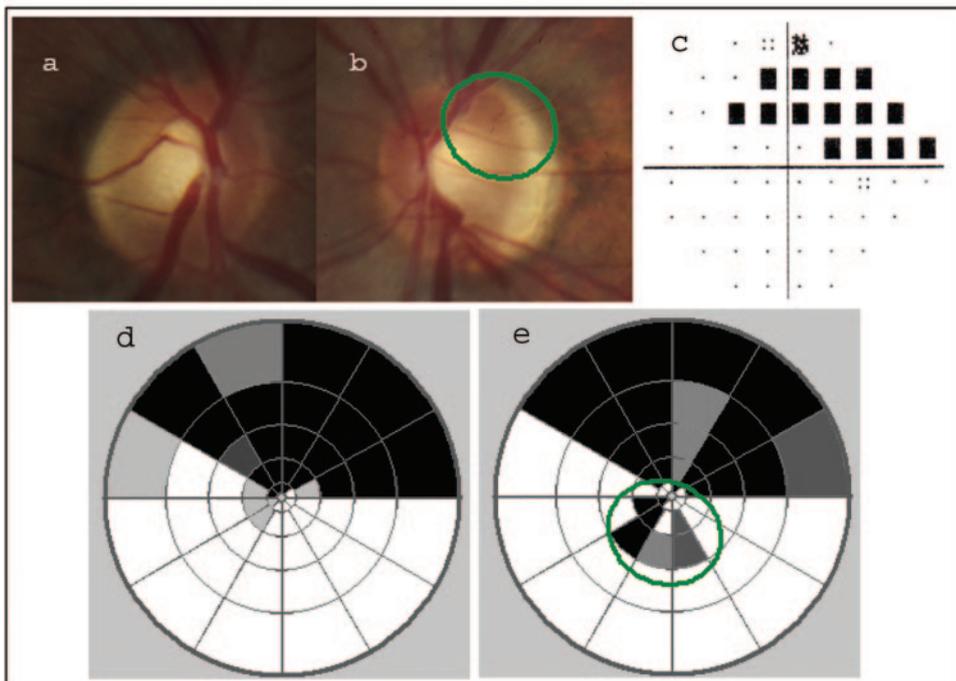


FIGURE 5. Examples of second abnormal hemifield detected by dichoptic mfVEP. (A, B) Main defect in superior hemifield of left eye detected on HFA (c) and asymmetry deviation plots of monocular (d) and dichoptic mfVEP (e) corresponds to the inferior notch in the photograph of the left eye (b). In addition, the inferior hemifield defect detected by dichoptic mfVEP (highlighted) was missed by HFA (c) and monocular mfVEP (d) but correlated with rim thinning (b, highlighted). Photograph of contralateral eye (a) shown for comparison.

locking the sampling of the signals to the reversals of presentations to each eye. Sato et al.²⁰ reported that PRBS could be used to independently stimulate right and left eyes, and the response of each eye could be calculated by cross-correlating the resultant response with the PRBS. Recently, James and coworkers demonstrated the applicability of this method to multifocal stimulation.¹²⁻¹⁵ They reported recording multifocal pattern VEP for each eye under dichoptic stimulation conditions using a liquid crystal polarizing shutter and associated polarizing spectacles.

In the present study of dichoptic mfVEP in glaucoma, virtual reality goggles were used to simultaneously stimulate multiple areas of the visual field in both eyes up to 18° of eccentricity. All HFA scotomas were identified by dichoptic mfVEP (100% sensitivity). Although the severity of the visual field defect varied considerably in the study group, 50% of patients had MD less than 7 dB, indicating good sensitivity of the technique in early glaucoma. Although glaucoma was unilateral in most patients, three patients (10%) had bilateral visual field defects, all which were detected by dichoptic mfVEP.

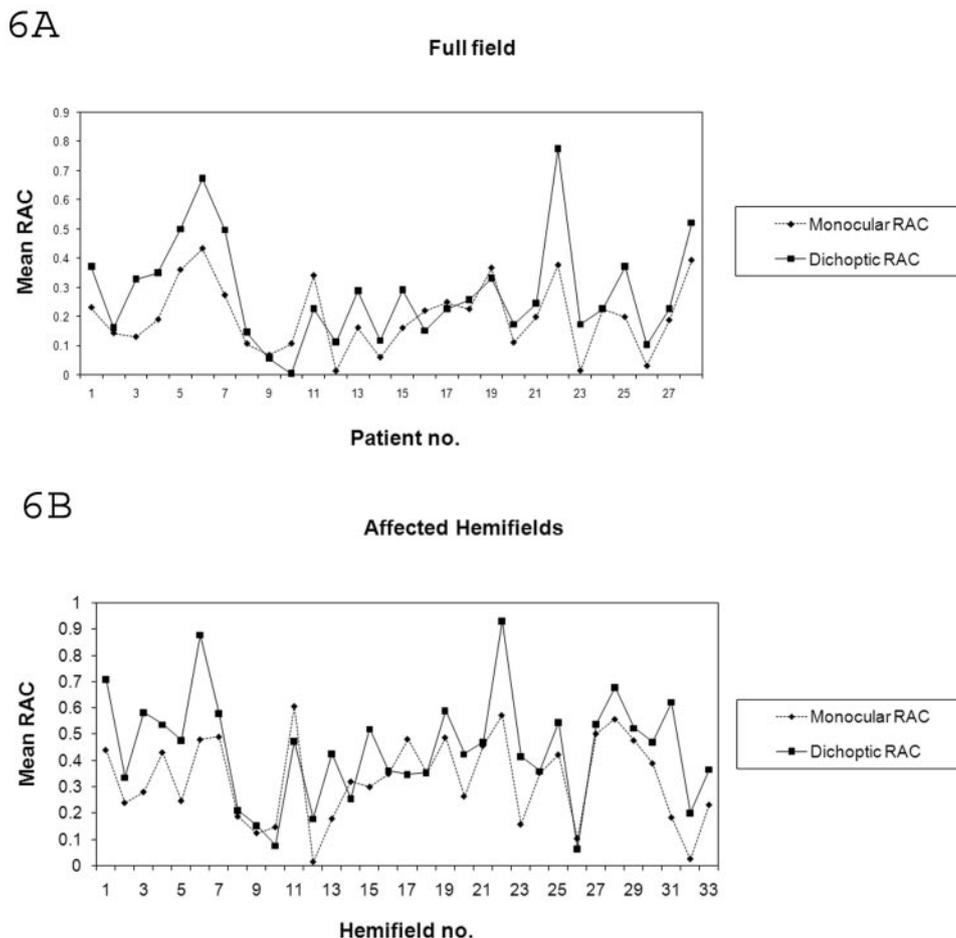


FIGURE 6. (A) Mean RAC of all segments of glaucomatous eyes ($n = 28$) on dichoptic and monocular testing showing larger RAC values on dichoptic testing. (B) Mean RAC of hemifields with HFA defects ($n = 33$) on dichoptic and monocular testing also showing larger RAC values on dichoptic testing.

In addition, when individual RACs were averaged across perimetrically affected hemifields, significantly larger values were demonstrated on dichoptic compared with monocular testing. In contrast, averaged RAC values in healthy subjects were significantly smaller on dichoptic stimulation. Furthermore, in one fifth of all patients tested (five patients), dichoptic mfVEP detected scotomas in hemifields that were normal on HFA. Four of the five defects were identified by asymmetry analysis. In all five patients, rim changes corresponding to the additional defect were noted.

The results of the present study suggest that dichoptic mfVEP not only accurately detects perimetric losses identified by subjective visual field analysis, it may also identify early functional loss in areas as yet unaffected on HFA and monocular mfVEP. The latter appears to be the result of more sensitive detection of abnormal asymmetry between eyes using dichoptic mfVEP. This is an unexpected finding and has not been reported before. Although the basis of this phenomenon cannot be conclusively explained, two possible explanations are suggested.

First, asymmetry was significantly smaller among healthy controls when dichoptic stimulation was used, possibly because signals from both eyes were recorded under identical conditions (simultaneously). Tighter asymmetry among normals produces a narrower statistical range in the normative database, which may in turn enhance the ability of the test to detect more subtle asymmetry. Second, under binocular viewing conditions in the presence of normal binocular vision, a relatively less-defined image from an eye with early ganglion cell damage may be further suppressed by the brain when the contralateral eye provides a better image. The traces shown in

Figure 4 demonstrate this effect. Traces are suppressed in most segments on dichoptic stimulation compared with monocular testing. The other eye was normal (not shown in the figure).

Compared with monocular mfVEP, dichoptic stimulation reduces testing time by approximately 30% (7 minutes for dichoptic compared with 10 minutes for monocular testing). All patients reported good acceptance. None of the patients tested had untoward eye strain or diplopia associated with simultaneous binocular viewing. The use of identical rotating fixation targets and stationary intersegment background, together with random, briefly appearing pattern-onset stimuli, may facilitate comfortable fusion of the images presented to both eyes. Although most studies of mfVEP in glaucoma have used pattern-reversal stimulation, we chose to use pattern-onset stimulation for monocular and dichoptic tests to maintain methodological consistency. In addition to methodological issues, another advantage of pattern-onset stimulation is the production of larger signals in the central part of the field compared with pattern-reversal stimulation.²¹ This, combined with scaling of signals based on background EEG activity and the use of specialized algorithms for enhanced noise detection and filtering available in the multifocal objective perimetry (Accumap; ObjectiVision Pty. Ltd.) machine, facilitates very good signal-to-noise ratios, with 5-minute per eye recordings for monocular tests and 7.5-minute recordings for dichoptic tests.

The technique of dichoptic mfVEP is, however, not without potential limitations. Persons with disorders of binocular vision such as amblyopia or microtropia may demonstrate suppression scotomas on dichoptic testing that would confound the results of testing for another ocular abnormality. Because the

advantage of the technique is based on detection of the asymmetry of damage, it may also not be as useful for early symmetrical glaucoma when both eyes are affected to relatively the same extent.

In conclusion, this study demonstrates the ability of dichoptic mfVEP to detect functional loss in glaucoma. It exploits the superior sensitivity of binocular vision to subtle unilateral defects and demonstrates its possible role as a new tool to detect early glaucomatous damage while also reducing testing time. Detailed investigation into the repeatability of this technique and its diagnostic performance in early glaucoma, in preperimetric glaucoma, and in the early detection of progression are required and will be the subject of future studies.

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