The Visual Evoked Potential in Glaucoma and Ocular Hypertension: Effects of Check Size, Field Size, and Stimulation Rate

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In order to determine the optimum stimulus conditions for the detection of optic nerve damage due to glaucoma and ocular hypertension, checkerboard pattern reversal visual evoked potentials (VEPs) were recorded from 20 glaucoma patients, 20 ocular hypertensive patients, and 20 age-matched normals. Two check sizes (12' and 48'), two field sizes (14° and 28°), and two alternation rates (1.9 and 7.5 alt/sec) were used. All subjects had visual acuities of 20/40 or better in each eye and equal pupils of 2 to 5 mm diameter. The largest number of VEP abnormalities were found with large checks (48') reversing at a fast rate (7.5 alt/sec). After correcting for the effects of age, visual acuity, and pupil size, 16 of 30 eyes with glaucomatous visual field defects had abnormally long VEP latencies under this condition (beyond the 99% confidence limit of the normal subjects). Nine of 40 ocular hypertensive eyes also had abnormally long latencies. Increased pattern VEP latency was significantly correlated with both the severity and location of visual field defects and the degree of cupping and pallor of the optic disc. VEP latency was not significantly related to intraocular pressure. Invest Ophthalmol Vis Sci 24:175–183, 1983

The pattern visual evoked potential (VEP) has been shown to be sensitive to optic nerve lesions caused by demyelinization,[1] ischemia,[2] and compression of the anterior visual pathway.[3] Glaucoma has also been reported to affect the VEP by causing both reductions in amplitude[4,5] and increases in latency.[4,6–10] Increased pattern VEP latency has been associated with optic disc cupping[5] and the presence of visual field loss.[4,6,8] In ocular hypertension the pattern VEP has been normal[9] unless eccentric viewing[6] or provocative techniques have been employed.[11–12]

In those nonprovocative studies in which abnormally long VEP latencies were obtained it is not clear whether the results were due, in part, to the confounding effects of miotic pupils,[9,13] advanced age,[14] or reduced visual acuity.[15] All three of these factors can cause VEP latency increases. The one study that carefully controlled for the effects of these three variables[8] reported a small group difference in relative interocular VEP latency for glaucoma patients and normal control subjects.

The purpose of the present study was to obtain VEP latencies for various stimulus conditions in carefully selected groups of ocular hypertensive and glaucoma patients and visually normal controls while controlling for the confounding effects of pupil size, age, and visual acuity.

Materials and Methods

Subjects

All subjects were free from neurologic disease, had clear media, visual acuities of 20/40 or better in each eye, and equal pupils of 2 to 5 mm diameter. The 60 subjects formed three groups of 20 subjects each, as described below.

Group 1: Normal controls. This group consisted of ten volunteers (five men and five women) less than 50 years of age ($\bar{x}$ = 30 years) and ten volunteers (six men and 4 women) older than 50 ($\bar{x}$ = 63 years). All of these subjects had normal fundi and discs, full and normal visual fields as measured on the Goldmann perimeter by static and kinetic methods, and ocular pressures less than 21 mmHg as measured by the Goldmann applanation tonometer. Stereoscopic fundus photographs were taken with the Donaldson stereoscopic fundus camera[16] from six of these subjects.

Group 2: Ocular hypertensives. This group consisted of 20 patients (8 men and 12 women), with a mean age of 51 years. All had full and normal visual fields, open angles, and ocular pressures above 21 mmHg on at least two occasions. Five of these patients were taking timolol and/or epinephrine drops. Stereoscopic fundus photographs taken with the Donaldson camera were obtained from 19 of these patients.

Group 3: Glaucoma patients. Sixteen of these patients had chronic simple (open-angle) glaucoma: ocular pressures above 21 mmHg on two or more occasions, open angles as observed by slit-lamp gonioscopy, increased cupping and pallor of the optic disc, and glaucomatous visual field defects. One had low tension glaucoma and three had chronic angle-closure glaucoma. Ten of these patients (three men and seven women), with a mean age of 54 years, had field losses in one eye only, including nasal step (four eyes), paracentral scotoma (one eye), arcuate scotoma (three eyes), double arcuate scotoma (one eye) and one quadrant loss (one eye). The visual fields from the ten fellow eyes were full and normal; two of these fellow eyes were ocular hypertensive. These patients had been diagnosed as having glaucoma for an average of 20.7 months. The other ten patients (five men and five women), with a mean age of 58 years, had field defects in both eyes, including nasal step (six eyes), paracentral scotoma (four eyes), arcuate scotoma (four eyes), one quadrant loss (four eyes), and two quadrant loss (two eyes). These patients had been diagnosed as having glaucoma for an average of 40.7 months. Fifteen of the 20 glaucoma patients were using one or more ocular medications: ten patients were using timolol, nine pilocarpine, six epinephrine, and seven were taking either carbocol, acetazolamide, or methazolamide. One unmedicated patient reported smoking marijuana regularly. Five were not treated because their glaucoma had only recently been diagnosed. Stereoscopic fundus photographs taken with the Donaldson camera were obtained from 19 of these patients.

Ocular Examinations

After the VEP recording session, all of the subjects received complete ocular examinations, which included static and kinetic perimetry with a Goldmann perimeter, tonometry with the Goldmann applanation tonometer, gonioscopy, and tonography. One of us (BS) estimated the percent area of the optic disc that appeared cupped and pale.[17]

Stimuli

Visual evoked potentials were obtained by instructing the subject to fixate a small red spot in the center of a 20 × 25 cm television screen on which a reversing checkerboard pattern was displayed. The subjects viewed this display from 1 m for the small field conditions (11 × 14 degrees), and from 50 cm for the large field conditions (22 × 28 degrees). The mean luminance of the display was 1.9 log cd/m^2. The contrast of the checks was 0.84.

Procedure

After the subjects signed an informed consent form and the application of the electrodes, they were seated in an electrically shielded, darkened cubicle at a chin rest and wore their optical corrections when necessary. After an initial binocular trial, monocular VEPs were recorded, first from the far viewing distance (small field) and then from the near distance (large field). The two check sizes were first presented at the slow alternation rate (1.9 alt/sec), which elicits a transient response, and then at the fast rate (7.5 alt/sec), which elicits a steady state response.[18] All subjects received the 12 conditions in the same order. The recording session lasted about 30 min. Nine of the glaucoma patients were asked to return to the laboratory to take the Farnsworth-Munsell 100 hue color arrangement test and another VEP recording session. VEPs were obtained while viewing the 48' checks through neutral density filters that attenuated the luminance of the screen by .5, 1.0, and 1.5 log units. A 2-mm artificial pupil was used to eliminate the effects of changes in pupil size as a function of luminance changes of the display.

Visually Evoked Potentials

The occipital EEG was derived from a 9-mm goldcup electrode placed 1 cm anterior to the inion on the midline (near Oz) and referenced to one earlobe; the other earlobe was grounded. Responses were amplified with half amplitude bandpass settings of 1 and 35 Hz for the 1.9 alt/sec conditions and 1 and 50 Hz for the 7.5 alt/sec conditions. The amplified potentials were digitized for 419 msec with a dwell time of 410 microseconds and were averaged online with the computer. Averages of either 64 or 128 accumulations were stored on a diskette. The computer was programmed to reject automatically trials containing abnormally large transients. The experimenter released a hand-held switch that interrupted recording if the subject experienced any difficulty maintaining fixation on the center of the display.

Measurements and Statistical Procedures

P_1 latency for the VEP waveforms collected at the slow alternation rate (1.9 alt/sec) was measured by
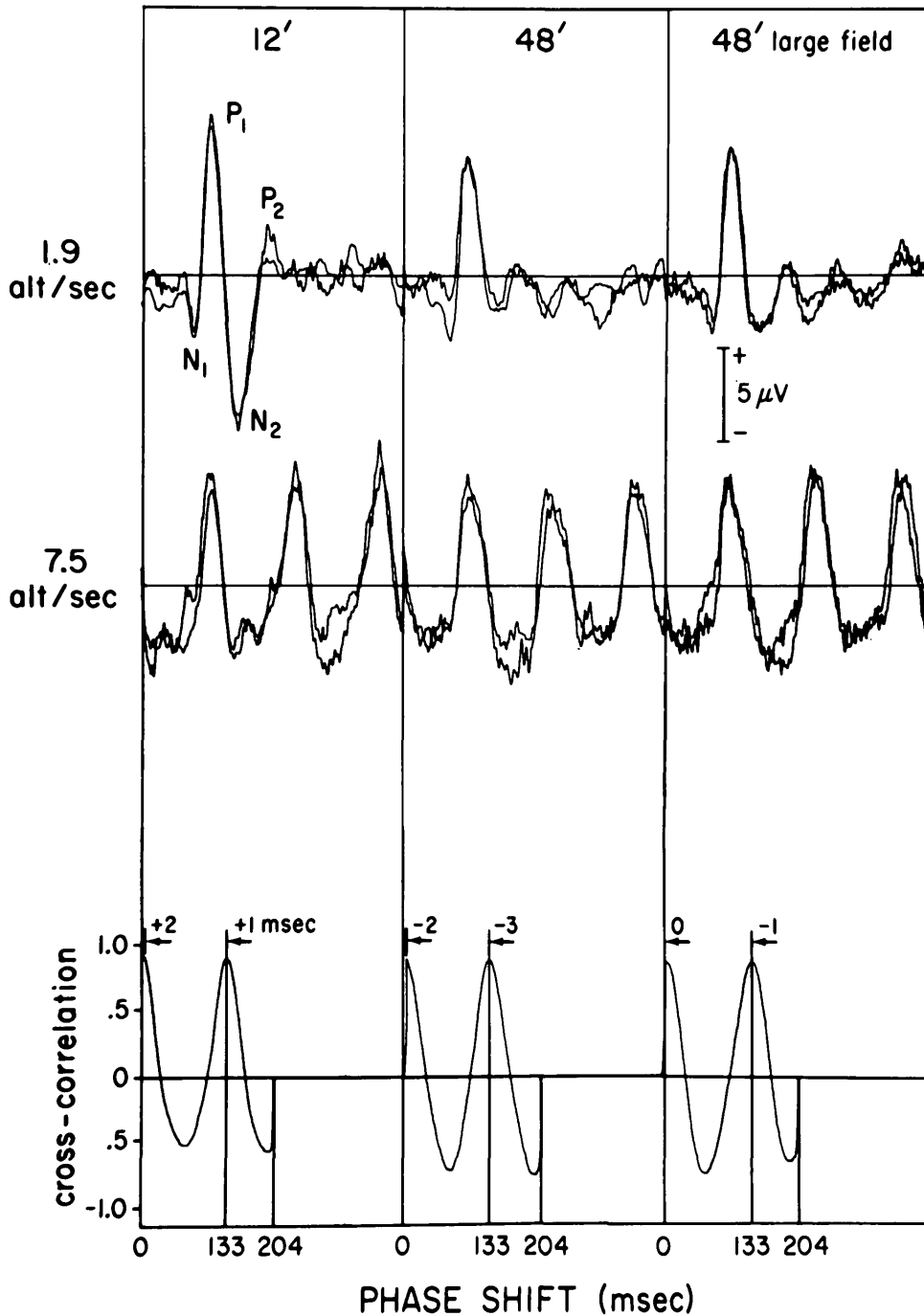
Subject GM
(young normal)

Fig. 1. Transient (1.9 alt/sec) and steady-state (7.5 alt/sec) pattern reversal VEP waveforms from a normal subject. Monocular VEPs from each eye have been superimposed. Bottom tracings are the cross-correlation functions obtained when the steady state VEPs from each eye are compared (see text). For this subject there is a 2–3 msec phase difference between the two eyes.

visual inspection with the aid of a software cursor. An objective time-lag cross-correlation procedure[19] was used to determine the phase shift (in msec) from the steady state VEPs obtained with the faster alternation rate (7.5 alt/sec). Cross-correlation functions were generated by iteratively calculating the corre-lation between two VEP waveforms (calculated from the first half of each waveform due to our digitizing conventions) while one was shifted forward in time relative to the other. The relative phase (latency) of the two waveforms was taken as the point at which this function peaked (i.e., the highest correlation; the

point of optimum alignment). Each VEP was also compared to "template" VEPs, created by averaging the VEPs from the normal subjects.

Visual fields of glaucoma patients were categorized according to the severity of the defect (0 = full and normal, 1 = nasal step, 2 = paracentral scotoma, 3 = arcuate scotoma, 4 = 1 quadrant loss, 5 = 2 quadrant loss) and related to VEP latency using the Spearman correlation coefficient (r_s). Visual loss was also quantified by (a) measuring the shortest radius between the point of fixation and the Goldmann O-4e and V-4e isopters, and (b) by determining the area of O-4e isopter with a planimeter.[20] The central 2° to 15° of the visual field was tested statically for scotomas at 100 locations by probing with a target whose luminance was chosen so that its kinetic isopter encompassed the blind spot. Pupil sizes were estimated at the beginning of the recording session by matching them with known pupil areas printed on a near vision card. Subjects were selected so that there was no significant difference between the groups in terms of their median age (Kruskal-Wallace $X^2 = 1.67$, df $= 3$ $P < 0.65$). Unless specifically stated otherwise, all statistical tests are two-tailed.

Results

Because there were different proportions of abnormal pattern VEPs obtained from ocular hypertensive patients, glaucoma patients with uniocular field defects, and glaucoma patients with field defects in both eyes, we have described the results from each of these groups separately. We could find no consistent difference between the VEPs of patients whose field defects were of different etiology, so we have grouped the four patients with angle-closure and low-tension glaucoma with the open-angle glaucoma patients.

Transient VEPs

At the slow stimulation rate (1.9 alt/sec) the normal VEP consisted of up to four separate peaks: an initial, small amplitude negative peak (N_1) at about 80 msec, followed by a large positive peak (P_1) at about 110 msec. A second negative peak (N_2) occurred at approximately 140 msec, followed by a second positive peak (P_2) at about 200 msec. Since only P_1 was unambiguously identified in the waveforms of all subjects under all conditions, only the latency of this peak will be described.

For normal subjects both the amplitude and latency of P_1 were similar for the two eyes (Fig. 1, upper tracings). In contrast to this, most glaucoma patients showed a latency difference between the two eyes. The upper tracings in Figure 2 show the VEP wave-

forms from a subject with open-angle glaucoma in the left eye. The amplitude of the response from the affected eye was reduced, and the latency was prolonged approximately 20–29 msec, depending on the stimulation condition employed. The maximum delay that we have observed in a glaucoma patient was 44 msec using transient stimulation.

Steady-State VEPs

The middle tracings of Figure 1 (normal subject) and Figure 2 (glaucoma patient) show the nearly sinusoidal waveform of the steady state VEPs. The lower panels of Figures 1 and 2 show the cross-correlation functions obtained when the steady state waveforms from the two eyes (superimposed tracings) were compared. For the normal subject, the cross-correlation functions show that a phase shift of only 2 to 3 msec was needed to align optimally the waveforms. For the glaucoma patient, the cross-correlation functions indicate that a 16–22 msec phase shift was needed to align the waveforms from the two eyes, ie, the VEP from the eye with glaucoma had about a 20 msec longer latency than its fellow eye.

The interocular difference in VEP latency between eyes of patients with field defects in both eyes is not a satisfactory measure of VEP delay because both eyes may have comparable latency increases. For this reason we compared the VEP obtained from each eye with a "normal template VEP." Normal template VEPs were generated for each condition by averaging together the monocular VEPs from the ten younger normal control subjects (20 waveforms for each condition). Similar templates were constructed from the VEPs for the ten older control subjects. All of the steady-state VEPs in the experiment were then compared to the normal template VEP from the appropriate condition and age group using the time-lag cross-correlation procedure.

Two examples of this procedure are shown in Figure 3. The top tracing shows the normal template VEP for 12' checks, created by averaging together the VEPs from the older normal control subjects. The VEP from one of these subjects is shown below it. To the right of this waveform is the cross-correlation function obtained when this waveform was compared to the template. A shift of between 4–5 msec was required to align the two waveforms. The lowest tracing is a poor quality record obtained from a glaucoma patient. The high noise level in this record makes it difficult to determine latency by visual inspection. However, the cross-correlation function (right) showed clear peaks at 0 and 7 msec, indicating that this patient's VEP was within normal limits.
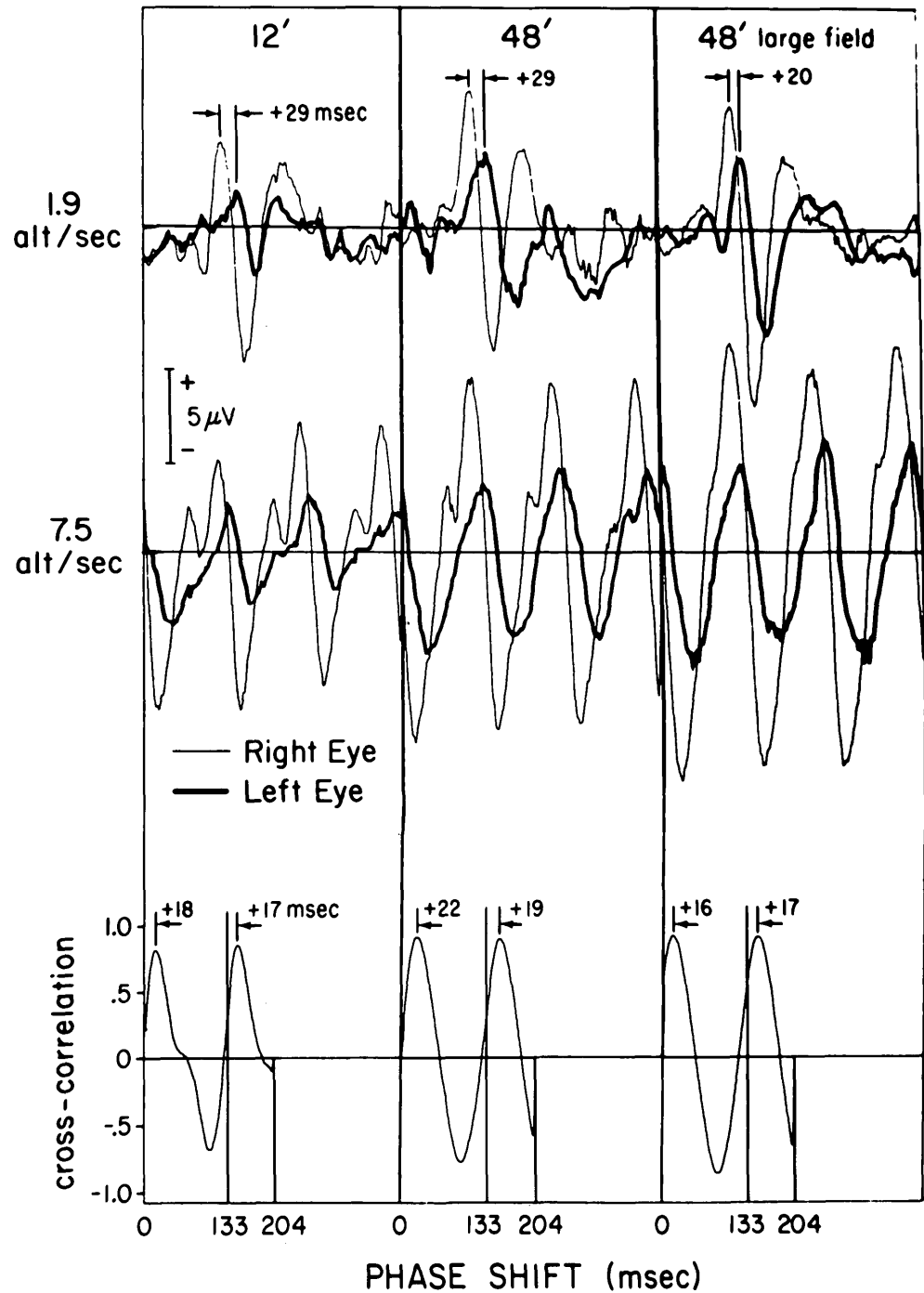
Subject JB
(open angle glaucoma left eye)

Fig. 2. Transient (1.9 alt/sec) and steady state (7.5 alt/sec) pattern reversal VEP waveforms from a patient with open-angle glaucoma of the left eye and ocular hypertension in the right eye. Note the delay in P_1 latency from the affected left eye with transient stimulation and the phase shift in the steady-state waveforms as evidenced by the cross-correlation functions (see text). If the two VEPs were of equal phase the cross-correlation functions would peak at 0 and 133 msec, as in Figure 1.

VEP Latency and Stimulus Conditions

The proportion of eyes that had abnormally long VEP latencies is shown in Figure 4 for each of the patient groups and stimulus conditions. VEP latencies that were beyond the 99% confidence limit (+2.3 SD, one-tailed test) of the VEPs from the right eye of the older normal subjects were considered abnormally long. There were no significant differences between their right and left eyes. The 99% confidence limits at 1.9 alt/sec were 140, 125, and 120 msec for the 12' and 48' small field and the 48' large field conditions, respectively, and the mean of the normals plus 13, 8, and 10, msec, respectively, for 7.5 alt/sec.
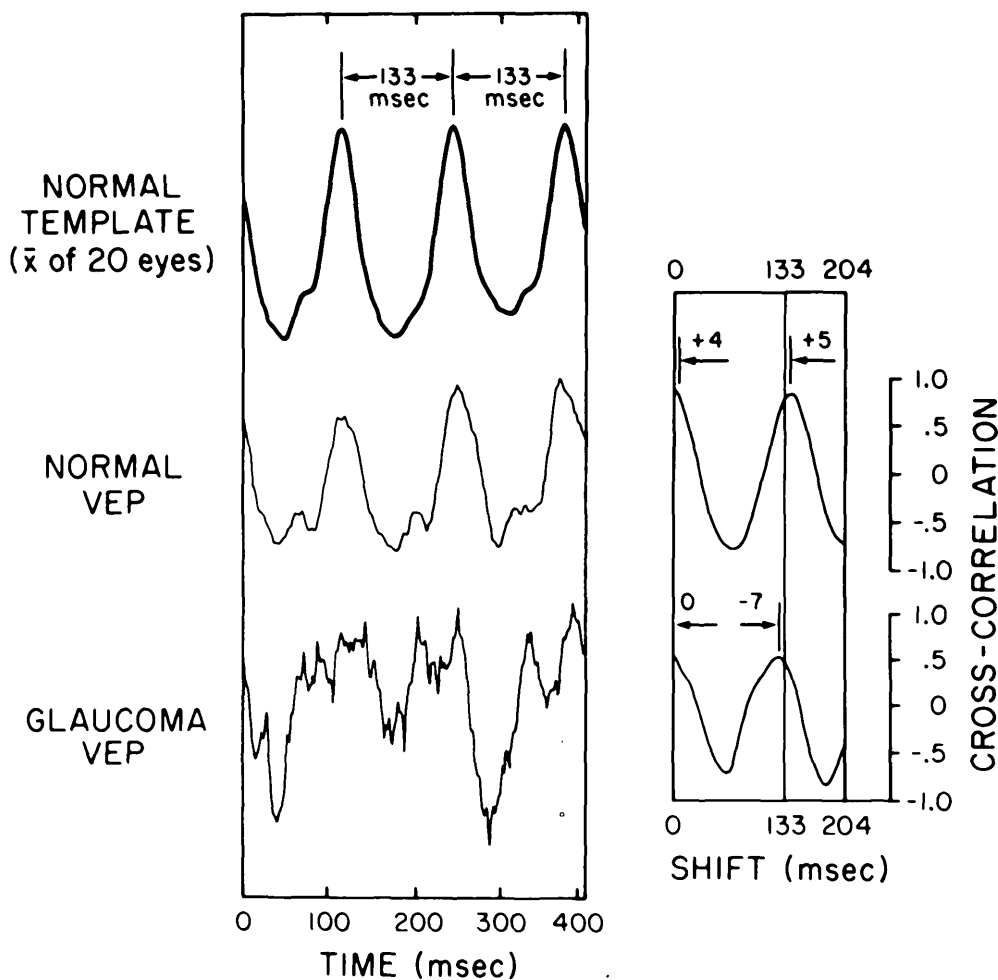
Fig. 3. Steady state VEPs of a normal and glaucomatous eye when 12' checks are presented (left). The top tracing is the normal template VEP used as a standard (see text). Right: Cross-correlation functions obtained when each of these waveforms is compared to the normal template VEP. The normal subject's VEP showed optimal alignment with the template with a shift of 4 and 138 msec, indicating that it was delayed 4.5 msec relative to the template [((4 − 0) + (138 − 133))/2 = 4.5] The cross correlation function from the glaucomatous eye peaked at shifts of 0 and 126 msec, indicating that this VEP was 3.5 msec *shorter* in latency than the template VEP [((0 − 0) + (126 − 133))/2 = −3.5]. Note that although the VEP waveform elicited by this glaucomatous eye was very irregular in form, the cross-correlation procedure gave a clear peak that was within normal latency limits.

These data were adjusted to eliminate the confounding effects of pupil size on VEP latency using the pupil size/latency function of Sokol et al.[9] All VEP latencies were adjusted to the equivalent of a 3-mm pupil.

There was a highly significant difference in the proportion of abnormal VEPs under the different stimulus conditions for both the right and left eyes of patients with field defects in both eyes ($P < .001$, Cochran Q = 32.4[21] (right eye), 29.0 (left eye), df = 5) (Fig. 4, bottom). There were no statistically significant differences in the proportion of abnormally long VEP latencies under the different stimulus conditions of either eye of the ocular hypertensive patients (Fig. 4, top) or glaucoma patients with uniocular field defects (Fig. 4, middle). This was probably due to the smaller proportion of abnormally long VEPs obtained for these two groups. The largest number of abnormally long VEPs were obtained when large checks (48') were presented at a fast alternation rate (7.5 alt/sec) in the smaller display (11 × 14 deg) for all three groups of patients. Under this stimulus condition, 16 of the 30 eyes with glaucomatous field defects had abnormally long VEP latencies. None of the VEPs from the normal subjects had abnormally

long latencies. It is of particular interest that 9 out of 40 of the eyes of ocular hypertensive patients had abnormally long VEP latencies. These nine eyes were from five patients.

VEP Latency and Field Defects

VEP latency for the 48' checks presented at the fast alternation rate in the small field was correlated positively with the severity of the field defect (r_s = .48, $P < 0.0001$, df = 58) as shown in Figure 5. The results of this categorical breakdown were supported by a quantitative analysis of the visual fields: VEP latency was negatively correlated with the distance to the O-4e isopter (r = −.46, $P < 0.01$, df = 28) and the V-4e isopter (r = −.35, $P < 0.01$, df = 29). VEP latency was also correlated negatively with the area of the O-4e isopter (r = −.43, $P < 0.01$, df = 28). All of these correlations indicate that the size and location of a visual field defect can influence VEP latency.

In spite of these significant correlations, it should be noted that nearly half of the eyes with glaucomatous field defects (14 of 30 eyes) generated normal VEPs even though many of these defects clearly en-
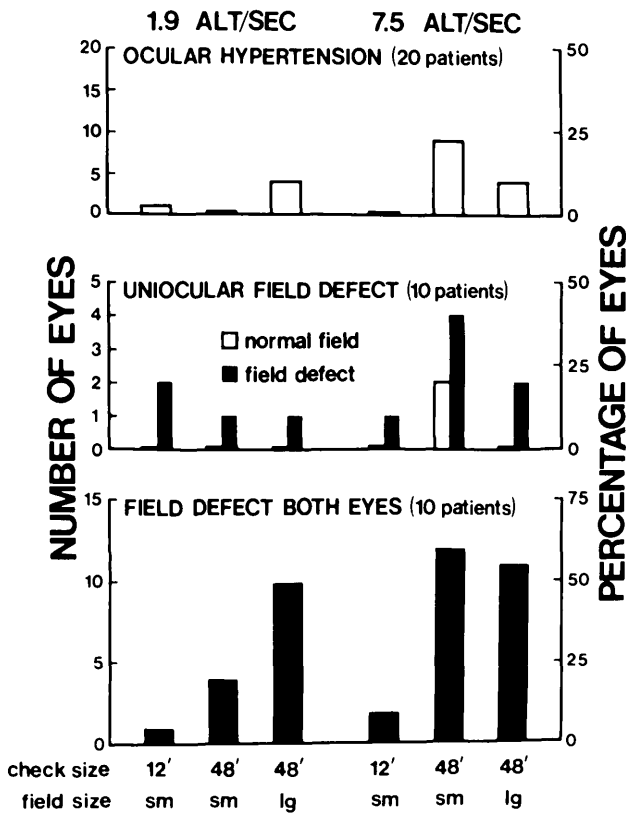
Fig. 4. The number of eyes of glaucoma patients and ocular hypertensive patients with abnormally long VEP latencies. The greatest number of abnormal VEPs were obtained when large checks (48') were presented at a fast alternation rate (7.5 alt/sec) in the smaller display (11° X 14°). sm—small, lg—large.

(either abnormally long in latency or unrecordable) in five of these nine patients. Seven of the nine had abnormal color discrimination, suggesting abnormal macular function even in the presence of a normal VEP.[22] Of the 16 eyes with glaucoma that had abnormaily long VEP latency, 10 had field defects that clearly entered the area of the macula. For the other six eyes with abnormally delayed VEPs, there was no evident field defect to which the delayed responses could be attributed since no scotomas were found with static testing of the macula.

VEP Latency and Ocular Chracteristics

There was a significant positive correlation between VEP latency and optic disc cupping ($r_s = .48$, $P < 0.001$, df = 42), and between VEP latency and optic disc pallor ($r = .32$, $P < 0.05$, df = 45). Interocular differences in cupping and pallor were not correlated significantly with interocular differences in VEP latency. There was no significant correlation between VEP latency, and intraocular pressure measured on the day that the VEPs were obtained either for the 40 subjects that were not taking ocular hypotensive medications or for all 60 subjects in the study.

Discussion

The pattern VEP was abnormally delayed in over half of 30 eyes with glaucomatous defects and in 9 of 40 ocular hypertensive eyes. This difference between normal control subjects and patients was maximized when large checks (48') were presented at a fast reversal rate (7.5 alt/sec) in a small display (11 X 14 degrees).[8] Increased VEP latency was not associated with intraocular pressure levels, but was associated with the degree of cupping and pallor of the optic disc and with the severity of the field defect and its distance from fixation. These results cannot be

croached upon the macula. We performed additional tests on 9 of these patients in an attempt to understand why these patients generated normal VEPs. Reducing the intensity of the stimulus display by as much as 1.5 log units—to the range of the targets used to map the visual fields—caused abnormal VEPs

Fig. 5. Distribution of VEP latencies for normal, ocular hypertensive, and eyes with various types of field defects. Dashed line indicates 99% confidence limit (one-tailed) for ten elderly normal right eyes. There was a statistically significant tendency for increased VEP latency to be associated with more severe field defects.
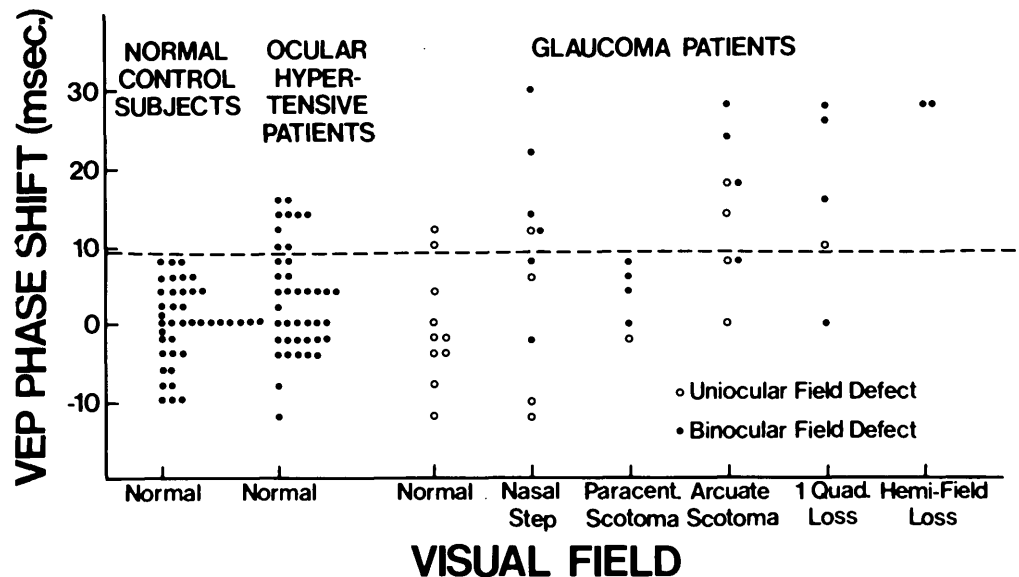
attributed to the confounding effects of miotic pupils, increased age, or reduced visual acuity.

VEP Latency and Pupil Size

Many glaucoma patients using drugs, such as pilocarpine, have very miotic pupils. A reduction in pupil diameter from 6 to 1 mm can increase VEP latency by as much as 20 msec,[9] which is as large as many of the delays we have observed with glaucoma. Previous studies that have reported higher detection rates than we have found have not mentioned whether they controlled for this effect.[5-7] Retinal luminance can be controlled with the use of: (1) pupil dilation, (2) artificial pupils, (3) neutral density filters, (4) a Maxwellian viewing system, (5) selection of subjects with a specific pupil size, or (6) post hoc latency corrections. We chose the last two alternatives. At least two studies have shown that the major increase in VEP latency related to pupil size is with small pupils, ie, less than about 3 mm in diameter.[9,13] Above this diameter pupil size has a less dramatic effect on VEP latency. Therefore, we chose to limit the range of pupil sizes in this experiment to from 2 to 5 mm in diameter. Even so, our glaucoma patients had significantly smaller pupils than our normals ($X^2 = 17.7$, $P < 0.001$, df = 3). Over this range of pupil sizes the VEP can be expected to change a maximum of about 7 msec. Even after we adjusted the data to the equivalent of a 3-mm pupil, the majority of glaucoma patients had abnormally long VEP latencies (see Fig. 5). Thus, we can conclude that the changes in pattern VEP latency that we observed were a direct effect of glaucoma and not an artifact of the small pupil size frequently associated with the condition.

VEP Latency and Age

The latency of the pattern VEP increases with age, more so for small checks than large checks.[14] To eliminate this possible confound in our data, we selected our group of normal controls so that there was no significant difference in age between them and the patients. Age has not always been controlled for in studies where between-subject comparisons have been made. For example, one study appeared to have found a large proportion of VEP latency abnormalities in their patients, but did not age-match their samples; there was more than a 30-year difference in the mean age of their glaucoma patients and control subjects.[7] When the age, acuity, and pupil size have been equated between glaucoma patients and controls,[8,9] smaller group differences have been reported.

VEP Latency and Field Defects

Although there was a general relationship between VEP latency and field defects, it is of particular in-

terest that almost half of the eyes with glaucomatous field defects in our experiment had VEP latencies that were within normal limits. There are at least two possible reasons for this result. First, the noninvolved portions of the optic nerve are probably conducting signals to the lateral geniculate nucleus and visual cortex without a delay, generating a normal latency VEP. Our finding that there is a positive correlation between the severity of the field defect and VEP latency generally supports this position: the more healthy ganglion cells present, the shorter the latency of the VEP. A more extensive analysis of the scalp distribution of the various components of the VEP in relation to the size and location of the field defect might show gross differences in these patients. Due to the retinotopic organization of visual cortex, a lower visual field loss, for example, might affect the VEP derived from an electrode placed more anteriorly, while the VEP at the location we recorded from might remain normal. Second, "absolute" scotomas that are defined with Goldmann perimetry (measured at a maximum of 1 lumen) may still retain some residual visual functioning. At the higher photopic luminance levels of the stimulus display used in this study, VEPs might still have been initiated by surviving ganglion cells within the scotoma. Data from our intensity series suggest that this might be the case with many of our glaucoma patients that had "normal" VEPs. The main problem with reducing the intensity of the stimulus is that the variability among the VEPs of normal subjects increases, yielding broader confidence limits.

In addition to the severity of the field defect, its location is also important in determining whether the VEP will be delayed.[4,6] In our data there was a significant tendency for deficits that approached the point of fixation to cause larger VEP latency increases. However, several of the eyes with abnormal VEPs did not have field defects that encroached directly upon the macula. A possible explanation of this finding is that glaucoma may act to reduce the sensitivity of ganglion cells outside of traditionally defined field defects. This is suggested by other studies that have reported abnormal color vision[22] and contrast sensitivity[23] in the presence of normal visual fields.

VEP Latency and Transient Channels

Because VEP latency increases were associated with optic discs exhibiting increased cupping and pallor, as well as more severe field defects, we conclude that increased VEP delay as we have observed here is a manifestation of optic nerve damage. This damage may not affect all ganglion cells equally, however. The finding that the larger checks presented at the

faster alternation rate yielded the largest difference between normals and glaucoma patients suggests that transient channels may be more susceptible to glaucomatous damage than sustained channels. Bodis-Wollner has reported similar findings in a glaucoma patient.[10] This is also suggested by a psychophysical study by Tyler,[24] who reported "notch" losses in flicker sensitivity at relatively high flicker rates. Atkin[23] found deficits in contrast sensitivity using patterns whose contrast changed at 8 Hz. It may be that ganglion cells comprising transient channels[25] are more susceptible to the increased pressure or ischemia hypothesized to play a role in glaucomatous damage.

VEP Latency and Ocular Hypertension

The finding that is of clinical importance is the presence of abnormally long VEP latencies in some patients with ocular hypertension. The abnormal prolongation of VEP latency in these eyes may reflect subclinical optic nerve lesions that have not been uncovered with other techniques. Post hoc evaluation of the nine ocular hypertensive eyes associated with abnormally long VEP latencies revealed no unusual clinical characteristics, including increased cupping and pallor of the optic disc, that would separate them from the 31 eyes with normal VEP latencies.

Of the several possible strategies that have been used to define VEPs in patients with glaucoma, our approach has several advantages. It is a rapid and noninvasive technique, avoiding the unknown risks of pressure elevation inherent in a provocative technique.[11,12] It was not necessary to dilate the patient's pupils, meaning that patients with narrow anterior chamber angles can be tested. The procedure requires no subjective responses from the subject, which can be a problem with some older or debilitated patients. The technique does not depend on the subject's ability to maintain excentric fixation, which is difficult to validate,[4,6] The use of relatively large checks makes the patient's visual acuity less of a factor in the results. The scoring procedure is quantitative and completely objective, avoiding the need for subjective judgments of abnormality on the part of the examiner. All of these characteristics enhance its desirability as a test for studying the VEPs of ocular hypertensive and glaucoma patients.

Key words: glaucoma, ocular hypertension, visual evoked potential, VEP.

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