The Photopic Negative Response of the Flash Electroretinogram in Primary Open Angle Glaucoma

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PURPOSE. To determine whether the photopic negative response (PhNR) of the electroretinogram (ERG) is reduced in patients with primary open angle glaucoma (POAG).

METHODS. ERGs were recorded with DTL electrodes from 62 normal subjects (16 to 82 years), 18 POAG patients (47 to 83 years) and 7 POAG suspects (46 to 73 years) to brief flashes (<6 ms), and also in a few subjects to long (200 ms) red, full-field ganzfeld flashes delivered on a rod-saturating blue background. At the time of ERG measurements, the intraocular pressures of most of the patients were controlled medically. Visual field sensitivities were measured with the Humphrey C24-2 threshold test and optic nerve head cup-to-disc ratio (C/D) was determined by binocular indirect ophthalmoscopy.

RESULTS. ERGs of normal subjects contained a slow negative potential following the a- and b-waves, the PhNR, that increased slightly in latency with age. The a- and b-wave amplitudes and implicit times of POAG patients were similar to age-matched controls. In contrast, their PhNRs were small or virtually absent. PhNR amplitudes were reduced even when visual sensitivity losses were small, and were correlated significantly (P < 0.05) with mean deviation (MD), corrected pattern SD (CPSD), and C/D across the population of POAG patients whose MD losses ranged from 1 to 13 db, CPSDs from 0 to 11 db and C/Ds from 0.6 to 0.9. PhNRs of most POAG suspects also were small.

CONCLUSIONS. PhNR amplitudes in POAG patients are smaller than those of normal subjects. PhNR amplitudes are reduced when visual field sensitivity losses are mild and become even smaller as sensitivity losses increase. There is a potential role for the PhNR in early detection and possibly in monitoring the progression of glaucomatous damage. (Invest Ophthalmol Vis Sci. 2001;42:514–522)

The flash electroretinogram (ERG) is the voltage change elicited at the cornea to a flash of light and reflects the summed electrical activity of different groups of retinal cells.1 Under light adapted (photopic) conditions when the rods are saturated, the ERG reflects the electrical activity of the cells in the cone circuits. It is well known that the initial waves of the ERG, the a- and b-waves, originate primarily from cells at early stages of retinal processing. The photopic a-wave is generated by cone photocurrents2–4 with additional contributions from depolarizing cone bipolar cells and perhaps horizontal cells.5 The photopic b-wave results from the combined activity of depolarizing and hyperpolarizing cone bipolar cells or horizontal cells and perhaps Müller cells.6

Recent studies in monkeys and cats have shown that the slow negative potential, the photopic negative response (PhNR), that follows the b-wave (and if the flash duration is long appears again after the d-wave) originates from the inner retina. The PhNR probably arises as a consequence of spiking activity of retinal ganglion cells.7–9 It is substantially reduced in eyes of macaque monkeys with experimental glaucoma when visual field defects measured by behavioral perimetry are still mild.10 The results in macaques whose retinas are very similar to those of humans raise the possibility that the PhNR may be a sensitive measure of retinal dysfunction in patients with diseases that affect the inner retina. In the present study, we investigated whether the PhNR was reduced in the ERG of patients with primary open angle glaucoma (POAG). Similar to observations in macaques with experimental glaucoma we found that PhNRs were greatly reduced in the patients’ ERGs, whereas a- and b-waves were not significantly altered. These results indicate that the PhNR holds promise for the clinical evaluation of retinal function in POAG. Results from this study have appeared previously in abstract form.10,11

METHODS

Subjects

We recorded flash ERGs from 18 POAG patients (10 females and 8 males) ranging in age from 47 to 85 years that were seen at the Optometry clinics of the University of Houston (see Table 1 for clinical details). ERGs also were recorded from 62 visually normal controls (30 females and 32 males) ranging in age from 16 to 82 years. The 18 patients met all of the following criteria for inclusion in our sample. Before any treatment, their intraocular pressure (IOP) was $\leq 21$ mm Hg on at least two consecutive occasions. Table 1 shows the highest pretreatment IOP recorded from these patients. The optic nerve head cup-to-disc ratio (C/D) as determined by binocular indirect ophthalmoscopy was $\leq 0.6$. Finally, they had reproducible visual field defects on the Humphrey 24-2 threshold test that includes at least two contiguous points in the same hemifield on the total deviation probability plot at the <2% level. These inclusion criteria are a subset of the criteria used in the Collaborative Initial Glaucoma Treatment Study.12 At the time of ERG recordings, the IOPs of all but 5 POAG patients were controlled with glaucoma medication; patients 3 and 10 had discontinued their medication and patients 4, 15, and 18 were never treated (see Table 1). Patients with ocular disease other than POAG were excluded from the study. We also recorded ERGs from 7 other patients (patients 19 through 25 in Table 1), all of whom had a history of elevated IOP but satisfied only one or the other of the remaining two inclusion criteria. We classified these 7 patients as POAG suspects.

ERGs from 18 eyes of 18 POAG patients were compared to those from 39 eyes of 39 age-matched controls (17 females and 22 males), ranging in age from 45 to 82 years. In cases where both eyes of a patient met our inclusion criteria, ERGs from the eye with the more severe visual field defects were selected for analysis. The best-corrected visual acuity of the glaucomatous eyes ranged from 20/20 to
ERG in Primary Open Angle Glaucoma

20/50, whereas for the control subjects it was 20/20 or better. The research protocol was approved by the University of Houston Committee for the Protection of Human Subjects and adhered to the Declaration of Helsinki; informed consent was obtained from each subject.

**ERG Recordings and Signal Processing**

ERGs were recorded differentially between DTL fiber electrodes\(^3\) moistened with carboxymethylcellulose sodium 1% lying in the lower cul-de-sac of each eye. Each DTL fiber was anchored with a dab of petroleum jelly near the inner canthus and electrically connected by a clip lead at the outer canthus. An adhesive silver/silver chloride EKG electrode (Sentry Medical Products, Irvine, CA), placed on the forehead served as the ground. Pupils were fully dilated (8 to 9 mm in diameter) with tropicamide (1%) and phenylephrine hydrochloride. Full-field stimulation was produced with a ganzfeld by rear illumination of a concave white diffuser (35 mm in diameter), positioned very close to one eye. Subjects maintained fixation with the nontested eye. Subjects maintained fixation with the nontested eye.

**Visual Stimulation**

Full-field stimulation was produced with a ganzfeld by rear illumination of a concave white diffuser (35 mm in diameter), positioned very close to one eye. Subjects maintained fixation with the nontested eye. Stimuli were red flashes of brief duration (<6 ms). In a few subjects, long duration (200 ms) stimuli also were used. flashes were produced by light emitting diodes (LEDs; peak output, 650 nm; half-height bandwidth, 40 nm) enclosed in a metal tube with matte white surface, 50 mm from the ganzfeld surface. Flash strength was altered by varying the LED pulse duration between 0.128 and 5.12 ms. Interstimulus intervals were of adequate duration to avoid adaptive effects. Steady background illumination sufficient to saturate the rods was provided by blue LEDs (peak output, 450 nm; half-height bandwidth, 40 nm) driven by a current source controlled by a digital-to-analog converter. Scotopic luminances (cd/m\(^2\)) were calibrated using an International Light photometer (model IL1700; Newburyport, MA) with CIE scotopic correction filters. Photopic luminance was calibrated using a Minolta spectroradiometer (model CS1000; Minolta Camera Co., Ltd., Osaka, Japan). Scotopic trolands (scot td) for the 200-millisecond red stimulus, and photopic trolands (phot td) for the 200-millisecond red stimuli, and photopic troland seconds (phot td · s) for the brief flashes were calculated for a pupil diameter of 9 mm, without a correction for the Stiles-Crawford effect. These stimuli were se-

### Table 1. Summary of Clinical Findings in the Primary Open Angle Glaucoma Patients

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Visual Acuity</th>
<th>IOP* (mm Hg)</th>
<th>MD† (dB)</th>
<th>CPSD‡ (dB)</th>
<th>C/D§ Horizontal</th>
<th>C/D§ Vertical</th>
<th>Medication</th>
<th>PhNR Amplitude (μV)</th>
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<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>M</td>
<td>20/20</td>
<td>20/20</td>
<td>-4.8</td>
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<td>0.65</td>
<td>Timoptic</td>
<td>8.9</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>F</td>
<td>22</td>
<td>20/20</td>
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<td>Xalatan</td>
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<tr>
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<td>20/25</td>
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<td>0.4</td>
<td>0.4</td>
<td>Xalatan</td>
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</table>

POAG patients (Subjects 1 to 18) and Suspects (Subjects 19 to 25) separated by a double line.

* Highest intraocular pressure before treatment.
† Mean deviation in decibels.
‡ Corrected pattern standard deviation in decibels.
§ Optic nerve head cup-to-disc ratio.

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\(^3\)最高的眼内压（mm Hg）
\(^\dagger\)平均偏差（dB）
\(^\ddagger\)修正的模式标准差（dB）
\(^\S\)视神经杯状比

**Declaration of Helsinki:** Informed consent was obtained from each subject.
lected because they were similar to those used in the study of macaque photopic ERG and the effects of experimental glaucoma that motivated the present one. The stimuli are particularly effective in eliciting the PhNR; alternative stimulus conditions are addressed later.

RESULTS

Normal Photopic ERG Responses

Figure 1 shows ERG recordings from three normal subjects (16, 51, and 79 years of age), encompassing the age range of the normal subjects in the present study. Although the three normal subjects whose ERGs are illustrated in Figure 1 were females, their ERGs are representative of both males and females as the ERGs of the two sexes were not distinguishable.

For all flash intensities, the ERGs were composed of a- and b-waves followed by a slow negative potential, the photopic negative response (PhNR). The amplitudes of all three potentials grew in size with increasing stimulus intensities; and the b-wave and PhNR generally saturated at the highest intensity tested (2.0 log phot td s). PhNRs were present in the ERGs of all normal subjects that we tested. Unless otherwise specified, in the remaining figures and for our analyses we selected ERG responses to the flash of 1.7 log phot td s, because the PhNR is prominent at this intensity and yet not fully saturated. For the 62 normal subjects, the a- and b-waves showed changes in implicit time and amplitude with age across the population (plots not shown here). The implicit times of both the a- and b-waves measured for the standard flash increased with age (a-wave, slope = 0.04 ms/year, r = 0.69, P < 0.001; b-wave, slope = 0.08 ms/year, r = 0.64, P < 0.001). Absolute values of the a-wave amplitude measured from baseline at its implicit time and the b-wave amplitude measured from the a-wave trough at its implicit time both decreased with age (a-wave, slope = −0.07 μV/year, r = −0.31, P < 0.01; b-wave, slope = −0.22 μV/year, r = −0.25, P < 0.05).

We also were interested in determining if the PhNR changed systematically with age. Unlike a- and b-waves whose peaks were well defined, the PhNR had a relatively broad trough, making it difficult to determine its exact implicit time. To be more confident of the implicit time, we grouped the normal subjects in age bins (of 10 years) and averaged the ERGs of the subjects in each bin. In general, the PhNR of the group-averaged response had a more clearly defined peak than the individual responses. This is illustrated with an example in the inset to Figure 2 where the thick line represents the averaged response of the 51- to 60-year-old age group for the standard intensity flash and the thin line represents the individual response of a 51-year-old female.

The average implicit times for each age group (open symbols) are plotted as a function of mean age in Figure 2 (the number of subjects in each group is shown in parentheses). Because there was only one subject less than 20 years old (the 16-year-old illustrated in Fig. 1), we did not include her ERG data. Figure 2 shows that the PhNR implicit time increased with age; the difference in the implicit time of the 21 to 30 and 71 to 80 year age groups was 8 milliseconds. The best fitting
linear regression of the data shows a strong correlation between PhNR implicit times and age (slope = 0.15 ms/year, \( r = 0.9, P < 0.005 \)). Similar results were obtained for PhNRs measured at other stimulus intensities reinforcing the importance of taking age into consideration while comparing the PhNR of patients to those of normal subjects. The PhNR amplitudes measured from baseline at the times interpolated from the best fitting line in Figure 2 showed a shallow decline with age but the correlation was not statistically significant (slope = \(-0.08 \mu V/\text{year}, r = -0.24, P < 0.07 \)). We examined the test-retest variability of the PhNR (for 6 normal subjects) and found that on repeated recording, the PhNR amplitudes were on average within \( \pm 15\% \) of the mean amplitude.

**ERG Responses in POAG**

Figure 3 shows the ERG of a 63-year-old patient (No. 6 in Table 1) with POAG (right) and an age-matched control subject (left). The visual fields of the patient (not shown) indicated substantial defects at the time of ERG measurement, the MD was -16.2 dB (\( P < 0.5 \% \)) and CPSD was 11 dB (\( P < 0.5 \% \)). The patient’s C/Ds were 0.9, both in the vertical and horizontal meridians, indicating a severe loss of ganglion cell axons. The age-matched control had normal visual field sensitivity and a normal C/D (0.3). The PhNR was reduced considerably in the patient compared to the control subject. A small positive deflection that is normally present on the falling edge of the b-wave at the higher intensities (1.1 log phot td · s and above) emerged as a more prominent wave. In contrast to the PhNR, the a- and b-waves from the glaucomatous eye were in the normal range. The findings illustrated for this patient were typical of those for the POAG patients.

PhNR amplitudes (standard intensity flash) of all the POAG patients (filled circles) and age-matched control subjects (open circles) are plotted as a function of age in Figure 4. The amplitudes have been expressed as absolute values of the negative-going responses. For comparison, PhNR amplitudes from the 7 POAG suspects also are shown (filled circles with center dot). Figures 5A and 5B show the absolute values of the a- and b-wave (squares and triangles) amplitudes of the 18 POAG patients and age-matched suspects (open symbols), in the same age range (open symbols) plotted as a function of age. The thick and thin lines represent the best-fitting linear regressions through the patient \((r = -0.24, P < 0.07)\) and control \((r = -0.26, P < 0.3)\) data, respectively. The PhNR amplitudes were measured from baseline at times specified by the straight line fit to the data in Figure 2.

Most of the patients were medically treated at the time of the ERG recordings, raising a potential inadequacy in the untreated normal control group. However, the POAG population contained 5 patients who were not receiving medical treatment. The PhNR amplitudes for these patients for whom the glaucoma variable was better isolated were well distributed across the range for the other patients (see Table 1). Further, individual treated patients were using medications with different mechanisms of action: \( \beta \)-blocker (Timoptic, Betagan, Beoptic), an \( \alpha \)-agonist (Alphagan) and a prostaglandin inhibitor (Xalatan).

We compared the \( y \)-intercepts and slopes of the best-fitting lines through the patient (thick lines) and age-matched control (thin lines) data illustrated in Figures 4 and 5. The difference in the \( y \)-intercepts for the PhNR amplitudes approached significance \(( P < 0.055)\), whereas all other differences were not significant \(( P \geq 0.3)\). Comparisons of the PhNR implicit time of patients and age-matched control subjects were not feasible because it was difficult to determine the implicit times of reduced PhNRs. However, qualitatively, we did not discern obvious differences in PhNR implicit times between individual patients and their age-matched controls.

As shown in Figures 4 and 5, there was substantial interindividual variation of PhNR and b-wave amplitudes in normal subjects. If the PhNR and b-wave amplitude varied similarly for each subject, then the ratio of the two amplitudes would show less variability and might prove to be a more useful measure than absolute PhNR amplitude. However, b-wave amplitudes were not significantly correlated with PhNR amplitudes, and
the b-wave to PhNR ratios were actually less effective than PhNR amplitude in separating glaucomatous eyes from normal eyes (data not shown).

Sensitivity and Specificity of the PhNR in POAG

Receiver operating characteristic (ROC) curves were used to evaluate the effectiveness of the PhNR amplitude in distinguishing between normal and glaucomatous eyes. Figure 6 shows ROC curves for PhNR, a-wave and b-wave amplitudes. These curves were generated by plotting sensitivity versus 1-specificity calculated for different cutoff values (or criterion responses). Sensitivity shows how well the PhNR amplitude performs as a test for detecting glaucoma. High sensitivity indicates that the test has a low false-negative rate. Specificity shows how well the PhNR amplitude identifies those subjects who do not have the disease. High specificity indicates that the test has a low false-positive rate. The cutoff values were selected in decrements of 1 μV from the range of values pooled from all POAG patients and control subjects to the standard 1.7 log phot td·s flash. As can be seen in Figure 6 and Table 2, the area under the curves (AOC) was largest (0.96) for the PhNR (circles) and smallest (0.56) for the b-wave (triangles). Correspondingly, PhNR and b-wave amplitudes had the smallest and largest general error rates (GER), which reflects the total percentage of false-positives and false-negatives (see Table 2). The optimal cutoff amplitude for the PhNR indicated by lowest GER, was 13 μV. The sensitivity and specificity associated with this cutoff amplitude were 83% and 90%, respectively, indicating that the criterion amplitude of 13 μV can quite effectively distinguish glaucomatous from normal eyes. These results show that of the three ERG potentials studied, only the PhNR provides good discrimination between normal subjects and POAG patients.

PhNR Versus Visual Field Indices and Cup-to-Disc Ratio

The scatter plots in Figures 7A and 7B respectively show the absolute values of the PhNR amplitudes of the POAG patients plotted as a function of two visual field indices, mean deviation (MD) and corrected pattern SD (CPSD). PhNR amplitudes declined with both MD and CPSD and demonstrated a low but

![Figure 5](image-url)  
**Figure 5.** (A and B) Amplitudes of a-waves (squares) and b-waves (triangles) for a flash intensity of 1.7 log phot td·s for all of the primary open angle glaucoma patients (filled symbols) and control subjects in the same age range (open symbols) plotted as a function of age. The thick and thin lines represent the best fitting straight lines through the patient and control data, respectively. For a- and b-wave amplitudes of control subjects, r values were −0.31 (P < 0.01) and −0.25 (P < 0.05), respectively, and for POAG patients, r values were −0.22 (P < 0.4) and −0.19 (P < 0.44), respectively. (C) Implicit times for a-waves (squares) and b-waves (triangles) for a flash intensity of 1.7 log phot td·s for all of the primary open angle glaucoma patients (filled symbols) and control subjects in the same age range (open symbols) plotted as a function of age. The thick and thin lines represent the best fitting straight lines through the patient and control data, respectively. For a- and b-wave implicit times of control subjects, r values were 0.7 (P < 0.0005) and 0.64 (P < 0.0005), respectively, and for POAG patients, r values were 0.39 (P < 0.11) and 0.65 (P < 0.005), respectively.

![Figure 6](image-url)  
**Figure 6.** Receiver operating characteristic (ROC) curves for PhNR, a- and b-wave amplitudes (circles, squares, and triangles, respectively) for a flash intensity of 1.7 log phot td·s.
Origin of PhNR Reduction in POAG

In the present study, we found that the PhNR can be markedly reduced in the ganzfeld ERG of patients with primary open angle glaucoma when their a- and b-waves appear normal. This finding is similar to previous observations in macaques with experimental glaucoma. The specific reduction in the ERG of the PhNR indicates that pathologic changes in primary open angle glaucoma, at least in the early stages, are associated with the retinal structures that are involved in generating the PhNR.

There are numerous reports of alterations in retinal ganglion cells and their axons in glaucomatous eyes or eyes with elevated IOP and more recently changes in glial cells have been described. When considering these reports in the context of animal studies investigating the retinal origins of the PhNR cited later, it seems likely that the reduction of PhNR in POAG patients is associated with the reduced or altered activity of both retinal ganglion and glial cells.

In macaques, in addition to the effects of experimental glaucoma, the PhNR also is reduced by intravitreal injections of tetrodotoxin (TTX). TTX is a voltage-gated Na\(^+\)-channel blocker that eliminates spiking activity in amacrine (interplexiform) and retinal ganglion cells. More distal retinal neurons traditionally have not been thought to produce Na\(^+\)-dependent spikes, and TTX is not known to have direct effects on their activity. Of the spiking neurons in the retina, only the ganglion cells (and their axons) are generally believed to be affected by experimental glaucoma (but see Ref. 32). This suggests that the PhNR arises from the spiking activity of retinal ganglion cells.

In related experiments in cats (which also have a TTX-sensitive PhNR), the PhNR, recorded intraretinally with micro-electrodes, was found to be most prominent near and within the optic disc where retinal ganglion cell axons dominate the tissue. Further, intravitreal injection of Ba\(^{2+}\), an ion that blocks K\(^+\) channels in glia,3,34 and blocks glial-mediated responses in the ERG (e.g., Ref. 35) selectively eliminated the PhNR from the photopic ERG. Its removal by Ba\(^{2+}\) suggests that the PhNR is mediated by K\(^+\) buffer currents in glia that are activated by an increase in extracellular [K\(^+\)] resulting from the spiking activity of retinal ganglion cell axons.

Stimulus and Recording Conditions for Eliciting the PhNR

An interesting issue is why the PhNR and its alterations in the photopic ganzfeld flash ERG of POAG patients were not described previously. Part of the reason may lie in the stimulus conditions that were used. Whereas ERG studies often use broadband white test stimuli on white backgrounds, we used red test flashes on a blue background to reduce spurious responses in the ERG (e.g., Ref. 35) selectively eliminate the PhNR from the photopic ERG. Its removal by Ba\(^{2+}\) suggests that the PhNR is mediated by K\(^+\) buffer currents in glia that are activated by an increase in extracellular [K\(^+\)] resulting from the spiking activity of retinal ganglion cell axons.
Patients. Our stimuli in the present study would have missed this S-cone driven response.

Monochromatic full-field test stimuli may produce more obvious PhNRs than broadband stimuli because they provide less opportunity for inhibitory center-surround interactions in the responses of spectrally opponent retinal ganglion cells. This could enhance ganglion cell responses, and increase the PhNR. Further, when both background and flash are both spectrally broadband, more opportunity exists for light adaptation of the cone pathways that produce responses to the test flashes. If inner retinal signals are adapted by backgrounds weaker than those affecting outer retinal signals (e.g., Ref. 38), then signals originating from hyperpolarizing bipolar cells, photoreceptors, and perhaps horizontal cells rather than from ganglion cells would provide the dominant negative potentials in the ERG. Supporting this suggestion is the pharmacological evidence that distally generated negative potentials dominate in macaque photopic ERGs when full field white flashes on white backgrounds are used.6

The recording conditions in our study also might have facilitated detection of the PhNR. For instance, we did not filter low temporal frequencies as is commonplace in ERG recordings in humans; we made DC recordings that would not distort slower contributions to the ERG than the a- and b-waves. With regard to electrode placement, whereas it is quite common to make bipolar recordings of ERGs from one eye, we recorded differentially across the eyes. This recording configuration might be particularly good for PhNR recording. Consistent with this idea, in their study of the optic nerve head component in the multifocal ERG, Sutter and Bearse39 pointed out that placing a reference electrode on the nonstimulated eye provides a conducting pathway for the optic nerve head component.

**PhNR Reduction and Visual Field Defects**

We observed that PhNR amplitudes could be markedly reduced when the patients' overall field losses (relative to the normal reference field, i.e., their MDs) were as small as -2 dB, and that the PhNR amplitudes showed a low (though significant) correlation with visual field indices (see Figs. 7A and 7B). One possible explanation for the correlations not being higher could be that the ganzfeld ERG reflects reduced ganglion cell function from a retinal area much larger than that covered by perimetric testing. The stimuli for the two tests differed in other properties, for example, wavelength, which also could have contributed to the low correlation. It is also possible that the reduced PhNR amplitude reflects in part, alterations that may not directly impact visual sensitivity, for example, early glial alterations.

We also observed a low but significant correlation between PhNR and vertical C/D in POAG patients. The increased C/D in

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**Figure 7.** (A) PhNR amplitudes (to a flash intensity of 1.7 log phot td.) for the primary open angle glaucoma patients plotted as a function of the mean deviation (MD) loss of visual field sensitivity. (B) PhNR amplitudes for the primary open angle glaucoma patients plotted as a function of corrected pattern SD (CPSD) of visual field sensitivity. (C) PhNR amplitudes for the primary open angle glaucoma patients plotted as a function of the vertical cup-to-disc ratio (C/D).
these patients indicates a loss of ganglion cell axons, and it is possible that with a more objective measure of nerve fiber layer thickness we might have obtained a better correlation. Again, however, glial alterations may have been a factor.

Effect of Age on the PhNR

The changes that we observed in the a- and b-wave implicit times and amplitudes in normal subjects corroborate previous reports of age-related changes in the photopic flash ERG. The pattern ERG (PERG), a response that is predominantly of inner-retinal origin, also has been reported to be reduced in amplitude with age (e.g., Ref. 42). We found, in addition, that the implicit time of the PhNR increases significantly with age and the amplitude tends to decrease although the latter effect was not statistically significant. Although these findings demonstrate the importance of taking age into account when studying ERG changes in disease processes, it should be noted that the age-related decrease in PhNR amplitude is not so large to preclude studies of patients with glaucoma who generally tend to be middle-aged or older.

Relation to the PERG

We have shown that reduction in PhNR amplitude is a sensitive indicator of glaucoma. Of the ERG tests currently in use, the PERG and particularly the slow negative potential that peaks approximately 95 milliseconds after each contrast reversal in the transient PERG (the N95, e.g., Ref. 43) has been shown in numerous studies to be altered in glaucomatous eyes (for reviews, see Refs. 44 and 45) and to be very sensitive for the detection of glaucoma.46 In macaques, the N95 of the transient PERG, like the PhNR of the uniform field ERG, can be removed either by experimental glaucoma or by intravitreal injections of TTX,9 indicating a common origin for the two responses. This commonality is supported by the finding in macaques that averaging of the photopic ERG responses to luminance increments and decrements of a uniform field reversed at a low temporal frequency (e.g., 1.7 Hz) quite adequately simulates the transient PERG to low spatial frequency stimuli. By virtue of canceling the linear components of the diffuse field response, the averaging isolates the nonlinear components, the largest of which was the N95 of the PERG.9

Although some care must be taken when comparing the PhNR and the PERG, it is quite likely that the PhNR in the flash ERG will be as sensitive as the N95 of the PERG in detecting glaucomatous damage. Some advantages of the PhNR over the PERG are that it is less affected by opacities in the ocular media, it does not require refractive correction, and it is a larger response than the PERG. Altogether, these results indicate a potential role for the PhNR in early detection and possibly in monitoring the progression of glaucomatous damage.

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References


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