The Pattern Electroretinogram in Glaucoma Patients with Confirmed Visual Field Deficits

Donald C. Hood,1 Li Xu,1 Phamornsak Thienprasiddhi,2 Vivienne C. Greenstein,3 Jeffrey G. Odel,2 Tomas M. Grippo,2 Jeffrey M. Liebmann,2 and Robert Ritch2

PURPOSE. To better understand the relationship between the amplitude of the pattern electroretinogram (PERG) and visual loss, measured with static automated perimetry.

METHODS. Transient PERGs were recorded in 15 patients (31–77 years) and 16 normal individuals (26–65 years). An eye was considered to have glaucomatous damage only if there was an abnormal disc, an abnormal 24-2 Humphrey visual field result (pattern stand deviation, glaucoma hemifield test, and cluster) and an abnormal multifocal visual evoked potential. All the worse (more affected) eyes of the patients and six of the better eyes met these criteria. The N95 amplitude of the PERG was measured from the positive peak (P50) at ~50 ms to the trough at ~95 ms. The ratio of N95 to P50—the N95 amplitude divided by the P50 amplitude—was also measured.

RESULTS. First, the PERG was within normal limits for 4 (26.7%) of the worse eyes. Overall, 6 (28.6%) of the 21 eyes that met the criteria for glaucomatous damage had normal PERGs on both PERG measures. Because the normal individuals were younger than the patients, an even larger number of normal PERGs might be expected with an age-appropriate control group. Second, the N95 amplitude was nonlinearly related to visual field sensitivity when sensitivity was plotted on a linear plot. Small field losses were associated with disproportionately large losses in PERG amplitude. Third, the PERG from both eyes of a patient were very similar, even when the visual fields suggested very different levels of damage.

CONCLUSIONS. These results are consistent with the view that very early damage can affect the PERG, even before the visual field shows a loss. At the same time, it is clear that patients with clear glaucomatous damage can have normal-appearing PERGs. An explanation is proposed to account for these findings.

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The problems involved in detecting glaucomatous damage with static automated perimetry (SAP) are well known. Because significant retinal ganglion cell damage can take place before SAP reveals a deficit1 and because SAP is a subjective test, the search for objective techniques continues. Recently, there has been renewed interest in a relatively old objective test, the pattern electroretinogram (PERG).

The PERG is recorded in response to a reversing black-and-white checkerboard or grating.2 The primary features of the transient PERG are labeled P50 and N95 and refer to a prominent positive peak at 50 ms (P50) and a slow, broad trough with a minimum at ~95 ms (N95). Based on the effects of different diseases, Holder3 suggested that these two peaks reflect different retinal sources. Pharmacologic dissection of the monkey PERG has identified possible sources. In particular, N95 is eliminated by tetrodotoxin (TTX), which blocks action potentials and is markedly reduced by experimental glaucoma.4 In humans, N95 is reduced by glaucoma and other diseases of the optic nerve. (For reviews of the extensive literature, see Refs. 5–9.) Together, the evidence indicates that N95 depends on action potentials generated by the ganglion cells. P50 is not affected by TTX, but it is reduced by glaucoma in monkeys and humans, although to a lesser extent than N95. Although there is more uncertainty about the origin(s) of P50, it is probably generated by the ganglion cell bodies and/or by structures distal to the ganglion cells.5–4

Although the connection between the PERG and glaucomatous ganglion cell damage is generally accepted,5–10 the PERG has not gained wide acceptance as an objective test for glaucoma. The lack of acceptance can be attributed, at least in part, to a belief that the test shows too much variability and/or is too difficult to perform well.11–19 Renewed interest in the test has been sparked by the work of Porciatti and Ventura,15 who developed a version of the PERG technique that is relatively easy to perform well.11–19 Renewed interest in the test has been sparked by the work of Porciatti and Ventura,15 who developed a version of the PERG technique that is relatively easy to implement in the clinic and that shows good reproducibility. With this technique, Ventura et al.19 reported that 52% of a group of 200 patients with suspected glaucoma (abnormal discs, but normal SAP) had abnormal PERGs. Further, the PERG correlated with known risk factors for glaucoma, leading the investigators to conclude that it may predict those patients in whom field defects will develop or progress.

Although the results of Ventura et al.19 suggest a clinical role for the PERG in detecting glaucomatous damage, other studies have shown that the PERG can be normal in patients with glaucomatous damage.5,11–19 Because we lack a gold standard for defining glaucomatous damage, these studies are open to criticism. In particular, how do we know the extent of damage or, in fact, whether glaucomatous damage was even present? To meet this criticism, we took a different approach. In common with other studies of glaucoma, the patients selected for inclusion had at least one eye with a glaucomatous disc and a field defect confirmed on SAP. However, in the present study, the local field defect on SAP had to be confirmed on a multifocal visual evoked potential (mfVEP) test as well. The mfVEP provides an objective electrophysiological measure of field topography (for review, see Ref. 20). Thus, the patients selected for study had confirmed field abnormalities in the same field location on two different tests. We can be reasonably certain that glaucomatous damage was present. Under these conditions, we find normal PERG amplitudes in some of
To avoid rim artifacts, the cluster could contain no more than one point from the outer ring of the 24-2 HVF points. 21,22 The mfVEP was considered to be abnormal if there was an abnormal cluster of points on the monocular and/or interocular test, as previously described. 23 The abnormal cluster of points on the mfVEP overlapped the cluster of points on the 24-2 HVF in the worse (more affected) eye of all patients. Table 1 contains the age, sex, and diagnosis of each patient. Both eyes were included in the analysis. Tables 1 (worse eye) and 2 (better eye) summarize the results of the HVF, mfVEP, and PERG tests.

Table 1. Field and ERG Findings in the Worse Eye of Patients with Glaucoma

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Age</th>
<th>Sex</th>
<th>Eye</th>
<th>Acuity</th>
<th>MD</th>
<th>PSD</th>
<th>GHT</th>
<th>Cluster</th>
<th>mfVEP</th>
<th>PERG</th>
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</thead>
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<tr>
<td>P1</td>
<td>OAG</td>
<td>62</td>
<td>F</td>
<td>OD</td>
<td>20/20</td>
<td>−3.81*</td>
<td>7.19*</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>P2</td>
<td>OAG</td>
<td>77</td>
<td>F</td>
<td>OS</td>
<td>20/20</td>
<td>−7.65*</td>
<td>10.15*</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>P3</td>
<td>OAG</td>
<td>72</td>
<td>M</td>
<td>OD</td>
<td>20/20</td>
<td>−7.79*</td>
<td>8.83*</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>P4</td>
<td>OAG</td>
<td>68</td>
<td>F</td>
<td>OS</td>
<td>20/25</td>
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<td>A</td>
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<td>A</td>
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<td>P5</td>
<td>OAG</td>
<td>49</td>
<td>M</td>
<td>OS</td>
<td>20/25</td>
<td>−2.97+</td>
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<td>48</td>
<td>M</td>
<td>OD</td>
<td>20/25</td>
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<td>OAG</td>
<td>65</td>
<td>M</td>
<td>OD</td>
<td>20/20</td>
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<td>NTG</td>
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<td>20/20</td>
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<td>OD</td>
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<td>OD</td>
<td>20/20</td>
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<td>11.07*</td>
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<td>8.68*</td>
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<tr>
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<td>F</td>
<td>OS</td>
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<td>−14.1*</td>
<td>16.21*</td>
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<td>A</td>
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<td>OAG</td>
<td>31</td>
<td>M</td>
<td>OS</td>
<td>20/25</td>
<td>−3.12+</td>
<td>4.18*</td>
<td>A</td>
<td>A</td>
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<tr>
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<td>NTG</td>
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<td>4.85*</td>
<td>A</td>
<td>A</td>
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<td>N</td>
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</table>

*P < 1%; +P < 5%; A, abnormal; N, normal.

Table 2. Field and ERG Findings in the Better Eye of Patients with Glaucoma

<table>
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<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Eye</th>
<th>Acuity</th>
<th>MD</th>
<th>PSD</th>
<th>GHT</th>
<th>Cluster</th>
<th>mfVEP</th>
<th>PERG</th>
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<td>−1.20</td>
<td>2.17+</td>
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<td>A</td>
<td>A</td>
<td>A</td>
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<td>OAG</td>
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<td>20/20</td>
<td>−0.93</td>
<td>1.96</td>
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<td>OAG</td>
<td>OS</td>
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<td>1.50</td>
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<td>OAG</td>
<td>OD</td>
<td>20/20</td>
<td>0.97</td>
<td>1.35</td>
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<td>OD</td>
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<td>OAG</td>
<td>OD</td>
<td>20/20</td>
<td>1.06</td>
<td>2.12</td>
<td>N</td>
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<td>N</td>
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<tr>
<td>P14</td>
<td>OAG</td>
<td>OD</td>
<td>20/25</td>
<td>−3.07</td>
<td>4.31</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>N</td>
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<tr>
<td>P15</td>
<td>OAG</td>
<td>OS</td>
<td>20/20</td>
<td>−1.56</td>
<td>1.83</td>
<td>N</td>
<td>N</td>
<td>N</td>
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*P < 1%; +P < 5%; A, abnormal; B, both; N, normal.
on the ipsilateral canthus. Stimulation and recording was controlled by an Espion System (Diagnosys, Boston, MA) with cutoffs at 1.25 and 100 Hz. Three recordings were obtained, each consisting of 250 trials. The records shown are the average of the three recordings.

Stimuli

The stimulus for the PERG was a 48° by 48° pattern-reversing checkerboard. The black-and-white checks, 0.8° on a side, had a mean luminance of 50 cd/m² and a contrast of 99%. The pattern reversed at a rate of four reversals per second. These values are all close to those suggested by ISCEV (International Society for Clinical Electrophysiology of Vision) standards. The size of the field was larger than that often used for clinical tests with the PERG. However, it is the size recommended for testing patients with glaucoma and has the additional advantage that it is approximately the same size as the mfVEP and HVF displays. The display was viewed at the same distance as the HVF display, and the individual wore the same corrective lens for each test.

RESULTS

PERGs in the Normal Range

Figure 1A shows a typical PERG with its two prominent waves, P50, the positive peak at ~50 ms, and N95, the negative trough at ~95 ms. The PERGs for both eyes of all 16 control subjects are shown in Figure 1B. To assess ganglion cell function, we measured the amplitude of N95. The ISCEV standards recommend measuring the distance between the peak of P50 and the trough of N95 as shown in Figure 1A, labeled N95. The N95 amplitudes in the control individuals are plotted on the right side of Figure 2A. Each of the two columns of symbols shows the results for one eye of the control subjects. The eye with the higher MD on the 24-2 HVF was deemed the better eye. As would be expected, in the control subjects, there was no difference between these two columns. The N95 amplitude ranged from 7.0 to 21.2 μV.

Ganglion cell damage is thought to have a greater effect on N95 than on P50. The ratio of N95 to P50 provides a way to measure this differential effect on the PERG. The two columns of symbols on the right side of Figure 2B show the ratios for the 34 control eyes. The ratio ranged from 1.2 to 1.9. The variation in the range of ratios can be seen in Figure 1C, where the responses in Figure 1B are normalized to have the same P50 amplitude.

The left columns in Figures 2A and 2B show the results for the 15 patients, with the results for the better (triangles) and worse (circles) eyes shown separately. As expected from previous work, on average, the patients show smaller N95 amplitudes and N95/P50 ratios, although there is considerable overlap with the control values.

One of our purposes was to identify patients with normal PERGs in eyes with clear glaucomatous defects. Consider first the worse eyes (Table 1). These eyes clearly had glaucomatous damage, as indicated by abnormal discs, 24-2 HVF test results (abnormal GHT, PSD, and cluster), and mfVEPs (cluster). To be conservative, we defined a PERG to be normal only if both the N95 amplitude and the N95/P50 ratio were normal. For these purposes, we define the cutoff as the second smallest of the control values. These cutoffs are shown as dashed lines in Figure 2. In the 15 worse eyes, five of the N95 amplitudes and eight of the ratios fell above these lines. Of these, four patients showed a worse eye that had both an N95 amplitude and an N95/P50 ratio in the normal range (above the dashed lines). These four patients are indicated by the N in the PERG column of Table 1, and their records are shown in the first four rows of Figure 3. (Had we used only the N95 amplitude, five eyes would have fallen above our criteria; and had we used as our cutoff the normal range, six eyes would have fallen in the normal range.)

The first two columns of Figure 3 show the probability plots for the 24-2 HVF (total deviation) and the mfVEP. There was obvious glaucomatous damage in all four eyes (P12, P13, P14, and P15). The discs were abnormal, and all four patients showed significant clusters of abnormal points in the upper
hemifield for both the HVF and the mfVEP. Even though both the HVF and mfVEP were abnormal, the amplitude and ratio measures of the PERG were in the normal range. These findings are shown in the records in columns 3 and 4 of Figure 3, where the patient’s PERG (color) is shown with the smallest PERGs (black) from the control subjects and a record (gray) representative of the median of the control subjects. In all cases, both the amplitude (absolute) and the ratio (normalized) measures fell between the values for the median and lowest measures in the control subjects. For comparison, the records from 2 of the 11 (worse) eyes with abnormal PERG records are shown in the bottom two rows of Figure 3. Patient P1 showed an abnormal amplitude and ratio, whereas patient P3 had a normal ratio but abnormal amplitude.

Of the 15 better eyes, 6 met our criteria for abnormal 24-2 HVF results (i.e., abnormal PSD, clusters, and GHT) as well as abnormal clusters on the mfVEP test. Two of these six eyes had an N95 and/or ratio falling above the normal cutoff. (Three eyes fell above this cutoff for each of the measures.) Thus, 6 of the 21 eyes that were abnormal on both HVF and mfVEP had normal PERGs.

The Relationship between PERG Amplitude and Visual Field Loss

To examine the relationship between visual field loss and PERG amplitude, we plotted the N95 amplitude and P50/N95 ratio as a function of the MD of the 24-2 HVF (Fig. 4). There was essentially no correlation between the amplitude (Fig. 4A) or ratio (Fig. 4B) measures and the MD.27 The patients’ eyes showed approximately the same range of PERGs across all MDs, including the eyes with normal MDs.

According to Garway-Heath et al.,19 the PERG amplitude (N95) is a linear function of field sensitivity, if field sensitivity is plotted on a linear axis. It is important to note that we used the same measure of N95 amplitude as they did, although our field of stimulation was larger. In Figure 5, the N95 amplitudes (from Fig. 4A) are plotted against the mean sensitivity (linear units) calculated from the 24-2 HVF data. The solid lines show the best linear correlation for the patients’ eyes (thin line, r = 0.25) and for the combined patients’ and control subjects’ eyes (bold line, r = 0.52). The low correlation coefficients suggest a rather weak linear relationship between N95 amplitude and
field sensitivity, and the slope for the fit to the patients' data is nearly zero. Overall, a straight line does not provide a good description of the data. The large \( \frac{H}{H_{10001}} \) is the mean N95 amplitude and sensitivity of the control subjects. The dashed line shows the prediction for a linear relationship in which halving sensitivity halved the amplitude. The patients' data tended to fall below this line if there were relatively small field losses and above it if there were relatively large field losses.

An Interocular Comparison of the PERG

The PERG of both eyes in a patient tended to be similar, even when the HVF and mfVEP indicated very different levels of defect. Figure 6 provides a quantification of this observation. In Figure 6A, the N95 amplitudes of the better and worse eyes are compared. For both patients and control subjects, the points fell near the line (dashed) of equal amplitude. That is, the amplitude of N95 tended to be similar in both eyes. As expected, there was a tendency for the better eyes of the patients to have larger responses. Notice that 10 of the N95 amplitudes fell above (better eye larger) the line of equality (dashed line), whereas 5 fell below (worse eye larger). The similarity between the PERG amplitudes in both eyes of a patient may be due to similar field defects. Figure 6B indicates that this is not the whole story. In this figure, the ratio of the N95 amplitudes (worse eye/better eye) were plotted against the difference in MD between these eyes (MD of worse eye minus MD of better eye). In the patients, there was a weak correlation between these measures (\( r = 0.54; \) solid line), but the range of the ratios of N95 amplitudes is not much larger than the range of the control ratios. This suggests that the similarity between the responses of the two eyes is not accounted for based simply on the similarity in HVF field defects.

Figure 7 illustrates four examples of a lack of agreement between the degree of glaucomatous damage, as seen on the HVF, and that measured with the PERG. In all four cases, the PERGs from the two eyes were more similar than one might expect from the visual fields. Certainly, there was less agreement than one would expect based on a linear relationship between HVF loss and PERG amplitude. For P10 (Fig. 7A), the PERGs are both abnormal, and essentially identical, whereas the HVF of the right eye was normal, and the MDs of the left eye more than 6 dB lower. P6, P13, and P12 (Fig. 7B–D) also show one eye with a near normal HVF and one with an abnormal HVF. The MD of the worse eye exceeds that of the better eye by more than 10 (P6), 15 (P13), and 5 (P12) dB. Although in each case the worse eye based on the HVF had a smaller PERG than did the better eye, the PERGs were more similar than one would expect, based on the field test results.

DISCUSSION

At least one eye of each patient in this study had glaucomatous damage demonstrated on three separate tests: fundus examination, SAP, and mfVEP testing. Thus, there can be little doubt that we recorded PERGs in patients with glaucomatous damage. Below, we summarize our three key PERG findings and present a possible explanation for them.

The Findings

First, more than 25% of the eyes with clearly documented glaucomatous damage had a PERG within the normal range. The PERG was within normal limits in four (26.7%) of the worse eyes. Overall, 6 (28.6%) of the 21 eyes that met our criteria for glaucomatous damage had normal PERGs. This finding is qualitatively consistent with previous reports of PERGs in patients with glaucoma. For example, it is surprisingly close to the value of 30% estimated from Figure 2 in Graham et al.,\(^5\) for a false-positive rate of 5%.

It should be pointed out that our criteria for an abnormal PERG were relatively lenient. If we had used only the N95 amplitude, as recommended by the ISCEV standards,\(^28\) two additional eyes would have been classified as normal. Further, as pointed out in the Methods section, our control subjects were younger than our patients. Because the PERG decreases
with age, an older control group would tend to increase the number of glaucomatous eyes classified as normal.

Second, the data do not support the Garway-Heath et al. hypothesis that there is a relationship between N95 amplitude and SAP field loss (on a linear scale). The bold solid line in Figure 5 is the best-fitting line to all the data. Small field losses are associated with greater than expected amplitude losses, and large field losses are associated with smaller than expected

**FIGURE 6.** (A) The N95 amplitude of the better eye is plotted against the N95 amplitude of the worse eye in the patients and control subjects. The dashed line has a slope of 1.0 and is the locus of points for which the amplitudes of both eyes are the same. Solid lines: the best-fitting lines to the patient and control data. (B) The ratio of the N95 amplitudes (worse eye/better eye) for each individual is plotted against the difference in MD in between the two eyes.

**FIGURE 7.** PERGs and HVF results in four patients illustrating how the PERGs from the two eyes (OS: gray; OD: black) can appear similar, even when the visual fields are very different.
amplitude losses. It is worth noting that, although our conclusion differs from that of Garway-Heath et al.19 our data are not that dissimilar from theirs. For the same measures of N95, we find an r² of 0.27 for the relationship in Figure 5 compared with an r² of 0.44 in their study. The higher correlation in their study may be because their PERG stimulus stimulated a smaller retinal region than did ours. In any case, unlike the mfVEP signal,20,29 the PERG amplitude is not linearly related to field loss.

Third, the PERG in both eyes of a patient were similar in amplitude, even when the field test results suggested very different levels of glaucomatous damage in both eyes. For example, the responses in both eyes can be relatively similar, even when the MDs of differ by more than 10 dB (see Figs. 7B, 7C). These results are further evidence that the PERG amplitude is not a linear function of field loss.

A Working Model of the PERG and Glaucomatous Damage

Our explanation for these findings is based on four assumptions. We start with the prevailing view of the components of the PERG mentioned in the introduction. In particular, we assume that the PERG is the sum of at least two components: one largely positive and one largely negative. The positive peak (P50) and negative trough (N95) reflect the fact that the largely positive component is faster than the largely negative one. Glaucoma has been shown to affect the negative component more than the positive one. The N95 measure used in this study and recommended by ISCEV guidelines20 clearly is influenced by both components. Currently, there is no way to measure the amplitude of these components in isolation. Second, we assume that the PERG is particularly sensitive to early damage, probably more sensitive in some cases than the HVF or mfVEP. Third, even relatively extreme damage does not reduce the PERG to zero (i.e., noise). (Although our noise level was well below 1 μV, the smallest PERG we recorded had an amplitude of 2.3 μV, and all other PERGs exceeded 3 μV.) Processes relatively unaffected by glaucoma generate part of the PERG response. Fourth, there is a wide range of PERG amplitudes in control subjects.5,11,16-17,19 There are undoubtedly many sources of this variability. For now, we simply assume that these sources can produce variations in overall ERG amplitude and variations in the ratio of the amplitudes of the positive and negative components.

With these assumptions, let’s consider our key findings. First, how do we explain the nonlinear relationship between the N95 amplitude and visual field loss? According to assumption 2, early damage, in some cases undetectable by the HVF, can cause a significant decrease in the PERG. Note in Figures 4A and 5 that the eyes with MDs (Fig. 4A) or mean sensitivities (Fig. 5) near normal tended to fall in the lower half of the normal range. Early damage differentially decreased N95. According to our assumptions, the glaucomatous damage, on average, decreased the N95 amplitude by 46%, almost by one half in these patients. Assuming that this percentage is independent of the initial amplitude, we can calculate the range of amplitudes expected in the patients. In particular, if a patient, before any damage, had an N95 amplitude of 19 μV (the upper limit of the control subjects), then after damage the expected amplitude would be nearly half as large. This result would put this patient’s PERG amplitude, approximately 10.3 μV, in the normal range for this study. In short, we should expect these false positives based on the range of control amplitudes and the estimated decrease due to glaucoma.

Summary

Based on our analysis, we suggest first that the PERG amplitude does not decrease linearly with linear SAP field loss. In some cases, the PERG changes can precede detectable field losses. In general, large decreases in PERG amplitude are associated with very early changes in field sensitivity. Further field sensitivity losses have a relatively small effect on the PERG. However, the PERG misses glaucomatous damage in some patients. This is clear in the results of the present study. These misses are due to two factors. First, there is a wide range of the PERG amplitudes among control subjects. Second, glaucomatous damage does not reduce the PERG amplitude to zero (noise level).

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References


