Pattern ERG as an Early Glaucoma Indicator in Ocular Hypertension: A Long-Term, Prospective Study

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PURPOSE. The conversion rate from untreated ocular hypertension (OHT) to glaucoma is only ~1% per year. Discrimination of nonconverters and potential converters would help reserve preventative treatment for those who need it and thus avoid unnecessary side effects and expenditure for those who do not. This prospective study was designed to assess the pattern electroretinogram (PERG) as an early indicator of dysfunction preceding glaucoma.

METHODS. Ninety-five eyes of 54 patients with intraocular pressure ≥25 mm Hg (or ≥23 mm Hg with additional risk factors), normal visual fields, normal optic disc cupping, and visual acuity ≥0.8 were evaluated. Every 6 months during a median follow-up of 8.2 years, the PERG and visual fields were obtained besides other standard diagnostics. PERGs were recorded in steady state mode in response to checkerboard stimuli at 15 reversals/s, and the amplitudes in response to check sizes of 0.8° and 16° as well as the ratio of the amplitude of responses to 0.8° over that to 16° checks were determined.

RESULTS. Glaucomatous visual field defects developed in eight eyes. For the PERG to 0.8° checks and for the PERG ratio, analysis of the receiver-operating characteristic (ROC) yielded steadily increasing ROC areas before conversion (i.e., an increasing ability of the PERG to predict nonconversion or conversion). One year before conversion, the ROC area of the PERG ratio was 0.78; at a threshold of 1.06 this corresponded to a sensitivity of 80% and a specificity of 71%.

CONCLUSIONS. The PERG can help to predict stability or progression to glaucoma in OHT at least 1 year ahead of conversion. (Invest Ophthalmol Vis Sci. 2006;47:4881–4887) DOI: 10.1167/iovs.05-0875

Ocular hypertension (OHT) is defined as elevated intraocular pressure (IOP) without glaucomatous visual field defects or optic disc changes. Elevated IOP is a major risk factor for glaucoma. Glaucoma is characterized by chronic retinal ganglion cell (RGC) loss, and a sizable fraction (25%–35%) of RGCs is already lost when visual field defects become apparent in automated visual field testing.1

These facts may lead to the conclusion that all patients with OHT should receive preventative IOP-lowering treatment. However, the conversion rate from untreated OHT to glaucoma is only ~1% per year.2 Accordingly, most patients with OHT never have glaucoma and thus do not need treatment. To avoid unnecessary side effects and expenditure from treatment of nonconverters, it would be desirable to identify and treat only the future converters, preferably well before the glaucomatous field defects develop.

The pattern electroretinogram (PERG) is an indicator of RGC function in primates.3–7 In glaucoma or high-risk OHT, the PERG (any component) is reduced in most cases8–17 (for a review, see Ref. 18). This suggests that the PERG can reflect damage to the RGCs before reliable field damage can be observed. In patients with OHT and hence normal visual field test results, a reduction of the PERG amplitude has been found.14,19–28 and several groups have shown that a pathologic PERG may predict impairment of the visual field in patients with OHT.20,25,26 The PERG is thus a promising candidate as an early glaucoma indicator in ocular hypertension.

We have performed a diagnostic long-term, prospective study to assess the predictive value of the PERG for the occurrence of visual field defects in patients with OHT. Preliminary results have been presented previously29; we here present our findings after a 12-year study.

METHODS

Patients and Follow-up

The study adhered to the tenets of the Declaration of Helsinki; informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study. For inclusion in the study, patients had to fulfill the following criteria: IOP (measured with Goldmann applanation tonometry at two different times) ≥25 or ≥23 mm Hg plus additional risk factors (glaucoma of the fellow eye, family history of glaucoma), normal and reliable visual field test results, as defined below, and normal optic disc at clinical examination and on photographs. Pressure-lowering treatment was not an exclusion criterion. Exclusion criteria were visual acuity <0.8, secondary glaucoma (e.g., pigment dispersion or pseudoxfoliation syndrome), and diabetic retinopathy or any other disease capable of causing visual field loss or optic disc damage.

Complete ophthalmic examinations including best-corrected visual acuity, tonometry, slit lamp biomicroscopy, funduscopy, optic disc photography, scanning laser tomography (Heidelberg Retinal Tomograph [HRT]; Heidelberg Engineering, Heidelberg, Germany), visual field examination (Octopus 123 program, G1x for glaucoma; Interzeg, Schlieren, Switzerland), and PERG recordings were scheduled every 6 months.

Treatment was actively recommended only to patients who converted to glaucoma or patients with an intraocular pressure >26 mm Hg. It was also offered to the other participants if they requested treatment after considering the pros and cons.

Visual Field Criteria

A 30° visual field was considered normal if the mean sensitivity was no lower than 2 dB below the age norm and no local defect was present. The two upper and two lower test points at the rim of the visual field were excluded, as they are susceptible to eyelid and occasional spectacle rim artifacts. A local defect was defined as a sensitivity loss.
relative to the age norm of ≥5 dB at three or more adjacent test points or ≥10 dB at two adjacent test points in either the upper or the lower visual field. In total the sensitivity loss of the local defects had to be at least 20 dB. Conversion to glaucoma was defined as a mean defect (MD; analyzed by linear regression) with an increase of ≥2 dB or a local defect occurring at the same location (or at directly adjacent test points) in at least two consecutive measurements. Linear regression was performed if at least five visual fields were available. We excluded visual fields obtained at the patients’ first visit, and fields with >30% false-positive or 30% false-negative responses or >25% fixation loss.

PERG: Stimulation, Recording, and Analysis

The stimulus was presented on a video monitor subtending 35° × 30° of visual angle at a distance of 57 cm. The checkerboards had a mean luminance of 45 cd/m², a contrast of 98%, and a check size of 0.8° or 16° and were counterphased at 15 reversals per second (thus evoking steady state responses). This frequency range seems to be optimal, as the PERG is less sensitive for detection of glaucoma at lower and higher rates.1,14,23,50 Because in the steady state response the so-called P50 and N95 PERG components11,32 cannot be distinguished, analysis is based solely on the magnitude at 15 Hz after Fourier analysis. Retinal potentials were recorded with corneal DTL electrodes33,34 placed near the lower limbus, and gold cup electrodes at the outer canthus served as reference. Signals were amplified and filtered with an analog band-pass of 1.6 – 70 Hz and then digitized to a resolution of 12 bits at a sample rate of 500 Hz by a computer that simultaneously generated the stimuli.35 Sweeps were averaged and displayed online; traces exceeding 100 µV were rejected as artifacts. The sweep duration was 1,066 s. During each examination, two PERG measurements were taken, and the mean of the traces was used for Fourier analysis, which yielded the raw PERG amplitude, signal-to-noise ratio, and noise-free amplitude.36,37

We analyzed the amplitudes of responses to 0.8° (uncorrected and age-corrected) and 16° checks and the PERG ratio (response amplitude to 0.8° checks divided by the response amplitude to 16° checks). In normal individuals, the PERG response amplitude to 0.8° checks is larger than the one to 16° checks (i.e., PERG ratio >1). In a glaucoma animal model and in patients with glaucoma, the PERG with 0.8° (± 1 octave) checks picks up glaucoma damage most sensitively.1,4,5,38 The responses to 0.8° checks in particular are more affected than those to 16° checks (i.e., the PERG ratio may become less than 1).

Statistics

The data were collected from January 1993 to January 2005. To base our evaluation on long-term data, we only considered eyes with a minimum follow-up of 3 years for analysis.

Our design uses the visual field results (as described earlier) as the “gold standard” and assesses the capability of the PERG to serve as a surrogate marker. From the PERG, various measures can be derived. Based on previous experience with the PERG, we analyzed four measures:

A. The response amplitude to 0.8° checks.
B. The age-corrected response amplitude to 0.8° checks. Rationale: Amplitude declines over age;59,60 and thus could be a confounder.
C. The response amplitude to 16° checks. A priori, we expected little correlation with glaucoma for this measure.14
D. The ratio of the response amplitudes to 0.8° and 16° checks (the “PERG ratio”). This measure should, in theory, reduce intraindividual and interindividual variability18 and should need no age correction since the age influence on these two amplitudes is similar.59

To assess these PERG measures without the need to preselect thresholds, ROC (receiver operating characteristic) analyses were performed. Based on the ROC results, several useful descriptive measures were derived. We report herein the sensitivities, specificities, and predictive values for the point on the ROC curve that represents the minimum error score (i.e., the point where the product of false positives × false negatives is minimal).

The longitudinal design allowed calculating ROCs for different times (at half-year intervals before conversion). For this, all time courses of the converting eyes were temporally aligned to the conversion time.

In addition, a regression analysis of all PERG measures over time was performed. For the converters, only the time course until and including the date of conversion was considered, and 1 and 2 years earlier. Subjects who had had fewer than three examinations in the analysis epoch were excluded, as well as slopes not significant on the 5% level.

The statistical calculations were performed in a commercial program (Igor Pro; WaveMetrics Inc., Oswego, OR) and checked with the R program,41 to verify correctness.

Results

Ninety-five eyes of 54 patients were analyzed. The patients had a median age of 52 years (range, 25–79) at the beginning of the study. Median follow-up time was 8.2 years (range, 3.2–11.9) (see Fig. 1).

Three subjects had glaucoma in the fellow eye, and three had a family history of glaucoma. The mean IOP of all eyes was 24.0 ± 2.6 mm Hg. The mean IOP of the converting eyes was 24.7 ± 5.2 mm Hg, and the mean IOP of the nonconverting eyes was 24.0 ± 2.3 mm Hg; the differences were not significant. The mean age of the converters was 55.6 ± 9.3 years, the mean age of the nonconverters was 49.4 ± 11.9 years, and the difference was not significant.

The patients’ desire to receive treatment was high. Thus, the cumulative rates of pressure-lowering treatment over the observation period were 56% eye drops, 2% laser, 16% laser+eye drops, and 8% trabeculectomy. The nonconverting eyes received an average of 0.7 different antiglaucoma eye drops. The converting eyes received an average of 1.5 different antiglaucoma eye drops before conversion and 1.7 after conversion. In five of the eight converting eyes, the IOP decreased with therapy (by 1–5 mm Hg), in the remaining three converting eyes, the IOP increased despite therapy (by 1–10 mm Hg).

Over the course of the study, manifest glaucoma developed in 8 of 95 eyes (five patients), defined by visual field defects, as
detailed earlier. Converters had PERG abnormalities more frequently than did nonconverters. Figure 2 gives an example of the development of PERG abnormalities in a converter.

Relations between glaucoma development and the PERG are shown in Figures 3 and 4. Of the various PERG measures, in Figure 3 the PERG ratio is plotted versus time for all eyes (Fig. 3A) and separately for the eyes that converted to glaucoma (Fig. 3B). The time intervals are identical, but the time courses are aligned to the conversion date.

The efficacy of all PERG measures in detecting glaucoma can be compared in Figure 4, where the ROC areas 1 year before conversion are depicted.

The ROC areas for all PERG measures enlarged with the approach of conversion. Figure 5 shows the areas of the ROC analyses at half-year intervals. Three years before conversion, the detection was near chance level.

**FIGURE 2.** PERG traces and their Fourier transforms. Left: a normal recording of an OHT patient before conversion; right: recording 4 years later from the same patient after conversion to glaucoma. Top: responses to 0.8° checks, bottom: responses to 16° checks. For each examination the time series (averages over 80 trials, 1 second in length) are depicted on the left, and the corresponding Fourier spectra on the right (from 1 to 100 Hz on a log scale). The latter show a prominent response at 15 Hz, some higher harmonics, and some noise at lower and higher frequencies. Note the larger response to 0.8° than to 16° before conversion and vice versa after conversion.

**FIGURE 3.** (A) All PERG ratios, plotted as time courses in all eyes. The x-axis depicts the follow-up time with measurements taken every 6 months. The y-axis depicts the ratio of the PERG amplitude to 0.8° over that to 16° checks. The overall PERG ratio showed a slight decline over time. (B) PERG ratios of converter eyes only, before (solid part of each line) and after (dotted part) conversion. The x-axis depicts the time course of the follow-up in time relative to conversion, y-axis as in (A). The overall PERG ratio of the converters was lower than that of the average patient with OHT (A) and showed a slightly steeper decline with time.

**FIGURE 4.** ROCs 1 year before conversion: (A) response amplitudes to 0.8° checks; (B) age-corrected amplitudes to 0.8° checks; (C) amplitudes to 16° checks; (D) PERG ratio. ROC areas are indicated.
values of these measures are depicted in Table 2. All measures checks; D, the PERG ratio [i.e., A divided by C]. The predictive corrected amplitudes to 0.8° checks; C, amplitudes to 16° checks. The predictive conversion were predicted to different degrees with differ-
nonconverters (Fisher exact test). As a trend, the PERG ratio is the only one that showed markedly more significant negative slopes than positive ones at conversion (5 vs. 1) and 1 year before (4 vs. 1).

Within 2 to 0 years before conversion, the PERG ratio yielded the greatest ROC areas. Lower ROC areas in decreasing order are found using response amplitudes to 0.8° checks, age-corrected 0.8° checks, and 16° checks. The results of regression analyses differed between the various PERG measures, similar to the single-date analyses. When the counts of significant negative versus positive slopes were considered, no significant findings were obtained (Table 1). As a trend, the PERG ratio performed best. When the slope was used as a discriminator for the ROC analysis, an ROC area of 0.78 was found for the time of conversion and 0.68 for 1 year before.

**DISCUSSION**

Over the median observation period of 8.2 years, 8 of the 95 OHT eyes converted to manifest glaucoma. Conversion and nonconversion were predicted to different degrees with different PERG measures (A, amplitudes to 0.8° checks; B, age-corrected amplitudes to 0.8° checks; C, amplitudes to 16° checks; D, the PERG ratio [i.e., A divided by C]). The predictive values of these measures are depicted in Table 2. All measures showed some correlation with development of glaucomatous field defects, the PERG ratio had the largest ROC area. With the threshold at 1.06 (minimum error score), the PERG ratio predicted conversion or nonconversion for the year after an examination with a sensitivity of 80%, a specificity of 71%, a positive predictive value of 23%, and a negative predictive value of 97%.

The slight superiority of the PERG ratio over the other PERG measures suggests that, indeed, normalization by the response to very large checks reduces variability. PERG amplitudes can vary by a factor of three between individuals. Because an individual with a large 0.8° PERG will also have a large 16° PERG, it is useful to compute the PERG ratio to reduce inter-individual variability. Moreover, the PERG ratio has the inherent advantage that electrode placement from session to session and electrode type are of little relevance: To a first approximation, the PERG ratio would not differ between electrode type, be it corneal or skin electrode, because the amplitude transfer factor would not depend on the check size and thus is factored out by computing the ratio. In the face of this theoretical advantage, we are somewhat surprised that the PERG ratio performed only approximately 10% better than the response amplitude to 0.8° checks.

With more severe glaucoma the PERG to 16° checks also decreases and hence the ratio misleadingly improves. Therefore, the PERG ratio would be a poor choice for monitoring of advanced glaucoma. In OHT, however, we are concerned with very early stages, and there the affection of 0.8° check amplitude responses and 16° check responses differ.

The lower yield of the age-corrected amplitude compared with the uncorrected amplitude suggests that age was a partial confounder. Indeed, converters were a bit older than nonconverters (55.6 vs. 49.4 years of age), but the difference is not significant.

Some problems in interpretation arose from the fact that treatment was allowed, which probably distorted the natural course. First, some patients may have received unnecessary treatment, and some may have converted without the treatment. However, this problem does not interfere with the study’s intent, which was to analyze the PERG’s ability for early detection of glaucoma, irrespective of treatment. Second, all converting eyes had received treatment before conversion, and the data seem to suggest that the particular treatment did not prevent conversion. However, as long as no conversion was present, treatment was only mild, and the mean achieved intraocular pressure was still 24.3 mm Hg, maybe more intensive treatment would have been able to halt the development of glaucoma. It is true that today’s treatment may not always be satisfactory in terms of preventing conversion from OHT to glaucoma. We hope that other established or innovative

**FIGURE 5.** Predictive capabilities of different spatial PERG measures expressed as ROC areas (y-axis) at half-year intervals (x-axis) before conversion: (A) response amplitude to 0.8° checks; (B) age-corrected amplitudes to 0.8° checks; (C) amplitudes to 16° checks; (D) the PERG ratio.

**Table 1.** The Count of Significant Positive or Negative Slopes, Arranged by Disease Course and PERG Measure

<table>
<thead>
<tr>
<th></th>
<th>0.8° Amplitude</th>
<th>0.8° Age Correction</th>
<th>16° Amplitude</th>
<th>PERG Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonconverters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant positive slopes</td>
<td>19</td>
<td>28</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Significant negative slopes</td>
<td>28</td>
<td>18</td>
<td>14</td>
<td>42</td>
</tr>
<tr>
<td>Converters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant positive slopes</td>
<td>0/0/0</td>
<td>0/0/0</td>
<td>0/1/0</td>
<td>1/1/1</td>
</tr>
<tr>
<td>Significant negative slopes</td>
<td>1/1/0</td>
<td>1/0/0</td>
<td>1/0/0</td>
<td>5/4/3</td>
</tr>
</tbody>
</table>

For the eyes that converted to glaucoma, the slope was calculated up to and including the date of conversion or 1 or 2 years earlier. No finding shows a significant difference between converters and nonconverters (Fisher exact test). As a trend, the PERG ratio is the only one that showed markedly more significant negative slopes than positive ones at conversion (5 vs. 1) and 1 year before (4 vs. 1).
therapies will be more effective. If so, techniques for early detection of glaucoma such as the PERG will be especially valuable.

This is the third longitudinal PERG study of glaucoma: Arai et al.\textsuperscript{51} looked at the transient PERG and found a decrease of the N95 after 40 months in OHT eyes, but not in normal eyes. Of their 15 OHT eyes, one developed glaucoma 2 years after PERG decrease. Pfeiffer et al.\textsuperscript{52} looked at high-risk eyes and thus, despite their short observation period (11–31 months), found that glaucoma developed in 5 of 29 eyes. This was predicted by the PERG with a sensitivity of 100% and a specificity of 71%. These longitudinal studies show that the suggestions based on cross-sectional studies\textsuperscript{14,21–24,26–28,44} seem valid: The PERG amplitude shows signs of glaucomatous damage earlier than is obvious from morphologic or psychometric measures (though it has been reported that not every patient with glaucoma has a pathologic PERG amplitude\textsuperscript{45}).

The PERG is one of several diagnostic methods that are designed to detect early dysfunction preceding glaucoma. On the one hand there are subjective tests designed to detect visual dysfunction before defects become evident on standard white-on-white (w/w) perimetry, like blue-on-yellow (b/y) perimetry (1.4%). This finding fits well with results obtained by b/y perimetry finding have an increased risk for developing of visual field defects: 91%/100% 1 to 2 years in advance (Goldmann perimetry),\textsuperscript{53} 51% to 61%/89% to 96% 1 year in advance,\textsuperscript{54} and 54%/68% 5 years in advance.\textsuperscript{55} However, in practice, nerve fiber photography is greatly impaired by variations in image quality and interobserver variability.\textsuperscript{56} For the GDx nerve fiber analyzer, longitudinal studies on OHT conversion to glaucoma are not yet available. An overall problem of morphometric methods is the distinction of glaucomatous changes from age-related optic disc changes. The PERG shares this problem. This obstacle can be circumvented, however, by calculating the PERG ratio, which stays largely constant during life and decreases only in the presence of disease.

Refractive errors decrease small check size amplitudes more than large check size amplitudes, mainly due to the reduction of visual acuity.\textsuperscript{57} In our study, we sidestepped this pitfall by including only patients with a best corrected visual acuity of \(\geq 0.8\), but this issue somewhat limits the general applicability of the PERG for early glaucoma detection.

A comprehensive cross-sectional comparison of methods was performed in a study of 43 patients with early glaucoma and 43 healthy individuals.\textsuperscript{15} The authors compared light threshold perimetry, short-wavelength automated perimetry, high-pass resolution perimetry, motion detection, flicker contrast sensitivity, and isoluminantly matched letter tests. The objective tests were pattern and flash electroretinography. Of all parameters the PERG performed best (sensitivity was 85.4%, specificity 87.8%).

In principle, and if noise affects all methodologies similarly, one would expect clinical function tests (like the PERG) to detect dysfunction preceding glaucoma earlier than would morphometric tests, because a diseased ganglion cell would first lose its specific function and then die and disappear.

### Table 2. Sensitivity, Specificity, and Positive and Negative Predictive Values

<table>
<thead>
<tr>
<th>Stimulus/PERG Ratio</th>
<th>ROC Area</th>
<th>Threshold</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Negative Predictive Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8° Checks</td>
<td>0.68</td>
<td>1.4 (\mu V)</td>
<td>70</td>
<td>73</td>
<td>22</td>
<td>96</td>
</tr>
<tr>
<td>0.8° Checks, age-corrected</td>
<td>0.64</td>
<td>1.43 (\mu V)</td>
<td>60</td>
<td>80</td>
<td>24</td>
<td>95</td>
</tr>
<tr>
<td>16° checks</td>
<td>0.62</td>
<td>1.31 (\mu V)</td>
<td>60</td>
<td>72</td>
<td>19</td>
<td>94</td>
</tr>
<tr>
<td>PERG Ratio</td>
<td>0.78</td>
<td>1.06</td>
<td>80</td>
<td>71</td>
<td>23</td>
<td>97</td>
</tr>
</tbody>
</table>

Based on findings 1 year before conversion, negative predictive values for amplitudes to 0.8°, 16° scores. These predictive measures refer to the year the data show sensitivity, specificity, positive and the PERG Ratio at the respective minimum error following an examination.
The above comparison of methods is hampered by the choice of threshold for each method, especially since there is no gold standard for the detection of glaucoma. For example, if one weakened the criteria for progression on w/w perimetry (i.e., increased its sensitivity), the advantage of the PERG—with the given PERG ratio threshold—would disappear. However, at the same time, the visual field test would produce more false positives. Therefore, a comparison of methods is nevertheless feasible when the thresholds of the tests are set at optimal sensitivity/specificity relations.

In conclusion, our long-term results suggest that the PERG, with the stimulus parameters applied in this study, helps to predict stability versus glaucomatous progression in OHT. Objectivity, reproducibility, and relative independence from age changes are advantages of this particular glaucoma tool—namely, the PERG ratio. It can help to discriminate between OHT eyes that may develop glaucomatosus visual field defects and those that probably will not.

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