

## **Pattern electroretinogram in glaucoma and ocular hypertension**

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**Abstract.** We recorded the pattern electroretinogram (PERG) to small ( $0.8^\circ$ ) and very large ( $15^\circ$ ) check sizes in normal subjects, in patients with early-stage glaucoma, and in patients with ocular hypertension. In glaucoma, the PERG amplitude was reduced. This reduction was more prominent for a check size of  $0.8^\circ$  as compared with  $15^\circ$  stimuli and for high (16/s) as compared with low (7.8/s) reversal rates. Using a discriminant analysis of the amplitudes for two different check sizes, we could distinguish the normal and the glaucoma groups with a specificity of 96% and a sensitivity of 91%. Of the ocular hypertension patients, 43% were classified as pathologic by the discriminant analysis. Thus multivariate analysis of the PERG may increase its diagnostic value.

### **Introduction**

Early detection of glaucoma could prevent impairment of vision in many patients. Accordingly, many attempts have been undertaken to detect glaucoma by psychophysical, structural, and physiological measurements. The pattern electroretinogram (PERG) may be a sensitive indicator of glaucomatous ganglion cell damage. The PERG is supposed to be generated mainly by the retinal ganglion cells [1, 2]; we found this even for checkerboard stimulation with very large check size [3]. A number of investigators have reported significant changes in the group means of PERG amplitudes in patients with early glaucoma and ocular hypertension (OHT) [4, 5, 6, 7, 8]. We previously reported that the PERG amplitude is preferentially affected in early glaucoma with  $0.8^\circ$  checks, whereas the amplitude with  $15^\circ$  checks is less affected [9]. We now present a classification method based on a discriminant analysis which is aimed at diagnosis of individual cases, not only at group comparisons. In addition, we extended our investigation by employing temporal frequencies of 7.8 and 16 reversals per second, as transient mechanisms may be preferentially involved in glaucomatous damage [10, 11, 12].

## Methods

Stimuli were presented on a visual display unit with a spatial resolution of  $480 \times 390$  pixels; the frame rate was 73 Hz. For pattern stimulation we used high contrast (98%) checkerboards, with a check size of  $0.8^\circ$  and  $13^\circ \times 17^\circ$ . For convenience, we will refer to the size of  $13^\circ \times 17^\circ$  as  $15^\circ$  throughout this report. In the  $15^\circ$  condition four checks covered the entire screen, subtending  $26^\circ \times 34^\circ$  of visual angle at the viewing distance of 57 cm. Spatial position of the light and dark checks was alternated with a rate of 7.8 or 16 reversals per second (corresponding to 3.9 or 8 Hz respectively). The borders of the checks met at the center of the screen for all sizes. Mean luminance was  $62 \text{ cd/m}^2$ . Subjects were asked to fixate a small cross in the center of the screen and report digits that appeared at random intervals for 300 ms in its place.

PERG responses were recorded with gold foil electrodes [13] placed in the lower lid and a silver cup electrode at the outer ipsilateral canthus as reference. Crosstalk from the other eye was below noise level with this reference [14]. The signal was amplified and filtered with a bandpass of 1–30 Hz. Eighty sweeps of 512 ms duration were averaged and displayed on-line. Sweeps exceeding  $\pm 100 \mu\text{V}$  were rejected as artifacts. At all stimulus conditions (7.8 and 16 rev/s,  $0.8^\circ$  and  $15^\circ$  check size) the measurements were performed at least twice in a balanced block design. The reversal frequency was adjusted to yield an integer number of reversals per sweep, eliminating spill-over in Fourier analysis. Evoked potential amplitude was measured in the frequency domain as the magnitude at the reversal frequency.

Three groups of subjects were studied:

1. Normal subjects: 27 eyes in 16 visually normal subjects, mean age 40 years ranging from 23 to 58 years.
2. Patients in early stage of glaucoma: 11 eyes in 7 patients, mean age 64 years ranging from 54 to 75 years. They had visual acuities above 0.8. Their visual fields corresponded to stage I (only relative scotomas, 4 eyes) stage II (absolute scotomas not connected to the blind spot, 5 eyes), or stage III (absolute scotomas connected to the blind spot, 2 eyes) according to the Aulhorn classification [15]. No patient received miotic therapy.
3. Subjects showing elevated intraocular pressure and normal visual fields (OHT group): 35 eyes of 19 subjects, mean age 50 years ranging from 21 to 75 years. The subjects were included according to the following criteria: normal visual acuity; normal visual fields as tested both manually at the Goldmann perimeter and the Octopus perimeter with the G1 program; intraocular pressure above 25 mmHg or above 21 mmHg if additional risk factors were present (glaucoma in the other eye, family history of

glaucoma, myopia > 5 D, cardiovascular disease, or diabetes mellitus). The intraocular pressure was averaged from four measurements per day over several days.

## Results

Figure 1 shows typical PERG findings in a 59-year-old subject with unilateral glaucoma in the right eye. He was examined on the day of admission before therapy was initiated. His visual acuities were 0.9 in both eyes. The visual field examination showed a Bjerrum scotoma (= stage II) in the right eye and no defects in the left eye. Peak intraocular pressure was 40 mmHg in the right eye, whereas normal pressures were found in the left eye. In the right (glaucomatous) eye, the PERG amplitudes to  $0.8^\circ$  check size stimuli were reduced for both temporal frequencies, whereas the response to large checks was normal. In the left (normal) eye, the amplitudes with 7.8 rev/s were similar for  $0.8^\circ$  and  $15^\circ$  checks. With 16 rev/s, the amplitude to large checks was slightly lower as compared with small checks. Only recordings using 16 rev/s are depicted.

The results from all normal and glaucomatous eyes with 7.8 rev/s are summarized in Fig. 2(a). The abscissa represents the amplitude with large checks; the ordinate represents the amplitude with small checks. Because the amplitudes for small and large checks are similar at 7.8 rev/s, all normals scatter along the  $45^\circ$ -line; all effects due to eye size, electrode placement, pupil

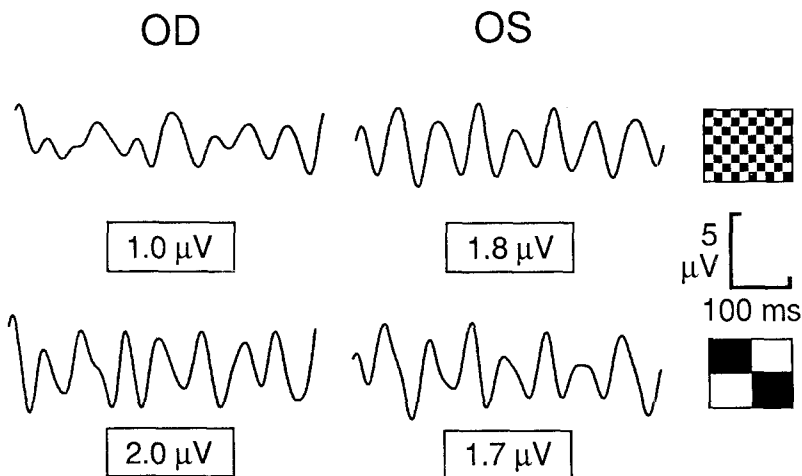


Fig. 1. PERG responses to 16 reversals/s in a case of unilateral glaucoma (OD) to check sizes of  $0.8^\circ$  (upper traces) and  $15^\circ$  (lower traces). Amplitudes as calculated by Fourier analysis at the reversal rate are indicated in boxes. Note amplitude reduction only for the small check size in the affected eye (upper left).

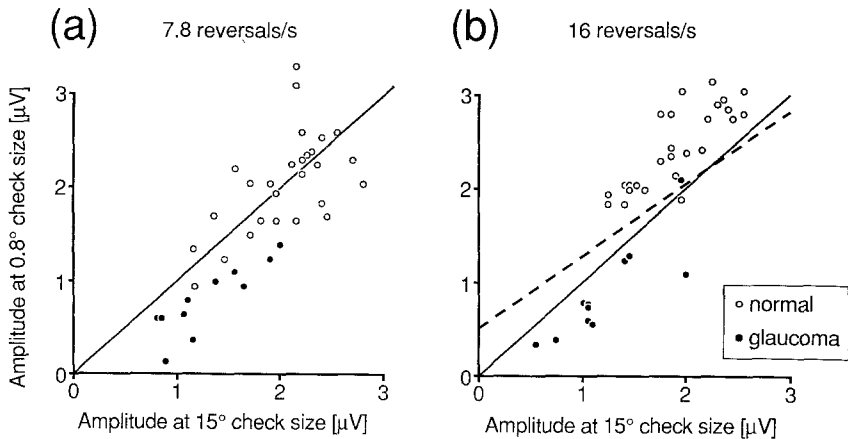


Fig. 2. Scatterplots of PERG amplitudes for 7.8 rev/s (left) and 16 rev/s (right panel) from normal (open circles) and glaucomatous eyes (filled circles). Abscissa: amplitude with 15° checks; ordinate: amplitude with 0.8° checks. The dashed line in the right diagram represents the “discriminating line”; eyes above this line are classified as normal by discriminant analysis (see text).

diameter and the like affect small- and large-check responses likewise. In contrast, nearly all data points of patients with early stages of glaucoma lie below the 45° line, implying that amplitudes evoked by small checks are more seriously affected than amplitudes evoked by large checks.

Figure 2(b) shows the results with 16 rev/s. All normals scatter above the 45° line, as some low spatial frequency attenuation occurs at this temporal frequency. Nearly all points representing the patients with early stages of glaucoma lie below the 45° line because of a stronger reduction of amplitude with small checks than with large checks. At 16 rev/s, the normal and glaucomatous eyes are more clearly separated than at 7.8 rev/s.

In Fig. 3 the values of the OHT group have been added to Fig. 2(b). The range of the OHT points encompasses both the normal and most of the glaucoma range.

As the normal and the glaucoma group were well separated, a classification of individual subjects as either normal or pathologic may be possible on the basis of PERG findings. This was done formally by a discriminant analysis, which, briefly, works as follows: For all eyes, the discriminant analysis looks at the data pairs (amplitudes at 0.8° [ $a_{0.8}$ ] and 15° check size [ $a_{15}$ ]) and the true classification (normal or pathologic). It then computes the coefficients  $c_1$  and  $c_2$  for the discriminant function  $f_d$ :

$$f_d = c_1 \cdot a_{0.8} + c_2 \cdot a_{15} \quad (1)$$

The coefficients ( $c_1$ ,  $c_2$ ) are determined such that classification based on  $f_d$

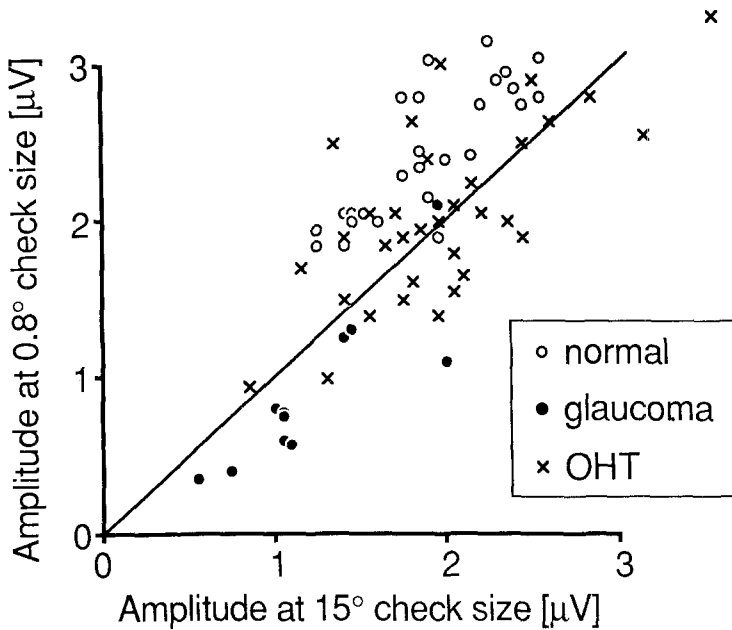


Fig. 3. Scatterplot of PERG amplitudes for 16 rev/s. In addition to Fig. 2(b) data of the OHT group (crosses) has been added. Responses from OHT patients scatter over both the normal and the glaucoma ranges.

gives the best reproduction of the true classification. For the present data set,  $f_d$  was found as follows:

$$f_d = 1.97 \cdot a_{0.8} - 1.32 \cdot a_{15} \quad (2)$$

Since the coefficients  $c_1$  and  $c_2$  have roughly equal size but a different sign, a parallel variation of the amplitudes  $a_{0.8}$  and  $a_{15}$  does not strongly affect the value of  $f_d$ . This can be graphically visualized by the discriminating line which divides the data into two groups (dashed line in Fig. 2(b); points above this line have a high  $f_d$ ).

Equation (2) was used to classify the OHT group. Figure 4 shows the number of cases as a function of  $f_d$  for the normal (1), the glaucoma (2), and the OHT group (★). Eyes with values  $f_d > -0.7$  are classified as normal,  $f_d \leq -0.7$  as pathologic. This classification border is shifted with respect to  $f_d = 0$  for statistical reasons (an a-priori probability of 0.5 and unequal frequencies in the two groups). Twenty-six of 27 normal eyes and 10 of 11 glaucomatous eyes were classified correctly. This corresponds to a specificity of 96% and a sensitivity of 91%. In the OHT group, 15 eyes (43%) were classified into the glaucoma class and 20 eyes (57%) as normal.

As a control for the influence of age, we plotted PERG amplitude versus

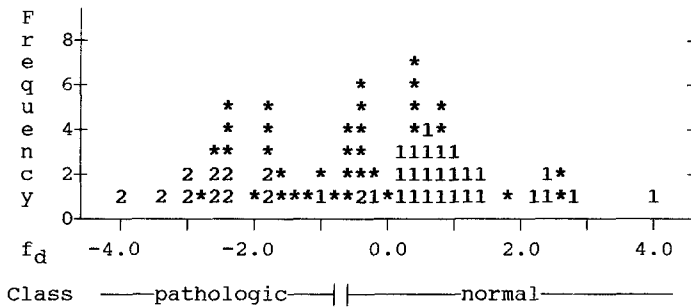


Fig. 4. Classification histogram as output by the discriminant analysis. The abscissa plots the value of the discriminant function  $f_d$  (equation 2). Eyes with  $f_d > -0.7$  are classified as normal,  $f_d \leq -0.7$  as pathologic. Symbols: 1 = normal, 2 = glaucoma, ★ = OHT. Twenty-six of 27 normal eyes and 10 of 11 glaucoma eyes were classified correctly. Fifteen OHT eyes are classified as pathologic, 20 as normal.

age for  $0.8^\circ$  checks and 16 rev/s for the three groups (Fig. 5). For the normal group, there is a reduction of amplitude with increasing age. Linear regression analysis showed a slight but insignificant age dependence of the PERG amplitude ( $r = 0.13$ , 25 degrees of freedom) over the range of 23–58 years.

**Discussion**

The amplitude of the PERG is diminished in early glaucoma. In accordance with our earlier study [9], the amplitude is more reduced when a check size of  $0.8^\circ$  is used as compared with  $15^\circ$ . The stronger reduction of PERG amplitudes at high temporal frequencies in glaucoma confirms earlier reports [11, 12] that the retinal mechanisms that are damaged by glaucoma are preferentially stimulated by high temporal frequencies. This supports the hypothesis [9] that the magnocellular pathway [16] may be predominantly involved in early glaucoma damage rather than the parvocellular pathway, considering that the magnocellular cells have a higher temporal resolution [17, 18].

The responses from both small and large check sizes at high temporal frequency stimulation show little overlap between the normal and the glaucoma groups in the discriminant analysis. The results of the discriminant analysis can be adjusted to reach the desired ratio of sensitivity and specificity by changing the discriminant value. The values for specificity and sensitivity as derived from the present data set are surprisingly high. Reliable conclusions, however, can be drawn only after long-term follow-up

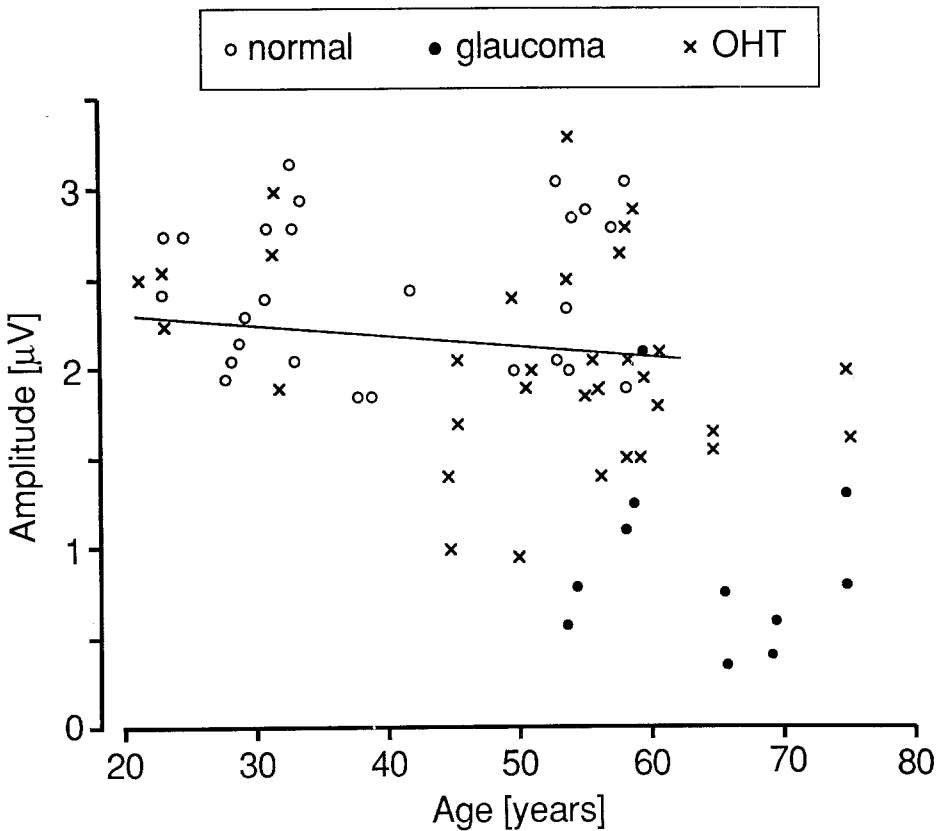


Fig. 5. PERG amplitude using  $0.8^\circ$  check size and 16 rev/s is plotted versus age for the three groups studied. A linear regression (thin line) of the amplitude of the normal eyes shows a shallow decline of amplitude with age.

of the OHT cases to establish a firm relationship between abnormal PERG and glaucoma.

One possible limitation of this approach is the age dependence of the PERG. Trick [19] and Porciatti and associates [20] reported a strong amplitude reduction with age, whereas Wanger and Persson [21] reported no significant age dependence. In the present study the groups were not age matched, so could the present results be affected by some age dependence of the PERG? Two ways in which the PERG may depend on age are (1) reduced quality of the optical image on the retina and (2) some general affection of the PERG amplitude, e.g. due to changes in the number of ganglion cells. We tried to reduce the influence of the first factor by selecting only patients with a visual acuity of  $\geq 0.8$  and employing a check size of  $\geq 0.8^\circ$ . The second influence may be reduced by the comparison of the

amplitude with small and large checks, reducing the influence of age on absolute amplitudes. We analyzed our data with respect to age and found an insignificant reduction of amplitude with age in our sample of normal subjects, which covered the range from 23 to 58 years of age. In contrast, a number of glaucoma patients did show a strong reduction of PERG amplitude below 60 years of age. Hence, in this age range, the good separation of the normal and the glaucoma group could not, in all likelihood, be attributed to age. Future studies might take age as an additional parameter into the discriminant analysis.

The data of the OHT group covered both the normal as well as the glaucoma range. This is to be expected, as the OHT group represents an inhomogeneous population; only a certain percentage of these eyes (3.2%–35% [22]), is expected to develop glaucoma later in life. Nearly half (46%) of the OHT eyes were classified as pathologic by the discriminant analysis. This high value could well be due to a selection bias, as most of the patients referred to our hospital had additional risk factors. A follow-up study of these patients will be necessary to assess the value of their PERG alterations.

The hypothesis that the magnocellular system is preferentially affected by glaucoma damage may help develop more sensitive diagnostic procedures for early detection of glaucoma.

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