

Little correlation of the pattern electroretinogram (PERG) and visual field measures in early glaucoma

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Accepted 21 July 1997

Key words: eccentricity, glaucoma, PERG, perimetry, visual field

Abstract. Pattern-electroretinograms (PERG) to checkerboard reversal at 16/s. 0.8° and 15° check size and visual fields (Octopus G1) were retrospectively analyzed in 40 eyes of 30 patients with early glaucoma. The mean visual field defect was calculated separately for the central 26° × 34° covered by the PERG stimulus (MDc) and the more peripheral area (MDp) surrounding the stimulus. Deeper field loss was correlated with a reduced pattern electroretinogram amplitude ($p < 0.01$ for both MDp and MDc), indicating that the pattern electroretinogram deteriorates as glaucoma advances. If the analysis was confined to those 18 eyes (16 patients) that had no field defect within the area covered by the PERG stimulus (normal MDc but abnormal MDp), 13 of these had an abnormal PERG amplitude ($p < 0.001$). The results suggest that the PERG can reveal impairment of ganglion cell function that is not detected by conventional perimetry.

Abbreviations: MD—mean defect; MDc—mean defect over the central area; MDp—mean defect over the peripheral area.

Introduction

The pattern electroretinogram (PERG) reflects the function of the retinal ganglion cells [1–4]. Thus, it is not surprising that the PERG is abnormal in manifest glaucoma [5–16]. It is also reported that the PERG is abnormal in some eyes with ocular hypertension and can even predict to some degree which eyes will develop field defects [17,18].

Still, the high sensitivity of the PERG to detect early glaucoma is surprising when one considers that a typical PERG stimulus covers only a small central part of the visual field, usually up to an eccentricity of less than 10° [19]. It is known that visual field defects in glaucoma typically begin in the mid periphery (Bjerrum area). Thus, the question arises as to what degree the PERG and the visual field are locally correlated: Is the PERG abnormal only if the stimulated area contains visual field defects? Or does it reflect impairment of ganglion cell function that is not always detectable in conventional visual field testing? To answer this question, we have calculated the mean visual

field defects within the area covered by the PERG stimulus and outside this area and compared these visual field measures with the PERG response in patients with early glaucoma.

Subjects and methods

Classification of the eyes examined

Inclusion criteria for 'early glaucoma' eyes were as follows: visual acuity ≥ 0.8 ; intraocular pressure > 25 mm Hg; or > 21 mm Hg if additional risk factors were present (glaucoma in the other eye, family history of glaucoma, myopia >5 D, cardiovascular disease or diabetes mellitus [but without diabetic retinopathy]); and visual fields corresponding to stage I (only relative scotomata) or stage II (absolute scotomata, but without connection to the blind spot) according to the Aulhorn classification [20]. To collect a sufficient number of eyes with normal central fields (normal MDc, see below), eyes with 'peripheral' defects (defects outside the area covered by the PERG stimulus) were preferred for inclusion in this study.

We analyzed 40 eyes of 30 patients in an early stage of primary open-angle glaucoma. Mean age was 59 ± 11 years (range, 25–76 years). Pupils were not pharmacologically influenced within 1 day before the examination and were at least 2.5 mm in diameter.

As normal controls we used results from 65 eyes of 43 visually normal subjects (mean age, 43 ± 15 years; visual acuity, >0.8 ; intraocular pressure, <22 mm Hg), whose data were collected in the same time range and with the same equipment as those of the patients.

Stimulation

Subjects viewed the stimuli binocularly on a video monitor with a frame rate of 73 Hz and a resolution of 480×390 pixels. The screen subtended $26^\circ \times 34^\circ$ of visual angle at a distance of 57 cm. Checkerboards with a mean luminance of 52 cd/m^2 and a check size of 0.8° or $13^\circ \times 17^\circ$ (= '15°') were counterphased at 16 reversals/s, contrast was 98%. We presented the stimuli in an interleaved block design ('stepwise sweep'). Each stimulus was presented for 6 s. In this interval, 10 sweeps of 500 ms duration were averaged, then the next stimulus followed. This sequence, comprising the two stimuli, cycled at least 12 times, resulting in a total of 120 sweeps for each condition. A small cross in the center of the screen served as a fixation point. To control for fixation and attention, subjects reported random digits that appeared every 5 to 20 s for 300 ms at the fixation point. The entire recording session, including refraction, lasted less than hour.

Table 1. Contingency table based on age-normalized PERG amplitude and PERG index*

	No. (%)	
	Normal eyes	Glaucomatous eyes
Age-normalized PERG amplitude, all eyes evaluated (μV)		
≥ 0.73	56 (86)	5 (28)
< 0.73	9 (14)	13 (72)
PERG index		
≥ 0	56 (86)	6 (33)
< 0	9 (14)	12 (66)
Age-normalized PERG amplitude, eyes averaged per subject (μV)		
≥ 0.73	37 (86)	5 (31)
< 0.73	6 (14)	11 (69)

* All comparisons $p < 0.001$, Fisher's exact test.

Recording and analysis

PERG responses were recorded with DTL electrodes [21, 22] placed in the lower limbus with a gold cup electrode at the outer ipsilateral canthus as reference. The signal was amplified and filtered with a bandpass of 1.6–70 Hz (first-order filter, Toennies Physiologic Amplifier). Signals were digitized to a resolution of 12 bits at a sampling rate of 435 Hz by a small laboratory computer (AT386 compatible), which simultaneously generated the stimuli. A sweep length of 500 ms contained eight responses of the 16 reversals. Sweeps were averaged and displayed on-line; those exceeding $\pm 100 \mu\text{V}$ were rejected as artifacts. Evoked potential amplitude was measured in the frequency domain as the magnitude at the reversal frequency, using Fourier analysis. The amplitudes from 0.8° and 15° check size stimulation were normalized for age [2].

To evaluate the PERG, two measures were analyzed: (1) the age-normalized amplitude to 0.8° checks and (2) the 'PERG index'. The 0.8° age-normalized amplitude was corrected for age by fitting a cumulative gaussian curve [23]. As lower limit of normal, we chose a value of $0.7 \mu\text{V}$. With this threshold, 14% of the normal control group would be classified as abnormal (Table 1). The odd threshold value of $0.73 \mu\text{V}$ was chosen to yield the same number of false positives as with a PERG index threshold of zero (see below). The PERG index [16, 18] was calculated by a linear combination of the amplitudes recorded with check sizes of 0.8° and 15° :

$$\text{PERG index} = -2.1 + 6.1 \cdot A'_{0.8} - 3.0 \cdot A'_{15},$$

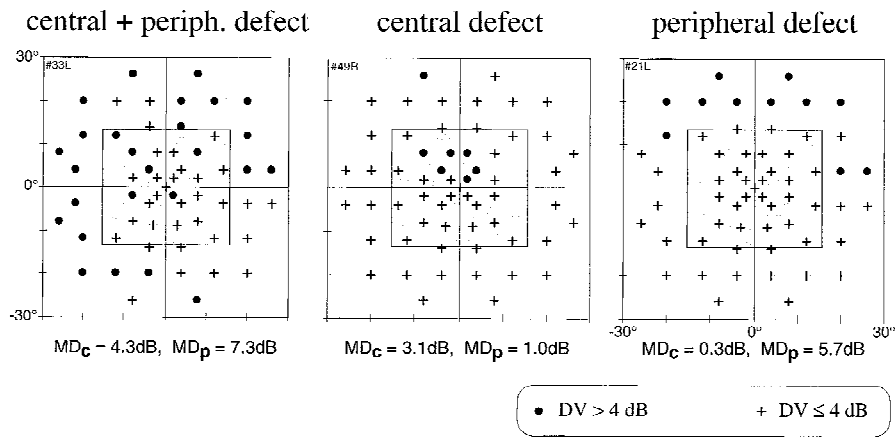


Figure 1. Three types of field defects found in glaucoma. The gray checkerboard within the 30° G1 fields indicates the size of the PERG stimulus; it divides the field into a central and a peripheral area. Normal local thresholds ($DV \leq 4$ dB) are indicated by mean defects ($DV > 5$ dB) by \bullet . The figures below each diagram represent the mean field defect in the central (MDc) or peripheral (MDp) area.

where $A'_{0.8}$ and A'_{15} denote the age-normalized amplitudes, measured at check sizes of 0.8° and 15° , respectively. The three constants were derived by logistic regression analysis. The PERG index is positive in most normal eyes and negative in most glaucomatous eyes. It is intended for diagnostic purposes to classify individual eyes as done in this study and has slightly less interindividual variability than the raw amplitude [24]. In our normal control group, 14% had a PERG index below zero.

Visual field measures

Visual fields were measured with an Octopus 2000 automated perimeter using the G1 program (± 30 field). All patients had had prior experience with this examination. The tabular output of the local defects was entered into another computer and averaged separately for two parts of the $60^\circ \times 60^\circ$ field: We define areal mean defects (MD) in two areas as follows: MDc ('c' for central) averages the local MDs over the central $26^\circ \times 34^\circ$ area, and MDp ('p' for peripheral) averages the local MDs over the surrounding $60^\circ \times 60^\circ$ field without the central $26^\circ \times 34^\circ$ area. The parts of the visual fields were termed normal if the MDc or the MDp was ≤ 2.0 dB, and abnormal if the respective MDs were > 2.0 dB.

Figure 1 illustrates these three types of field defects in three patients from this study. The central checkerboard indicates the size of the PERG stimulus, dividing the field into a central and a peripheral area. The numbers below each diagram represent the MDc and MDp. The left field displays peripheral and central defects, the middle displays only central defects and in the right field defects are confined to the peripheral range, as common in early glaucoma.

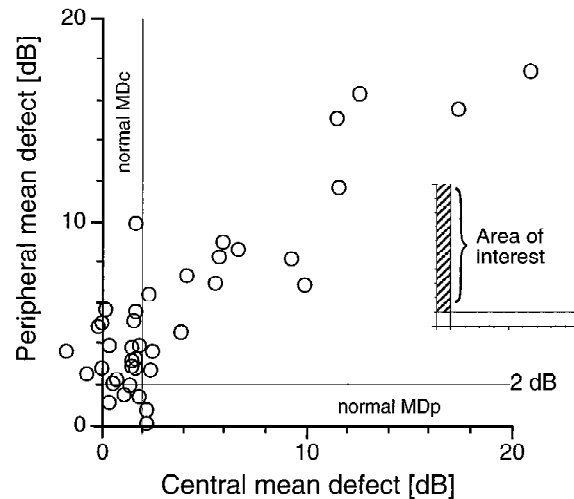


Figure 2. Peripheral versus central field defects. The shaded areas indicate 2 dB, here used as the border to abnormality. Gross field defects are not confined to either the central or the peripheral region. Mild field defects are preferentially confined to the periphery and spare the center. The inset on the right indicates the area of interest; eyes falling into that area are further analyzed and depicted in Figure 3b.

Results

To give an impression of the range of field defects covered in this study, Figure 2 presents the peripheral and central field defects in all glaucomatous eyes studied. Obviously, gross defects are not confined solely to the central or peripheral region. For small defects, the pattern is different: there are more eyes with abnormal peripheral fields ($MD_p > 2$ dB) in which the central field is still normal ($MD_c \leq 2$ dB). This preferred population of the 'area of interest' is in part due to our preferential selection of eyes with normal MD_c .

Figure 3a depicts the relationship between the age-normalized PERG amplitudes and the two visual field measures MD_c and MD_p for all eyes studied. Large field defects ($MD > 5$ dB) are always associated with an abnormal PERG (normalized amplitude below $0.73 \mu V$). Normal visual fields ($MD < 2$ dB) are associated with either normal or abnormal PERGs.

Our goal was to analyze those eyes that presented normal $MD (< 2$ dB) averaged over the area covered by the PERG stimulus. Therefore, we examined the subgroup of eyes falling into the 'area of interest' of Figure 2, where the central visual field was considered normal ($MD \leq 2$ dB) and the peripheral field was clearly abnormal ($MD_p > 2$ dB). Thus, Figure 3b results (note that the abscissa is rescaled with respect to Figure 3a). Only 18 eyes (16 patients) of the 40 eyes in Figure 3a remain, as the peripheral and central defect is

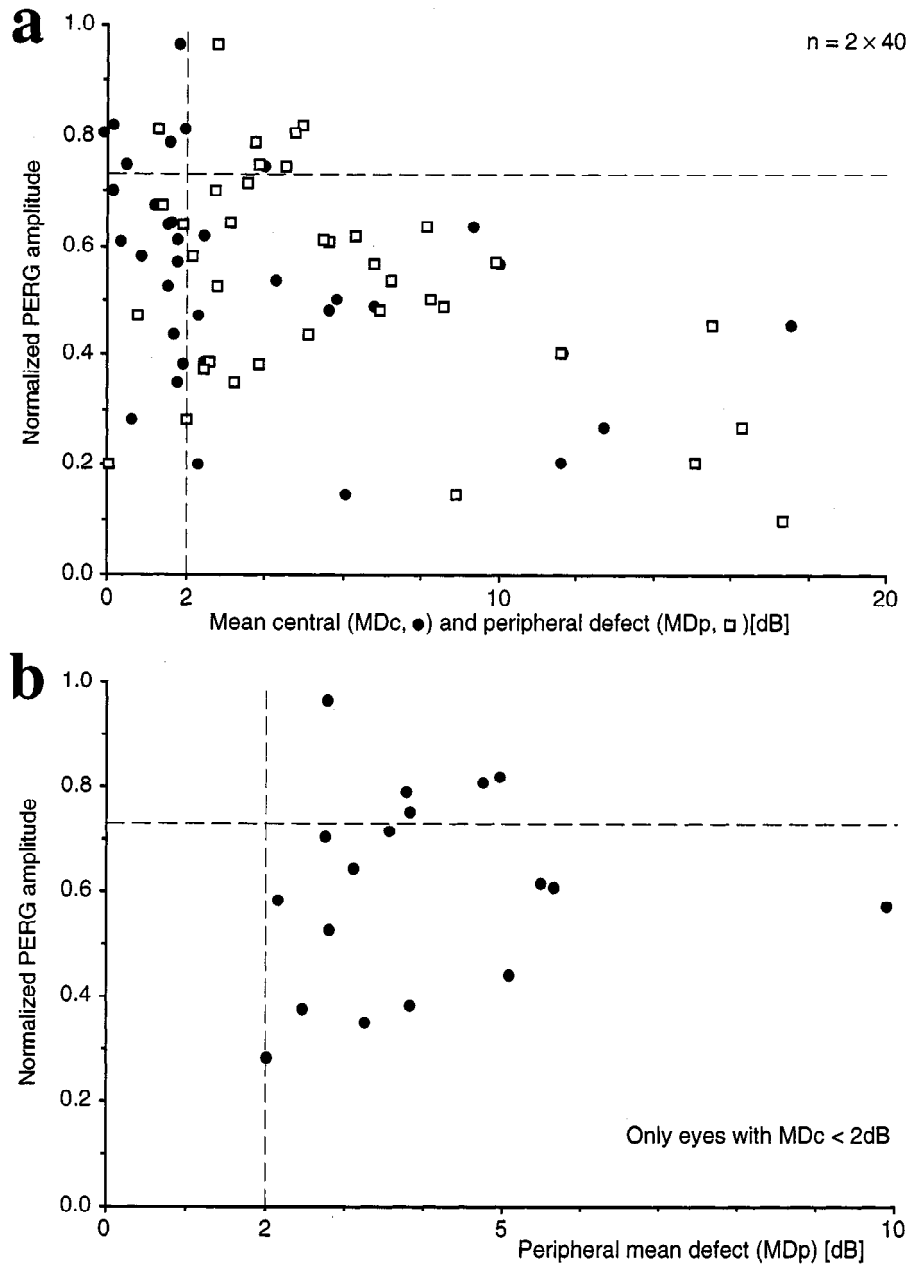


Figure 3. PERG versus field defect. The abscissa plots the peripheral mean defect (MDp, squares) or the central mean defect (MDc, dots); the dashed vertical line indicates 2 dB MD; the ordinate plots the PERG amplitude. Values below the horizontal dashed line or right of the vertical dashed line are considered abnormal. (a) Large field defects are always associated with an abnormal PERG. Normal visual fields (MD < 2 dB) are associated with both normal and abnormal PERGs. (b) Only those eyes from (a) are depicted whose central visual fields (MDc) were normal; of the 40 eyes in (a), 18 fulfilled this criterion. Thirteen of 18 eyes display an abnormal PERG, indicating that the PERG revealed ganglion cell damage not detected by perimetry at the same location.

to some degree correlated (see Figure 2), and eyes with normal MDp are missing as well. The mean MDc in this group was 0.87 ± 1.02 dB; the mean age was 59.8 ± 2.1 years. Although the visual field in the PERG stimulus area is normal, 13 eyes (11 patients) of these 18 eyes display an abnormal PERG (normalized amplitude below 0.73; the mean age of this subgroup was 60.2 ± 13.0 years). Compared with our normal control group (Table 1), the probability is below 0.1% that this could have happened by chance (fourfold table, Fisher's exact test).

When the analysis is based on the PERG index, the results are similar: here 12 of 18 eyes with a normal MDc display a pathologic PERG. This distribution also differs highly significantly from the control group (Table 1b, $p < 0.1\%$).

Discussion

We calculated the MD separately in the central area covered by the PERG stimulus (MDc) and in the more peripheral area outside the PERG stimulus but within the 30° Octopus G1 field. We found that deep defects were always present in both regions, while mild defects would preferentially occur for MDp. This is expected, as MDp represents roughly both Bjerrum arcuate scotomata and enlarged blind spots (see the defect frequency studies, e.g. [20]). However, in the present study the relative number of visual fields with damage confined to the periphery is not representative, as we preferentially selected eyes (by visual inspection of the field plots) with normal MDc.

Comparing visual field defects and PERG measures, we found that deep defects are associated with an abnormal PERG. This is expected, as both visual field measures and the PERG represent aspects of ganglion cell function. It ties in with results by Marx and Zrenner [25], who found strongly reduced PERG responses when scotomata were selectively stimulated.

Analyzing only those eyes with a normal average visual field (MDc) in the area of the PERG stimulus, we found 13 of 18 eyes to present an abnormal PERG. This significant finding ($p < 0.001$) suggests that the PERG unveils some impairment of the ganglion cell function that is not revealed by Octopus perimetry. This may be related to results by Quigley et al. [26], who found that half of the ganglion cells need to be missing before visual field defects become obvious.

One possible limitation of the PERG is its age dependency. Trick [27] and Korth et al. [28] reported a strong amplitude reduction with age, whereas Wanger and Persson [9] and Bach and Speidel-Fiaux [16] reported no significant age dependency. We interpret these differing findings as follows. In principle, there should be some age dependency, but it may only start above

a certain age and not be obvious in a linear analysis. We here modeled age dependency by a cumulative gaussian [23], where no sizable reduction of the PERG amplitude occurs before 65 years of age; seven of 18 eyes with normal MDc fell in this group. Consequently, any age effect would affect only some of our eyes. Furthermore, the age normalization should correct for any age effect. We conclude that age artifacts have not played a major role.

When results from both eyes of the subjects are analyzed, interocular correlation needs to be considered to avoid faulty significance estimates [29, 30]. To test to what degree our results suffer from this limitation, we reanalyzed both our patients and control subjects, averaging over the eyes whenever they were from the same patient. Table 1 demonstrates that the present results are still highly significant, although there are fewer data points.

Our inclusion criteria allowed diabetic patients, which might confound our findings. However, only in one patient was blood glucose level slightly elevated (without signs of diabetic retinopathy). In this patient, one eye had a normal and the other a pathologic PERG index.

At the moment, there are two views about the pattern of visual field damage in early glaucoma. Originally, the diagnosis of glaucoma was mainly based on perimetric detection of localized field defects in the Bjerrum area such as paracentral scotomata, arcuate defects and development of a nasal step [31–36]. Narrowing of the isopters in Goldmann perimetry was regarded as an unreliable sign. However, with the widespread use of computerized static perimetry, diffuse loss in early glaucoma stages was recognized as well [37–39]. Caprioli and collaborators [40] were able to detect two distinct groups of glaucoma patients: the first group showed diffuse depression of light sensitivity throughout the entire visual field, while the second group had localized, deep scotomata without depression of the remaining field. The first group was associated with higher intraocular pressures than the group with more localized visual field loss.

We think that our present results are compatible with all these findings and could support the following hypothesis [41]: Glaucoma starts with ‘subclinical’ panretinal damage of the ganglion cells, reflected in the PERG, but not necessarily in conventional visual field examination [8]. In the progress of the disease, measurable scotomata appear preferentially in the Bjerrum area, showing focally pronounced damage.

A morphologic study [26] suggested that a sensitivity loss of 5 dB in static perimetry within the central 30° of the retina corresponds to a loss of 20% of the retinal ganglion cells. These authors also concluded that a 5-dB loss within the central 10° corresponded to about 50% loss of ganglion cells. However, their data were not conclusive as to whether this loss is similar in the central and paracentral areas and whether cell loss is focal or diffuse.

In conclusion, the present results suggest that the PERG reveals beginning ganglion cell damage in incipient glaucoma that may not be evident in conventional visual field testing. Thus, PERG recording may be of use in counseling patients with ocular hypertension. This hypothesis needs to be tested in a longitudinal study of patients with ocular hypertension.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 325, Tp B3) and by the Meyer-Schwartz-Stiftung. We thank Wolf Lagrèze and Jörg Meyer for helpful critical comments on the manuscript.

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