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Check-size specific changes of pattern electroretinogram in patients with early open-angle glaucoma

MICHAEL BACH,[1] PETER HISS[2] & JENS RÖVER[3]
[1]Universitäts-Augenklinik, D-7800 Freiburg, BRD; [2]Universitäts-Augenklinik, D-2400 Lübeck, BRD; [3]Augenklinik der Städt. Krankenanstalten, D-4800 Bielefeld, BRD

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Abstract. The pattern electroretinogram was recorded in patients with initial stages of visual field defects due to open-angle glaucoma and in age-matched normal subjects. Both normal subjects and glaucoma patients had a visual acuity above 0.8. Counterphasing checkerboard patterns were used as visual stimuli with a range of check sizes from 0.8° to 15° at 7.8 reversals/s. Whereas the amplitude in glaucoma patients was nearly normal for large check sizes, it was significantly reduced for small check sizes ($p = 0.003$). Possibly two separate mechanisms that generate the pattern electroretinogram for small and large checks are differentially affected; they may be related to the magnocellular and parvocellular systems. The difference between normals and glaucoma patients was even more significant when the ratios of the amplitudes at small and large check sizes were compared ($p < 0.0002$). When this ratio is used, the amplitude variability can be partly overcome and the pattern electroretinogram can be a sensitive indicator of ganglion cell function.

Introduction

The earliest recognizable signs of chronic open-angle glaucoma are changes in the retinal nerve fiber layer and the optic nerve head, which usually occur earlier than the visual field defects. As detection of ganglion cell damage by ophthalmoscopy has a great variability between different examiners and often does not give positive results in early stages of the disease as judged by visual field examination, a number of investigators have tried to find early psychophysical disturbances in glaucoma, for a recent review see Drance and Airaksinen [1]. Statistical differences of group means for psychophysical parameters in glaucoma and also in patients with ocular hypertension have been found. Electrophysiological studies in glaucoma revealed amplitude reduction in the visual evoked potential and the pattern electroretinogram (PERG) with pattern-reversal stimuli, while the luminance ERG remained unaltered [2, 3, 4]. However, the wide overlap between parameters of normal and glaucomatous eyes made it impossible to draw diagnostic conclusions for a given individual on the basis of these tests.

In a study concerning the functional origin of the PERG, we found a loss of response to all check sizes, including very large checks (15°) in patients with nearly complete optic atrophy. To study the transition from the normal to the atrophic condition, the present study was designed to analyze the dependency of check size in the PERG in **early** stages of glaucoma.

Material and methods

Glaucoma patients and visual normals

We examined 15 eyes of 9 patients (mean age 60 ± 9 years) with chronic open-angle glaucoma with glaucomatous visual field defects in stage 1 and 2 (stage 1, only relative defects; stage 2, spot-like, or arcuate, absolute defects, not connected with the blind spot [5]) and 8 eyes of 8 age-matched visual normals (mean age 58 ± 6 years). The visual acuity was 0.8 or better, and the visual acuities in normal (mean visual acuity 0.95 ± 0.13) and glaucomatous eyes (mean visual acuity 0.94 ± 0.09) were closely matched. The visual acuity should always be taken into consideration, as reduction of visual acuity to 0.6 by cataract or defocus reduces the PERG amplitudes, especially for small ($\leqslant 0.8°$) checks [6, 7]. No patient included in this study received miotic therapy. Any effect of pupil diameter [8] would thus affect both groups. The refraction was corrected for the viewing distance of 57 cm. The visual fields were tested with an automated static perimeter (Octopus 2000R, program G1).

Stimulation

Steady-state stimuli were presented on a TV monitor with a resolution of 704 × 290 pixel at a frame-rate of 50 Hz. For pattern-stimulation we used high-contrast (98%) checkerboards with a mean luminance of 62 cd/m^2. Check sizes ranged from 0.8° up to a size determined by the stimulus displayed where four checks covered 26° × 34° at the viewing distance of 57 cm (this check size we will refer to as 15°). For all check sizes the borders of the checks met at the center of the screen. The temporal frequency was 3.9 Hz (corresponding to 7.8 reversals/s). Luminance stimulation was performed by flashing the unpatterned display between luminances of 0.1 and 124 cd/m^2 at a flash rate of 7.8/s with a bright-to-dark ratio of 0.5. As no bright surround was provided, some stray light could stimulate the peripheral retina. In the center of the screen a small cross served as fixation mark.

The other eye was patched. To monitor the attention of the subjects, we asked them to report a randomly chosen digit which appeared for 300 ms every 5–10 s instead of the cross.

Recording

ERG responses were recorded with gold foil electrodes [9] placed between lower lid and sclera and referenced to the forehead; one ear was grounded. The signal was amplified and filtered by a standard electroencephalography machine (Tönnies) with a bandpass setting of 1.6–70 Hz (first order filters) and recorded by a small computer (Z80, CP/M +). Analog to digital conversion was performed with a resolution of 10 bits and a sampling rate of 500 Hz. Sweeps of 512 ms duration were averaged and continuously displayed. Sweeps exceeding an adjustable artifact threshold (usually 100 μV) were rejected. The computer also generated the stimuli.

To facilitate Fourier analysis of steady-state responses, the reversal frequency was adjusted to yield an integer number of reversals per sweep, thus eliminating effects of 'spillover' in the spectrum. The amplitude was measured in the frequency domain as the magnitude of the first harmonic at the reversal frequency of 7.8 Hz. An estimate of the noise amplitude, based on the average of the two neighboring frequencies, was subtracted (with extinguished PERG, this procedure occasionally leads to negative amplitudes).

Triggering was frame-locked (thus avoiding latency jitter) and occurred only on even reversals, i.e. only when the top left square became bright. Otherwise luminance responses due to asymmetries, e.g. by erratic fixation in the large check condition, would not be detected and might lead to artifactual high amplitudes at the reversal frequency [10]. With even triggering, asymmetries are easily detected as they produce a strong fundamental response at 3.9 Hz. All stimulus conditions were counterbalanced and measured at least twice to assess the reproducibility.

Results

Fig. 1 depicts PERG traces for a check size of 0.8° (left column), 15° (center), and unpatterned luminance stimulation (right) in a normal subject (top row), a patient with beginning glaucomatous disturbances (middle), and one with advanced optic atrophy due to glaucoma (bottom). Note that under these stimulus conditions the PERG is virtually identical for the small and large check conditions in the normal subject. Optic atrophy (bottom

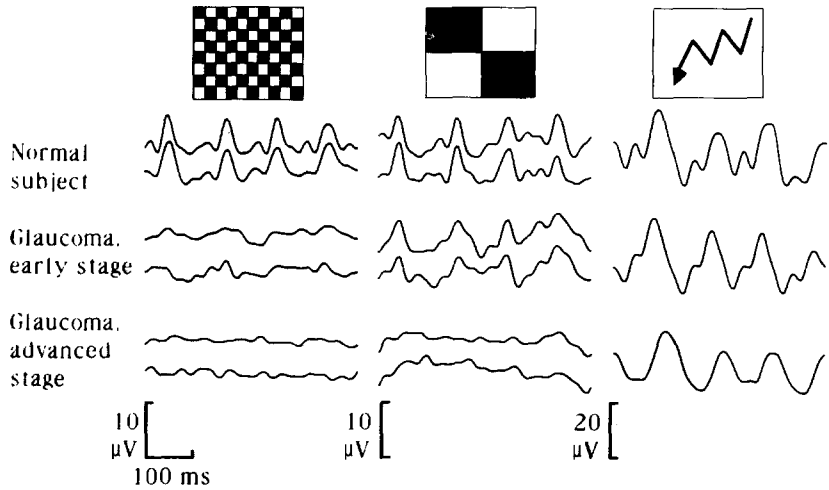

Fig. 1. PERG traces for a check size of 0.8° (left column), 15° (center), and unpatterned luminance stimulation (right). Three cases are depicted: a normal subject (top row), a patient with beginning glaucomatous disturbances (middle), and a patient with advanced optic atrophy due to glaucoma (bottom). The PERG is virtually identical for the small and large check condition in the normal subject. In an early stage of glaucoma (middle row), attenuation of PERG depends on check size. Progressive optic atrophy leads to PERG loss irrespective of check size, while luminance responses are not reduced.

row) leads to PERG loss irrespective of check size, but the luminance response remains intact (the more sinusoidal appearance was not a consistent finding). In early stages of glaucoma we found selective attenuation of PERG amplitude: very low response to 0.8° checks, but near-normal levels when we used 15° checks. This difference in amplitude (based on Fourier analysis) with small and large check sizes is further demonstrated in Fig. 2. Mean amplitudes for normals are about equal for all check sizes, while in early glaucoma patients there is a threefold increase from a low value at 0.8° to an amplitude close to normal at 15° check size. The reduction of mean amplitudes is highly significant ($p < 0.003$) for small check sizes (0.8°), whereas there is no significant difference at large check sizes ($p > 0.05$). The standard error of the mean (SEM) looks higher in the normal eyes. This can be attributed, however, to the lower sample size and to the higher mean amplitude; the relative variance is comparable between normal and early glaucoma eyes.

Our results for the 0.8° check size condition are replotted in Fig. 3, which shows the PERG amplitudes of all eyes and the mean with 96% confidence limits ($\mu \pm 2\,SD$). The categories from left to right indicate normal and glaucomatous eyes in stage 1 and 2 of glaucomatous visual field defects [5]. Although the mean amplitudes of normal and glaucomatous eyes differ

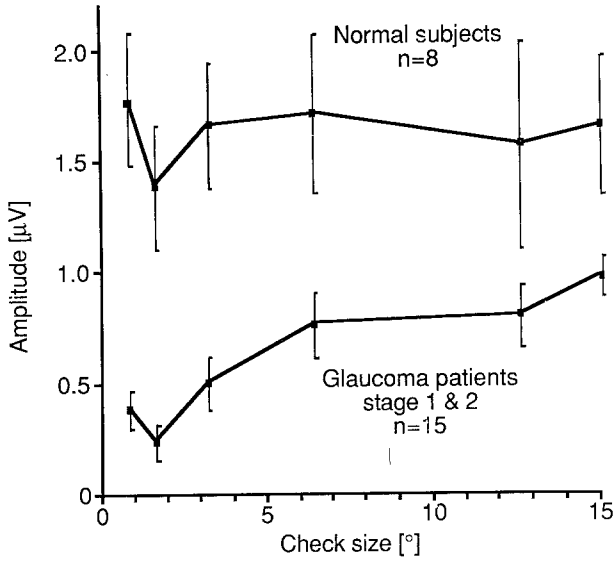

Fig. 2. Mean amplitude (harmonic component at 7.8 reversals/s) and standard error of the mean in 8 normal eyes (top) and 15 glaucomatous eyes (bottom) in stage one and two of visual field defects. The difference between normal subjects and glaucoma patients is most pronounced for a check size of 0.8°.

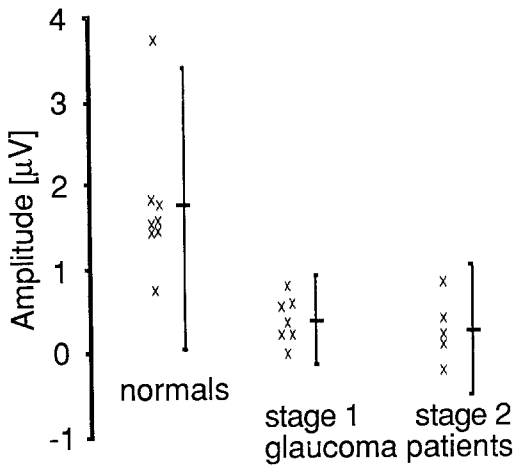

Fig. 3. Raw PERG amplitudes (crosses), mean amplitudes and confidence limits ($\mu \pm 2$SD) for a check size of 0.8°; subjects as in Fig. 2. The confidence interval for normal eyes nearly overlaps the range of the glaucomatous eyes.

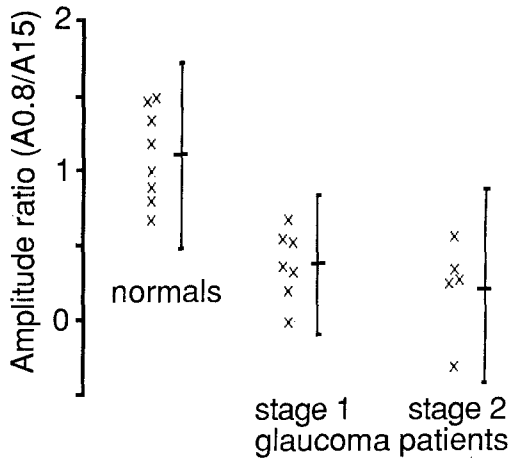

Fig. 4. Raw values, mean values, and 96% confidence limits of the **ratio** of the amplitudes for a check size of 0.8° and at 15°; subjects as in Fig. 2 and 3. The overlap of the confidence intervals of normal subjects and glaucomatous eyes is reduced when compared with raw amplitudes (Fig. 3), increasing diagnostic sensitivity.

significantly, the confidence limit of the normal eyes nearly covers the range of the glaucoma eyes, making it impossible to reliably detect eyes that show an abnormal PERG.

In spite of the large interindividual variability of absolute amplitudes, all individual amplitude vs. check size curves of normal and glaucomatous eyes have a shape similar to the curves obtained when the mean amplitudes of each group are considered (Fig. 2). The curves of the normal eyes generally are horizontal, whereas the curves of glaucomatous eyes ascend when check size increases. This suggests that the **ratio** obtained by dividing the amplitude to 0.8° checks by the amplitude to large (15°) checks (amplitude ratio) might be a better parameter for detection of ganglion cell damage than raw amplitudes. We statistically tested this amplitude ratio and Fig. 4 shows that the overlap of the confidence limits is lower compared with Fig. 3. The difference of the mean amplitude ratio between normals and patients in early stages of glaucoma is highly significant ($p < 0.0002$).

Discussion

The present study shows that the PERG amplitude is differentially affected in early glaucoma, the response to the smaller checks being more affected.

This extends the results of Trick [11] who reported a similar amplitude reduction for check sizes from 0.25° to 2° in glaucoma.

We believe that our results are not due to blurred vision because both patients and normal controls had a visual acuity of 0.8 or better and PERG amplitude reduction in glaucomatous eyes at a check size of 3.2° is comparable with the one at 0.8° (Fig. 2).

The different reduction of the PERG at various check sizes supports the hypothesis that two different mechanisms generate the PERG, one operative at high spatial frequencies (small checks), the other at low spatial frequencies (large checks). The similarity of the amplitude at all check sizes would thus be of an accidental nature. Drasdo et al. [12] have considered the effective retinal contrast, which is reduced because of the optical modulation transfer function of the eye. They postulate a pattern-specific response activated by small checks, while for large checks local luminance may be the relevant stimulus dimension. We agree with this interpretation and add the observation that the latter mechanism is also related to ganglion cell activity, as the response to both large and small checks decreases in advanced and complete optic atrophy. These two mechanisms may possibly be related to the magnocellular and parvocellular systems [13, 14]. The magnocellular system has high contrast sensitivity and may thus predominate for the small check stimulation. In this light, the selective PERG attenuation in glaucomatous eyes for small-check stimulation fits well with recent histological evidence by Quigley et al. [15]. They demonstrated that the large optic nerve fibers, projecting to the magnocellular layers in the lateral geniculate nucleus, are more vulnerable to elevated intraocular pressure than the small fibers.

In spite of the high interindividual variability of the PERG, the *interocular* variability in individuals is low [16]. Consequently, it seemed that individual PERG abnormalities are apparent only in interocular comparison in unilateral eye diseases [2]. Using this technique, Wanger and Persson [17] even found PERG alteration prior to development of glaucoma in patients with ocular hypertension. Using the amplitude *ratio* (amplitude to small checks divided by the one to large checks) also reduces variability and avoids the restriction to uniocular diseases.

Thus the PERG with combined small and large check stimulation overcomes the interindividual variability and increases the sensitivity of the PERG to detect early ganglion cell damage.

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Address for offprints: Dr. M. Bach, Universitäts-Augenklinik, Killianstr. 5, D-7800 Freiburg, BRD.