

Electrophysiological assessment of visual pathways in glaucoma

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ABSTRACT: Purpose. To assess nerve conduction in visual pathways in patients with open-angle glaucoma.

Methods. Pattern-electroretinograms (PERG) and visual-evoked potentials (VEP) were simultaneously recorded in 16 patients with open-angle glaucoma (POAG) and 15 age-matched controls. The visual stimuli were checker-board patterns (the check edges subtend 15'; the contrast was 70% and reversed at the rate of 2 reversals/s).

Results. POAG patients showed significantly higher PERG and VEP latencies (ANOVA: $P < 0.01$) and significantly lower amplitudes than controls; the retinocortical time (RCT: difference between VEP P100 latency and PERG P50 latency) was longer ($P < 0.01$) in POAG than controls and the longer RCT was correlated with the reduced PERG amplitude ($r: 0.798$, $P < 0.01$).

Conclusions. This suggests that POAG patients have an involvement of the innermost retinal layers and impaired nerve conduction in their visual pathways. (Eur J Ophthalmol 1997; 7: 229-35)

KEY WORDS: Visual-evoked potentials, Pattern electroretinograms, Retinocortical time, IOP, Open-angle glaucoma

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INTRODUCTION

The clinical diagnosis of glaucoma is made when intraocular pressure (IOP) is over 21 mmHg, and characteristic optic nerve head cupping and visual field defects are seen.

Clinical evaluation of the retina and optic nerve function may be improved by recording the electroretinographic signals evoked by flash or patterned stimuli (flash or pattern ERG) and the cortical potentials evoked by patterned stimuli (Visual-evoked potentials - VEP).

After section of the optic nerve in cats and monkeys, Maffei and Fiorentini (1-3) observed a decrease in amplitude, and eventually the disappearance, of the electroretinographic signal evoked by pattern stimuli, but the ERG signal evoked by flash stimuli was preserved. These electrophysiological changes were related to ganglion cell degeneration (4, 5).

While the flash ERG originates mostly in the outer

retinal layers, the pattern ERG (PERG) reflects the bioelectrical activity of the innermost retinal layers. By comparing the VEP peak latency (P100) and the PERG peak latency (P50) an index of postretinal nerve conduction can be constructed. We call the difference between VEP P100 latency and PERG P50 latency retinocortical time (RCT - Celesia et al) (6, 7).

Using simultaneous recordings of PERG and VEP, an increase in latency of PERG and VEP and unmodified RCT were observed in patients with maculopathies, suggesting an increase in latency only at the retinal level. Patients with optic nerve demyelination had normal PERG, delayed VEP and prolonged RCT, suggesting a delay in their postretinal visual pathways (6, 7).

Patients with open angle glaucoma (POAG) have been found in several studies to have a normal flash-ERG 8-18, delayed PERG (14, 16, 19-25) and VEP (20, 25-33), but the RCT has never been assessed.

Our goal was to establish whether a correlation existed in ocular hypertensives between the involvement of retinal layers and nerve conduction in the postretinal visual pathways.

SUBJECTS AND METHODS

Simultaneous recordings of PERG and VEP were made on 31 subjects: 15 controls (C) with normal IOP (15 eyes) and 16 patients with POAG (16 eyes). The subjects were informed of the type of examination and its diagnostic uses and gave their informed consent to the study.

The control subjects had IOP <21 mmHg, normal visual acuity, normal visual field (Goldmann perimetry), and no ocular or neurological problems. Their mean age was 50.6 ± 4.4 years. They were age-matched to the POAG patients.

The POAG patients had IOP >21 mmHg, cup/disc ratio >0.5 and mean age 52.1 ± 4.7 years. POAG patients all had typical arcuate visual field loss not involving the tested area (12.5°) and treated only by beta-blockers. Miotic or midriatic drugs were never used.

The participants' main characteristics are reported in Tables I and II.

The subjects were seated for examination in a semi-dark, acoustically isolated room in front of the display that was surrounded by a uniform field of luminance 5 cd/m^2 . VEP and PERG were recorded using the following method. The visual stimuli were checkerboard patterns (contrast 70%, mean luminance 110 cd/m^2) generated on a TV monitor and reversed in contrast at the rate of 2 reversals/s. At the viewing distance of 114 cm the check edges subtend $15'$ and the entire monitor display subtended 12.5 degrees.

VEP response is generated by retinal neurons lying within 2 degrees of the fovea, while the PERG is obtained from a larger retinal area. In accordance with several studies (34-36), we used $15'$ of visual arc because this smaller size is considered "optimal to stimulate the fovea" (36) also in pattern electroretinography. The stimulation was monocular, with occlusion of the other eye.

PERG recordings. The PERG was recorded using platinum hook electrodes inserted into the lateral canthus of the inferior eyelid. Monocular electroretinograms were derived bipolarly between the tested and

the patched eye using the method described by Fiorentini et al (37). Local anesthesia was provided by application of novesine 0.4%. The ground electrode was on the left arm. The inter-electrode resistance was maintained lower than 10 KOhms. The signal was amplified (gain 50000), filtered (band-pass 5-50Hz) and averaged (200 events free from artifacts were averaged for every trial). The analysis time was 250 msec.

The transient PERG response is characterized by a number of waves with three peaks, of negative, positive, and negative polarity, in that order. In normal subjects and in the conditions of our experiment, these peaks have the mean latencies of 35, 50 and 95 msec.

VEP recordings. Cup-shaped electrodes of silver-silver-chloride were fixed with collodion in the following positions: active electrode in Oz, reference electrode in Fpz, ground in left arm. The inter-electrode resistance was kept below 3KOhms. The bioelectric signal was amplified (gain 20000), filtered (band-pass 1-100 Hz) and averaged (200 events free from artifacts were averaged for every trial) using a BM 6000 (Biomedica Mangoni, Pisa, Italy). The analysis time was 250 msec.

The transient VEP response shows a complex wave with an initial negative peak (EEG convention, negative upward) followed by a later positive trough and a second negative peak. In normal subjects and in the conditions of our experiment, these peaks have mean latencies of 75, 100 and 145 msec.

Simultaneous PERG and VEP were recorded at least twice in the recording session and the resulting waveforms were superimposed to check the repeatability of the results.

For all PERG and VEP the peak latency and peak amplitude of each wave were measured directly on the displayed records using a pair of cursors.

We accepted PERG and VEP signals with a signal-to-noise ratio >2. The noise was measured by recording the bioelectrical signals while the monitor was screened with cardboard and was <0.1 microvolt (mean 0.085 microvolt) in all cases.

RESULTS

We considered the results from:

- PERG in control and POAG eyes;
- VEP in control and POAG eyes;

TABLE IA - CONTROL EYES: MAIN FEATURES

| Init. | Eye | Sex | Age | IOP | C/D | VA | VF | P 100 | P 50 | P 50 / N95 | RCT |
|-------|-----|-----|-----|-----|------|---------|----|-------|------|------------|-----|
| VP | l | f | 51 | 15 | 0.20 | 10 / 10 | n | 110 | 56 | 1.8 | 54 |
| PB | r | f | 55 | 16 | 0.20 | 10 / 10 | n | 110 | 57 | 1.6 | 53 |
| ID | r | m | 54 | 13 | 0.30 | 10 / 10 | n | 102 | 53 | 1.9 | 49 |
| CM | r | f | 50 | 14 | 0.30 | 10 / 10 | n | 108 | 55 | 1.9 | 53 |
| LT | r | f | 49 | 15 | 0.35 | 10 / 10 | n | 112 | 60 | 1.7 | 52 |
| AF | l | m | 45 | 14 | 0.20 | 10 / 10 | n | 106 | 53 | 1.8 | 53 |
| CP | r | m | 48 | 16 | 0.30 | 10 / 10 | n | 115 | 63 | 1.5 | 52 |
| LP | l | f | 47 | 13 | 0.30 | 10 / 10 | n | 109 | 58 | 2.0 | 51 |
| CP | r | m | 53 | 15 | 0.25 | 10 / 10 | n | 101 | 52 | 2.0 | 49 |
| RP | l | f | 47 | 13 | 0.20 | 10 / 10 | n | 100 | 52 | 2.3 | 48 |
| FR | r | f | 56 | 15 | 0.30 | 10 / 10 | n | 109 | 53 | 1.3 | 56 |
| RP | l | m | 53 | 14 | 0.30 | 10 / 10 | n | 102 | 47 | 1.4 | 55 |
| PR | l | f | 50 | 13 | 0.20 | 10 / 10 | n | 94 | 48 | 3.1 | 46 |
| MC | r | f | 52 | 12 | 0.30 | 10 / 10 | n | 101 | 47 | 1.8 | 54 |
| FC | r | m | 48 | 15 | 0.25 | 10 / 10 | n | 115 | 63 | 1.7 | 52 |

TABLE IB - POAG PATIENTS: MAIN FEATURES

| Init. | Eye | Sex | Age | IOP | C/D | VA | VF | P 100 | P 50 | P 50 / N95 | RCT |
|-------|-----|-----|-----|-----|------|---------|----|-------|------|------------|-----|
| SP | l | f | 53 | 25 | 0.70 | 10 / 10 | i | 129 | 62 | 0.8 | 67 |
| CP | l | m | 49 | 30 | 0.60 | 10 / 10 | a | 134 | 62 | 0.4 | 72 |
| SS | l | m | 54 | 28 | 0.70 | 10 / 10 | n | 137 | 73 | 0.9 | 64 |
| AS | r | f | 47 | 26 | 0.80 | 10 / 10 | g | 133 | 63 | 0.2 | 70 |
| MA | r | f | 51 | 25 | 0.90 | 10 / 10 | g | 153 | 67 | 0.2 | 86 |
| MP | l | m | 48 | 25 | 0.90 | 10 / 10 | g | 151 | 68 | 0.4 | 83 |
| PP | l | f | 49 | 27 | 0.60 | 10 / 10 | a | 130 | 60 | 0.5 | 70 |
| PE | r | f | 54 | 24 | 0.60 | 10 / 10 | n | 133 | 65 | 0.6 | 68 |
| PI | l | m | 50 | 23 | 0.50 | 10 / 10 | a | 129 | 67 | 1.4 | 62 |
| RF | r | m | 48 | 26 | 0.60 | 10 / 10 | s | 129 | 61 | 0.7 | 68 |
| ME | l | f | 51 | 27 | 0.70 | 10 / 10 | g | 135 | 71 | 1.2 | 64 |
| CD | r | m | 46 | 24 | 0.70 | 10 / 10 | a | 131 | 67 | 1.2 | 64 |
| VF | l | f | 54 | 28 | 0.70 | 10 / 10 | g | 137 | 70 | 0.9 | 67 |
| DP | l | f | 51 | 25 | 0.70 | 10 / 10 | g | 133 | 62 | 0.6 | 71 |
| CF | l | m | 49 | 24 | 0.90 | 10 / 10 | g | 151 | 69 | 0.2 | 82 |
| FC | r | m | 55 | 27 | 0.90 | 10 / 10 | g | 144 | 73 | 0.5 | 71 |

IOP = Intraocular pressure in mmHg (mean of several measures) ; C / D = cup to disk ratio; VA = best corrected Snellen visual acuity; VF = Goldmann visual field; n = nasal step; a = Arcuate scotoma; i = Inferior nasal arcuate scotoma; g = General constriction; s = Superior nasal step; P 100 = latency (msec) to VEP peak P 100; P 50 = latency (msec) to PERG peak P 50; P 50-N95 = PERG amplitude (microvolt); RCT = retinocortical time (difference between VEP P 100 latency and PERG P 50 latency - msec).

TABLE II - MEAN AND STANDARD DEVIATION (±) OF VEP AND PERG RECORDS IN CONTROLS (C) AND PATIENTS WITH OPEN ANGLE GLAUCOMA (G)

| | P 100 | N 75 - P 100 | N 75 / N 145 | P 50 | P 50 - N 95 | RCT |
|---|--------------|--------------|--------------|--------------|-------------|--------------|
| C | 106.27 ± 6.1 | 9.70 ± 2.3 | 54.7 ± 7.6 | 54.47 ± 5.14 | 1.85 ± 0.43 | 51.80 ± 2.76 |
| G | 136.82 ± 8.3 | 5.12 ± 2.4 | 57.3 ± 7.5 | 66.25 ± 4.27 | 0.67 ± 0.37 | 70.56 ± 7.16 |

P100: VEP P100 latency (msec) ; N75 - P 100 : VEP N75 - P100 amplitude (microVolt) ; N75 - N145: VEP time difference N75 / N145 (msec) ; P 50: PERG P50 latency (msec); P50 - N95: PERG P50 - N95 amplitude (microVolt) ; RCT: retinocortical time: difference between VEP P 100 latency (msec) . * P< 0.01 (ANOVA).

TABLE III - REGRESSION ANALYSES AND CORRELATION

| Statistic | Group | No. | r | t | P= |
|--------------------------|-------|-----|-------|-------|-------|
| P50-N95 amplitude vs RCT | C | 15 | 0.851 | 5.846 | 0.000 |
| | POAG | 16 | 0.798 | 4.961 | 0.000 |
| P50 latency vs RCT | C | 15 | 0.093 | 0.336 | 0.742 |
| | POAG | 16 | 0.007 | 0.027 | 0.979 |

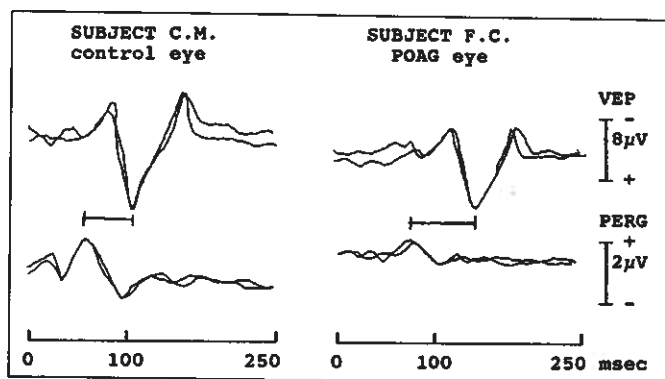


Fig. 1 - Simultaneous recordings of VEP and PERG from subjects C.M. (control eye), and F.C. (POAG eye). POAG eyes had longer VEP P100 latency and PERG P50 latency than the control eye. PERG and VEP amplitudes were reduced in POAG eyes. Retinocortical time (difference between VEP P100 latency and PERG P50 latency - |-----| -) was longer in the POAG eye than the control eye.

were statistically analyzed by one-way analysis of variance (ANOVA) for repeated measures.

Example of simultaneous PERG and VEP recordings from a normal control and POAG patient are shown in Figure 1.

PERG recordings

The mean data are presented in Table II. In the control eyes PERG findings (P50 peak latency, and P50-N95 amplitude) were within normal limits, ie, mean \pm 1SD for P50-N95 amplitude, and mean \pm 3SD for P50 latency. P50 peak latency was significantly longer in POAG eyes than in the control eyes ($F(1, 29) = 48.43, P < 0.01$) and the P50-N95 amplitude was significantly lower in POAG than in control eyes ($F(1, 29) = 67.34, P < 0.01$).

VEP recordings

The mean data are presented in Table II. In the control eyes VEP findings (P100 peak latency, time difference N74/N145, N75-P100 amplitude) were within normal limits, ie, mean \pm 1SD for N75-P100 amplitude, and mean \pm 3SD for P100 latency. P100 peak latency was significantly longer in POAG eyes than in control eyes ($F(1, 29) = 135.38, P < 0.01$) and the N75-P100 amplitudes of the POAG eyes were lower than controls ($F(1, 29) = 28.83, P < 0.01$). The time difference N75/N145 was comparable in the two groups.

Retinocortical time

The mean data are presented in Table II. In the control eyes the RCT was within normal limits, ie, mean \pm 3SD. RCT was significantly higher in POAG eyes than in control eyes ($F(1, 29) = 90.4, P < 0.01$); RCT was inversely related to the PERG amplitude (Fig. 2) and no correlation we found between P50 latency and RCT. Regression analysis is reported in Table III.

DISCUSSION

In agreement with several other reports (19-33), we found delayed PERG and VEP peak latencies and reduced PERG and VEP amplitudes in POAG patients. Since the PERG originates in the innermost retinal

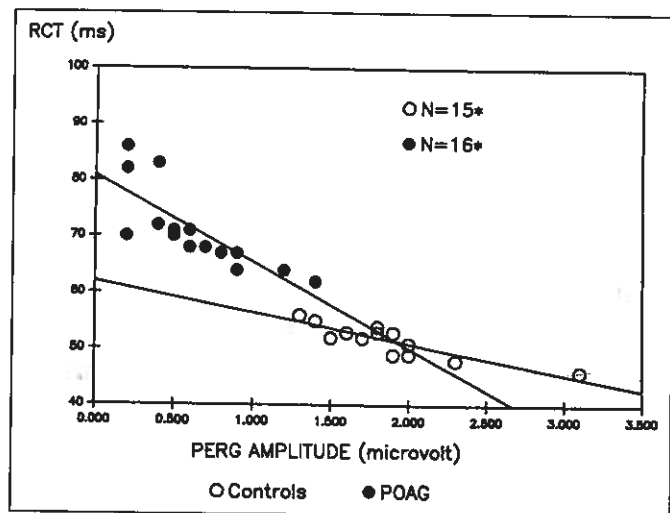


Fig. 2 - P50-N95 PERG amplitude plotted against retinocortical time in control and POAG patients. Least-squares regression analysis - see Table III. * Control couples VP and MC, LT and FC, POAG patient couple ME and CD had the same RCT and PERG amplitudes (see Tables I and II).

— RCT (retinocortical time: difference between VEP P100 peak latency and PERG P50 peak latency) in control and POAG eyes.

In the analysis of PERG records we evaluated the P50 latency and the P50-N95 amplitude. In the analysis of VEP records we evaluated the P100 latency, the temporal difference N75/N145 and the N75-P100 amplitude.

The differences between the control and POAG eyes,

layers these findings indicate that the IOP elevation causes some functional involvement of these layers. This dysfunction may precede the enlargement of the optic nerve head cup and the defects of the visual field, as observed in patients with ocular hypertension and without optic nerve head cupping and visual field defects (19, 22, 23).

We observed an enlargement of the optic head cup in POAG (ratio cup/disc >0.4), ascribed to a loss of ganglion cells and their fibers.

Histological studies in monkeys (38) and humans (39, 40) with chronic glaucoma revealed a loss of retinal ganglion cells (particularly of the class with larger axons) and an enlargement of the optic nerve head cup. This loss of ganglion cells is associated with a reduction in amplitude of the PERG signals, as observed experimentally in monkeys with monocular glaucoma induced by laser photocoagulation of the trabecular meshwork (41).

Although the PERG originates in the ganglion cell layer, we cannot exclude that preganglionic retinal elements of the central retina may contribute to the delayed PERG response. In fact, glaucoma may reduce the amplitude and delay the focal ERG (42-44). This could imply pressure-induced dysfunction of the outer retinal layers, including photoreceptors.

Our POAG patients had a longer RCT and delayed VEP peak latencies. It is unlikely that RCT indicates the real transit time of nerve conduction between the retina and visual cortex; we do not believe that the bioelectrical signal takes 50 msec to travel from the retina to visual cortex in normal subjects. Nonetheless, the data in patients with maculopathies and optic nerve demyelination (6, 7) suggest that RCT can be considered an index of nerve conduction in the postretinal visual pathways.

VEP peak latency increases when the stimulus luminance drops, or when the image outlines are blurred. Glaucoma patients showed impaired contrast sensitivity (45), which might explain the delay in VEP latencies; the blurred image outlines seemed not to influence our electrophysiological tests and in fact our patients presented typical arcuate field loss not involving the tested area (12.5°).

Another way to explain these electrophysiological abnormalities is based on the effects of glaucoma at the dorsal lateral geniculate nucleus (dLGN). Dandona et al (46) observed a decrease in the axonal

transport to the dLGN in monkeys with chronic IOP elevation; in the early stages of the disease they found damage to the ganglion cells that project to the dLGN (magnocellular (M) > parvocellular (P) layers) and loss of dLGN neurons (M>P). After 16 weeks of chronic IOP elevation, P and M layers were both impaired. In five patients with a documented history of glaucoma Chaturvedi et al. (47), on autopsy section of the LGN, observed a loss of magnocellular tissue, but no real difference in the parvocellular layer compared to controls.

The dLGN dysfunction might be a cause of functional changes in those cells that produce the visual evoked response; this is likely to be related both to the increase in RCT and to the delayed VEP observed in POAG patients. The longer RCT in POAG is related to a reduced PERG amplitude, impairment of the innermost retinal layers might well have a specific role in postretinal dysfunction. Thus, in patients with POAG there are two sources of functional impairment, one retinal and one postretinal.

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