# Clinical Ability of Pattern Electroretinograms and Visual Evoked Potentials in Detecting Visual Dysfunction in Ocular Hypertension and Glaucoma

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**Objective:** To assess the presence of normal or abnormal pattern electroretinogram (PERG) and visual evoked potential (VEP) responses in patients with ocular hypertension or open-angle glaucoma (OAG).

**Design:** Retrospective, cross-sectional, case–control study.

**Participants:** Eighty normal control subjects (mean age, $51.77 \pm 6.04$ years; 80 eyes), 68 ocular hypertension patients (mean age, $51.58 \pm 7.12$; 68 eyes; intraocular pressure [IOP] $< 18$ mmHg under pharmacological treatment; Humphrey field analysis [HFA] 24/2 mean deviation [MD] $> -2$ decibels [dB]), and 84 OAG patients (mean age, $52.77 \pm 5.28$; 84 eyes; IOP $< 18$ mmHg under pharmacological treatment; HFA 24/2 mean deviation between $-2$ and $-23$ dB) were enrolled.

**Methods:** Simultaneous recording of PERGs and VEPs using high-contrast (80%) 15′ checkerboard stimuli reversed at the rate of 2 reversals per second.

**Main Outcome Measures:** Pattern electroretinogram P50 and VEP P100 implicit times were considered delayed when exceeding the limit of mean values of controls plus 2 standard deviations (SDs). Pattern electroretinogram P50 to N95 and VEP N75 to P100 amplitudes were considered reduced when exceeding the limit of mean values of controls minus 2 SDs.

**Results:** Pattern electroretinogram: P50 implicit times were delayed in 58 of 68 (85.30%) ocular hypertension eyes and 83 of 84 (98.80%) OAG eyes; P50 to N95 amplitudes were reduced in 47 (69.12%) ocular hypertension eyes and 84 (100%) OAG eyes. Visual evoked potential: P100 implicit times were delayed in 58 (85.30%) ocular hypertension eyes and 84 (100%) OAG eyes; reduced N75 to P100 amplitudes were observed in 39 (57.35%) ocular hypertension eyes and 73 (86.90%) OAG eyes. Ocular hypertension eyes showed no significant correlations (Pearson test, $P > 0.01$) between electrophysiological parameters and age, IOP before or under medical treatment, HFA, and corneal thickness values. Significant correlations ($P < 0.01$) were observed in OAG eyes between electrophysiological results and HFA values. Pattern electroretinogram and VEP responses were normal in all control eyes.

**Conclusions:** Combined PERG/VEP recordings identified a large percentage of ocular hypertension eyes with impairment of the innermost retinal layers, notwithstanding normal optic disc morphology and normal HFA. In OAG eyes, PERG P50 to N95 amplitude and VEP P100 implicit time showed the highest sensitivity/specificity for the detection of a visual dysfunction. The presence of abnormal PERG and/or VEP responses did not allow a clearcut separation between ocular hypertension and OAG eyes. *Ophthalmology 2006;113:216–228 © 2006 by the American Academy of Ophthalmology*

The clinical diagnosis of open-angle glaucoma (OAG) commonly is based on the presence of an increase in intraocular pressure (IOP), characteristic optic nerve head cupping, and typical visual field (VF) defects. In particular, standard static threshold white-on-white perimetry, using an automatic system such as the Humphrey Field Analyzer (HFA; Zeiss, San Leandro, CA), gives useful information to aid in the early recognition of glaucomatous VF damage, and its quantification is used in the assessment of the progression of VF loss.[1–3]

Humphrey Field Analyzer perimetry, however, does not selectively reveal which structures contribute to the impairment of the visual system observed in glaucoma. Alternatively, electrophysiological methods may allow us to explore the different structures that contribute to visual function.

The function of retinal preganglionic elements can be evaluated objectively by recording electroretinographic signals evoked by flash stimuli.[4] Studies in animals[5–7] and humans[8–11] suggest that the function of retinal ganglion cells (RGCs) and their fibers can be assessed by electroretinographic signal recordings evoked by pattern stimuli (PERGs). The function of the entire visual pathway can be assessed by recording cortical potentials evoked by patterned stimuli (visual evoked potentials [VEPs]).[12]

Several studies performed in groups of patients with ocular hypertension without VF defects or in groups of patients with glaucoma showed the presence of normal or impaired electroretinographic signals evoked by flash stimuli,[13–15] impaired PERG,[16–36] and impaired VEP[31–49] responses when compared with the responses obtained in groups of normal subjects.

Nevertheless, notwithstanding these published studies[16–49] and, in particular, those regarding ocular hypertension patients, the assessment of PERG or VEP responses is still not generally used in clinical practice for the evaluation of glaucomatous functional defects. This could be related to the lack of data regarding the clinical ability of PERGs and VEPs to detect visual dysfunction in each ocular hypertensive patient and to distinguish glaucomatous patients from normal subjects.

Therefore, the aim of our work is to evaluate the presence of normal or abnormal PERG and VEP responses in patients with ocular hypertension or OAG and to assess the specificity and sensitivity of PERGs and VEPs to detect visual dysfunction with respect to white-on-white perimetry in glaucoma.

## Materials and Methods

### Patients

Eighty eyes of 80 normal control subjects (age range, 35–65 years [mean, 51.77±6.04]), 68 eyes of 68 patients affected by ocular hypertension (range, 35–64 [mean, 51.58±7.12]), and 84 eyes of 84 patients affected by OAG (range, 38–62 [mean, 52.77±5.28]) were recruited. Each patient had had previous experience with automatic perimetry (at least 6 reliable examinations within the previous 3 years). Ocular hypertension and OAG patients were selected from a large population (272 ocular hypertension and 387 OAG patients) on the basis of inclusion criteria (see below).

Normal subjects had an IOP of ≤21 mmHg; best-corrected visual acuity (BCVA) of 20/20 or better, with a refractive error between −1.00 and +1.00 spherical equivalent (SE); normal 24/2 full-threshold VF (HFA 740), with a mean deviation (MD) of >−0.5 decibels (dB) and corrected pattern standard deviation (CPSD) of <1 dB; and no ocular, metabolic, or neurological diseases.

Inclusion criteria for ocular hypertension patients were

- IOP ≥ 22 mmHg (average of the 2 highest readings of the daily curve [from 8 AM to 6 PM, 6 independent readings, 1 every 2 hours]) without medical treatment
- HFA with an MD of >−2 dB; CPSD <+2 dB; fixation losses, false-positive rate, and false-negative rate each <20%
- BCVA of 20/20 or better
- normal optic discs, based on color stereoslide evaluation performed by one of the authors, which excluded the presence of any of the following signs: rim notch(es), peripapillary splinter hemorrhages, increased vertical-to-horizontal

cup-to-disc (C/D) ratio, C/D asymmetry between the two eyes <0.2
- mean refractive error (when present) between −1.00 and +1.00 SE
- no history or presence of diabetes; optic neuritis; or any disease involving the macula, retina, or visual pathways
- pupil diameter ≥ 3 mm without mydriatic or miotic drugs.

Inclusion criteria for OAG patients were

- IOP > 23 mmHg and < 28 mmHg (average of the 2 highest readings of the daily curve [from 8 AM to 6 PM, 6 independent readings, 1 every 2 hours]) without medical treatment
- HFA with an MD of <−2 dB; CPSD > +2 dB; fixation losses, false-positive rate, and false-negative rate each <20%
- BCVA of 20/20 or better
- ≥1 papillary signs on conventional color stereoslides: presence of a localized loss of neuroretinal rim (notch), thinning of the neuroretinal rim, generalized loss of optic rim tissue, optic disc excavation, vertical or horizontal C/D ratio > 0.5, C/D asymmetry between the two eyes > 0.2, peripapillary splinter hemorrhages
- refractive error (when present) between −1.00 and +1.00 SE
- no history or presence of any disease involving the cornea, lens, macula, or retina
- no history or presence of diabetes, optic neuritis, or any disease involving the visual pathways
- pupil diameter ≥ 3 mm without mydriatic or miotic drugs.

Because it is known that PERG responses can be modified by the pharmacological reduction of IOP,[50–55] we enrolled only ocular hypertension and OAG patients with IOP values of <18 mmHg on β-blocker monotherapy, maintained during the 8 months preceding the electrophysiological evaluation. Intraocular pressure was assessed as the average of the 2 highest readings of the daily curve (from 8 AM to 6 PM, 6 independent readings, 1 every 2 hours).

The research followed the tenets of the Declaration of Helsinki. The protocol was approved by the local institutional review board. Upon recruitment, each patient gave informed consent.

### Electrophysiological Examinations

In agreement with previously published studies,[9,31–36] simultaneous PERG and VEP recordings were performed using the following methods. The PERG and VEP recordings were assessed in ocular hypertension and OAG patients in the presence of an IOP of <18 mmHg with topical treatment (see inclusion criteria).

Subjects were seated in a semidark acoustically isolated room in front of the display, surrounded by a uniform field of luminance of 5 candelas (cd) per meter squared. Before the experiment, each subject was adapted to the ambient room light for 10 minutes, and pupil diameter was approximately 5 mm. Mydriatic or miotic drugs were never used. Stimulation was monocular after occlusion of the other eye. Visual stimuli were checkerboard patterns (contrast, 80%; mean luminance, 110 cd/m²) generated on a television monitor and reversed in contrast at the rate of 2 reversals per second; at the viewing distance of 114 cm, the check edges subtended 15′ of visual angle. The monitor screen subtended 18°. The PERG and VEP recordings were performed with full correction of refraction at the viewing distance. A small red fixation target, subtending a visual angle of approximately 0.5° (estimated after taking into account spectacle-corrected individual refractive errors), was placed at the center of the pattern stimulus. At every PERG and VEP examination, each patient positively reported that he or she could clearly perceive the fixation target. The refraction of all subjects was corrected for viewing distance.

**Electroretinographic Signal Recordings Evoked by Pattern Stimuli.** The bioelectrical signal was recorded by a small silver/

silver chloride skin electrode placed over the lower eyelid. The PERGs were derived bipolarly between the stimulated (active electrode) and the patched (reference electrode) eye using a previously described method.[56] As the recording protocol was extensive, the use of skin electrodes with interocular recording represented a good compromise between signal-to-noise ratio and signal stability. A discussion on PERG using skin electrodes and its relationship to the responses obtained by corneal electrodes can be found elsewhere.[57,58] The ground electrode was in the Fpz scalp location.[59] Interelectrode resistance was lower than 3000 ohms. The signal was amplified (gain, 50 000), filtered (band pass, 1–30 hertz [Hz]) and averaged with automatic rejection of artifacts (200 events free from artifacts were averaged for every trial) by the BM 6000 (Biomedica Mangoni, Pisa, Italy). Analysis time was 250 milliseconds. The transient PERG response is characterized by a number of waves with 3 subsequent peaks (of negative, positive, and negative polarity, respectively). In normal subjects, these peaks have the following implicit times: 35, 50, and 95 milliseconds (N35, P50, N95).

**Visual Evoked Potential Recordings.** Cup-shaped electrodes of silver/silver chloride were fixed with collodion in the following positions: active electrode, Oz[59]; reference electrode, Fpz[59]; and ground, left arm. Interelectrode resistance was kept below 3000 ohms. The bioelectric signal was amplified (gain, 20 000), filtered (band pass, 1–100 Hz), and averaged (200 events free from artifacts were averaged for every trial) by the BM 6000. Analysis time was 250 milliseconds. The transient VEP response is characterized by a number of waves with 3 subsequent peaks (of negative, positive, and negative polarity, respectively). In normal subjects, these peaks have the following implicit times: 75, 100, and 145 milliseconds (N75, P100, N145).

During a recording session, simultaneous VEPs and PERGs were recorded at least twice (2–6 times), and the resulting waveforms were superimposed to check the repeatability of the results.

All control, ocular hypertension, and OAG eyes underwent at least 2 recording sessions 1 to 7 days apart, to determine test–retest variability. For all PERGs and VEPs, implicit times and peak-to-peak amplitudes of each of the averaged waves were measured directly on the displayed records by means of a pair of cursors.

In each subject or patient, the signal-to-noise ratio of PERG and VEP responses was assessed by measuring a noise response while the subject fixated on an unmodulated field of the same mean luminance as the stimulus. At least 2 noise records of 200 events each were obtained, and the resulting grand average was considered for measurement. The peak-to-peak amplitude of this final waveform (i.e., average of at least 2 replications) was measured in a temporal window corresponding to that at which the response component of interest (i.e., VEP, N75–P100; PERG, P50–N95) was expected to peak. Signal-to-noise ratios for this component were determined by dividing the peak amplitude of the component by the noise in the corresponding temporal window. An electroretinographic noise of <0.1 microvolts (mean, 0.085; range, 0.065–0.095, resulting from the grand average of 400–1200 events) and an evoked potential noise of <0.15 microvolts (mean, 0.093; range, 0.072–0.112, resulting from the grand average of 400–1200 events) were observed in all subjects tested. In all subjects and patients, we accepted VEP and PERG signals with a signal-to-noise ratio of >2.

**Central Corneal Thickness Evaluation.** Ultrasonic pachymetry was performed in both eyes of each patient using AL 2000 Bio & Pachymeter (Tomey Corp., Nagoya, Japan). The pachymeter was calibrated at the beginning of each session. After the instillation of a topical anesthetic (oxibuprocain 0.4% [Novesina, Novartis, Origgio, Italy]), the probe was placed perpendicularly on the center of the cornea with an undilated pupil, until a beeping sound, produced by the instrument, was audible. Central corneal thickness measurement was repeated 3 times per eye by a well-trained
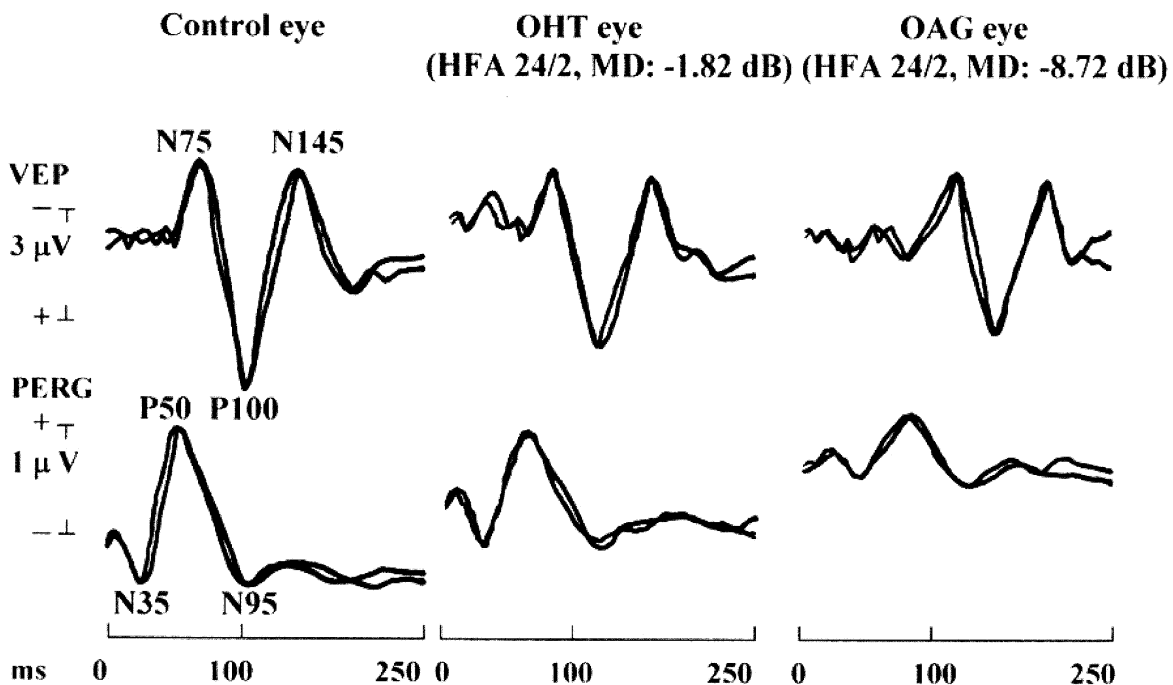


**Figure 1.** Layout of simultaneous recordings of visual evoked potentials (VEPs) and electroretinographic signal recordings evoked by pattern stimuli (PERGs) in one control subject, one eye with ocular hypertension (OHT), and one eye with open-angle glaucoma (OAG). With respect to the control eye, OHT and OAG eyes showed delayed VEP P100 and PERG P50 implicit times and reduced VEP and PERG amplitudes. dB = decibels; HFA = Humphrey field analysis; MD = mean deviation; ms = milliseconds; μV = microvolts.

Table 1. Number of Tested Eyes in Control, Ocular Hypertension (OHT), and Open-Angle Glaucoma (OAG) Groups, with Normal and Abnormal Electrophysiological Responses and Relative Percentage with Respect to the Total Number of Subjects Tested

| | Controls (N = 80) | | OHT (N = 68) | | OAG (N = 84) | |
|---|---|---|---|---|---|---|
| **Parameter** | *Normal* | *Abnormal* | *Normal* | *Abnormal* | *Normal* | *Abnormal* |
| PERG P50 implicit time | 80 (100%) | 0 (0%) | 10 (14.70%) | 58 (85.30%) | 1 (1.20%) | 83 (98.80%) |
| PERG P50–N95 amplitude | 80 (100%) | 0 (0%) | 21 (30.88%) | 47 (69.12%) | 0 (0%) | 84 (100%) |
| VEP P100 implicit time | 80 (100%) | 0 (0%) | 10 (14.70%) | 58 (85.30%) | 0 (0%) | 84 (100%) |
| VEP N75–P100 amplitude | 75 (93.75%) | 5 (6.25%) | 29 (42.65%) | 39 (57.35%) | 11 (13.10%) | 73 (86.90%) |

PERG = electroretinographic signal recordings evoked by pattern stimuli; VEP = visual evoked potential.

operator (MC), and the mean of these values was used in the statistical analysis.

## Statistics

In ocular hypertension and OAG patients, HFA, MD, and CPSD values observed in the last examination (performed during a period of 1–7 days with respect to the electrophysiological assessment) were considered in the statistical analysis. In separate sessions, test–retest data for PERG and VEP results were expressed as the mean difference between 2 records plus or minus the corresponding standard deviation (SD) of this difference. Ninety-five percent confidence intervals (CIs) of test–retest variability in normal subjects and patients were established assuming a normal distribution. Taking into account this test–retest variability, in all normal and affected eyes the PERG recording with the smallest amplitude values was selected, and the corresponding electrophysiological parameters (either PERG or VEP) were considered in the statistical analysis.

To evaluate the presence of normal or abnormal PERG and VEP responses independently from the clinical conditions of the tested subject, all electrophysiological examinations were performed by one operator (VP), who did not know if the tested subject belonged to the category of control subjects or ocular hypertension or OAG patients, as classified by 2 other operators (GM, MC).

Normal limits were obtained from control subjects by calculating mean values + 2 SDs for PERG and VEP implicit times and mean values − 2 SDs for PERG and VEP amplitudes.

Receiver operating characteristic (ROC) analysis was performed on continuous variables derived from each electrofunctional test (PERG and VEP). We plotted the ROC curves, which graph sensitivity versus 1−specificity for each possible cutoff point across the range of measurements for each PERG and VEP parameter. The cutoff was established between the greatest value observed for controls and the lowest value observed for pooled ocular hypertension and OAG eyes. Sensitivity refers to the ability of a test to detect electrophysiological abnormalities in the presence of ocular hypertension or OAG, whereas specificity evaluates the presence of a normal response in subjects without ocular hypertension or OAG. Sensitivity and specificity were calculated by means of standard formulas. We subsequently calculated the area under the ROC curve, termed $A_z$, using Hanley and McNeil's method.[60] $A_z$ represents the aggregate ability of the PERG or VEP parameter to separate normal eyes from ocular hypertension or OAG eyes, and ocular hypertension from OAG eyes.

Results from controls and ocular hypertension and OAG eyes were compared by 1-way analysis of variance. The Pearson correlation was used to correlate age, IOP, central corneal thickness, MD, and CPSD values to all electrophysiological parameters.

In all analyses, a *P* value < 0.01 was considered statistically significant.

## Results

Examples of simultaneous PERG and VEP recordings from a normal subject, an ocular hypertension patient, and an OAG patient are shown in Figure 1. The presence of normal and abnormal electrophysiological responses in control, ocular hypertension, and OAG groups and relative percentages with respect to the total number of subjects tested are reported in Table 1. Mean data and relative statistical analysis of electrophysiological parameters observed in control subjects and ocular hypertension and OAG patients are presented in Table 2.

Table 2. Mean Values ± 1 Standard Deviation of Electrophysiological Parameters Observed in Control Subjects (C) and Ocular Hypertension (OHT) and Open-Angle Glaucoma (OAG) Patients

| Group | N | Age (yrs) | HFA 24/2 MD (dB) | PERG P50 Implicit Time (ms) | PERG P50–N95 Amplitude (microvolts) | VEP P100 Implicit Time (ms) | VEP N75–P100 Amplitude (microvolts) |
|---|---|---|---|---|---|---|---|
| Controls | 80 | 51.77±6.04 | −0.79±0.65 | 52.288±2.87 | 1.695±0.26 | 105.41±3.10 | 8.03±1.09 |
| OHT | 68 | 51.59±7.12 | −1.19±0.59 | 62.79±4.19 | 1.039±0.28 | 116.53±4.99 | 5.24±1.60 |
| A vs. C ($F_{1,146}$) | | 0.03, P = 0.86 | 22.72, P<0.01 | 323.9, P<0.01 | 212.1, P<0.01 | 273.3, P<0.01 | 157.41, P<0.01 |
| OAG | 84 | 52.77±5.28 | −8.43±4.34 | 66.91±3.85 | 0.506±0.17 | 133.19±6.00 | 3.60±1.65 |
| A vs. C ($F_{1,162}$) | | 0.128, P = 0.260 | 248.4, P<0.01 | 754.52, P<0.01 | 1168.5, P<0.01 | 1367.1, P<0.01 | 407.32, P<0.01 |
| A vs. OHT ($F_{1,150}$) | | 0.140, P = 0.239 | 186.2, P<0.01 | 38.74, P<0.01 | 209.3, P<0.01 | 1345.6, P<0.01 | 22.72, P<0.01 |

A = 1-way analysis of variance; dB = decibels; HFA = Humphrey field analysis; MD = mean deviation; ms = milliseconds; N = no. of eyes tested; PERG = electroretinographic signal recordings evoked by pattern stimuli; VEP = visual evoked potential.

## Electroretinographic Signal Recordings Evoked by Pattern Stimuli

Figure 2 shows individual values of PERG P50 implicit time and PERG P50 to N95 amplitude observed in control subjects and ocular hypertension and OAG patients plotted as a function of the corresponding values of MD of HFA 24/2.

In control subjects, test–retest data for PERG P50 implicit times and P50 to N95 amplitudes were, respectively, mean, 0.042 milliseconds (SD, 0.83; 95% CI, −1.618 to 1.702), and mean, 0.0038 microvolts (SD, 0.086; 95% CI, −0.168 to 0.175).

In all control eyes, PERG parameters (P50 implicit time and P50–N95 amplitude) were within our current 95% CIs. Therefore, because no control subject showed abnormal implicit time or amplitude values, the specificity of P50 implicit time and specificity of P50 to N95 amplitude were estimated to be 100%.

In ocular hypertension eyes, test–retest data for PERG P50 implicit times and P50 to N95 amplitudes were, respectively,

mean, 0.047 milliseconds (SD, 0.81; 95% CI, −1.573 to 1.667), and mean, 0.0042 microvolts (SD, 0.092; 95% CI, −0.179 to 0.188).

In ocular hypertension eyes, P50 implicit time was normal in 10 of 68 (14.70%) eyes and delayed in 58 of 68 (85.30%) eyes, and the P50 to N95 amplitude was normal in 21 of 68 (30.88%) eyes and abnormally reduced in 47 of 68 (69.12%) eyes. On average, P50 implicit time was significantly ($P<0.01$) delayed, and P50 to N95 amplitude was significantly ($P<0.01$) reduced, with respect to the control group. Table 3 reports the correlations between PERG parameters and other clinical characteristics of ocular hypertension eyes. No significant correlations ($P>0.01$) were observed between P50 implicit time or P50 to N95 amplitude and age, IOP before pharmacological treatment, percentage decrease in IOP under pharmacological treatment with respect to IOP before pharmacological treatment, central corneal thickness, and HFA 24/2 MD or CPSD.

In OAG eyes, test–retest data for PERG P50 implicit times and P50 to N95 amplitudes were, respectively, mean, 0.052 milliseconds (SD, 0.88; 95% CI, −1.708 to 1.812), and mean, 0.0046 microvolts (SD, 0.099; 95% CI, −0.193 to 0.202). In OAG eyes, P50 implicit time was normal in 1 of 84 (1.20%) eyes and delayed in 83 of 84 (98.80%) eyes, and the P50 to N95 amplitude was reduced in all 84 (100%) eyes.

The greatest P50 to N95 amplitude attenuation was found in OAG eyes with the greatest VF deficits (amplitude values around 0.2 microvolts). Notwithstanding this marked impairment, in none of these eyes was PERG considered as not recordable, because the signal-to-noise ratio was always >2 (i.e, the eye with the lowest amplitude was OAG no. 34, with an amplitude of 0.19 microvolts and a noise of 0.078 microvolts obtained from 600 events). Considering the number of abnormal responses in OAG eyes, the sensitivity of P50 implicit time was calculated to be 98.80% and the sensitivity of the P50 to N95 amplitude was 100%. On average, we observed significantly ($P<0.01$) delayed P50 implicit times and significantly ($P<0.01$) reduced P50 to N95 amplitudes, when compared to the corresponding values of the control group.

Figure 2 shows individual OAG P50 implicit time values and P50 to N95 amplitude values plotted as a function of corresponding values of MD of HFA. Significant correlations ($P<0.01$) were found between P50 implicit time or P50 to N95 amplitude and HFA 24/2 MD. In addition, CPSD was correlated significantly with P50 implicit time ($r = 0.421$, $P<0.01$) and P50 to N95 amplitude ($r = -0.546$, $P<0.01$).

Figure 3 shows individual ocular hypertension and OAG P50 implicit time values plotted as a function of corresponding values of P50 to N95 amplitude values. In ocular hypertension eyes, there is a weak correlation between the increase in P50 implicit time and the reduction in P50 to N95 amplitude, whereas this correlation was tighter in OAG eyes.

Figure 4 reports the ROC analyses and the $A_z$ scores for PERG P50 implicit time and P50 to N95 amplitude. The $A_z$ score suggests that PERG P50 implicit time and P50 to N95 amplitude may allow a good separation between control and ocular hypertension eyes and between control and OAG eyes. A weak separation can be observed when ocular hypertension eyes are compared with OAG eyes.

## Visual Evoked Potential

Figure 5 shows individual values of the VEP P100 implicit time and VEP N75 to P100 amplitude observed in control subjects and ocular hypertension and OAG patients plotted as a function of the corresponding values of HFA 24/2 MD.

In control subjects, test–retest data for VEP P100 implicit times and N75 to P100 amplitudes were, respectively, mean, 0.046
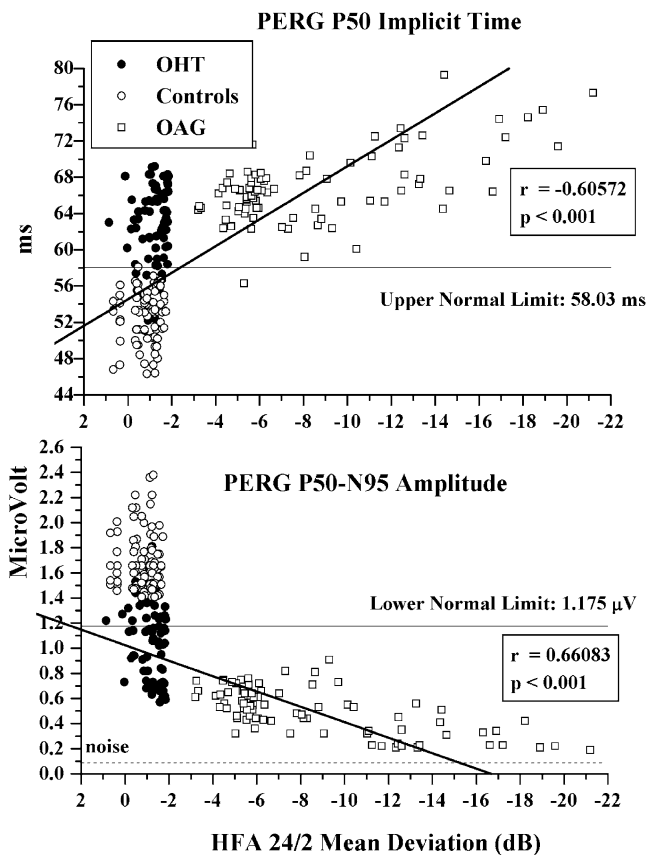


**Figure 2.** Individual electroretinographic signal recording evoked by pattern stimuli (PERG) P50 implicit time values and PERG P50 to N95 amplitude values plotted against Humphrey field analysis (HFA) 24/2 mean deviation (MD) in control, ocular hypertension (OHT), and open-angle glaucoma (OAG) eyes. For PERG P50 implicit time, the normal upper limit was obtained by calculating the mean value observed in our control subjects plus 2 standard deviations (SDs). For the PERG P50 to N95 amplitude, the normal lower limit was obtained by calculating the mean value observed in our control subjects minus 2 SDs. In OAG eyes, PERG P50 implicit time values and PERG P50 to N95 amplitude values also were correlated to the corresponding values of Humphrey 24/2 parameters (MD). The Pearson test was used for regression analysis and correlations. dB = decibels; ms = milliseconds; μV = microvolts.

Table 3. Correlation (Pearson Test) between Electrophysiological Responses and Other Clinical Characteristics in Eyes with Ocular Hypertension

| | Age (yrs) | IOP-B (mmHg) | IOP-D (mmHg) | CCT (μm) | MD (dB) | CPSD (dB) |
|---|---|---|---|---|---|---|
| PERG P50 implicit time (ms) | | | | | | |
| r | 0.093 | 0.097 | 0.088 | −0.130 | −0.089 | 0.202 |
| P | 0.458 | 0.948 | 0.742 | 0.583 | 0.512 | 0.091 |
| PERG P50–N95 amplitude (μV) | | | | | | |
| r | −0.127 | −0.054 | −0.063 | 0.111 | 0.278 | −0.074 |
| P | 0.301 | 0.674 | 0.574 | 0.640 | 0.072 | 0.572 |
| VEP P100 implicit time (ms) | | | | | | |
| r | 0.099 | −0.049 | −0.083 | 0.293 | −0.008 | 0.194 |
| P | 0.418 | 0.687 | 0.572 | 0.097 | 0.942 | 0.082 |
| VEP N75–P100 amplitude (μV) | | | | | | |
| r | 0.038 | −0.196 | −0.107 | 0.230 | 0.154 | 0.073 |
| P | 0.753 | 0.107 | 0.193 | 0.389 | 0.192 | 0.581 |

CCT = central corneal thickness; CPSD = corrected pattern standard deviation of Humphrey field analysis 24/2; dB = decibels; IOP-B = intraocular pressure before pharmacological treatment; IOP-D = percentage decrease in IOP under pharmacological treatment with respect to the IOP before pharmacological treatment; MD = mean deviation of Humphrey field analysis 24/2; ms = milliseconds; μV = microvolts; PERG = electroretinographic signal recordings evoked by pattern stimuli; VEP = visual evoked potential.

milliseconds (SD, 0.79; 95% CI, −1.534 to 1.626), and mean, 0.0046 microvolts (SD, 0.126; 95% CI, −0.247 to 0.256). In all control eyes, VEP P100 implicit times were within our current 95% CI. Because no control subject showed abnormal implicit time or amplitude values, the specificity of P100 implicit time was
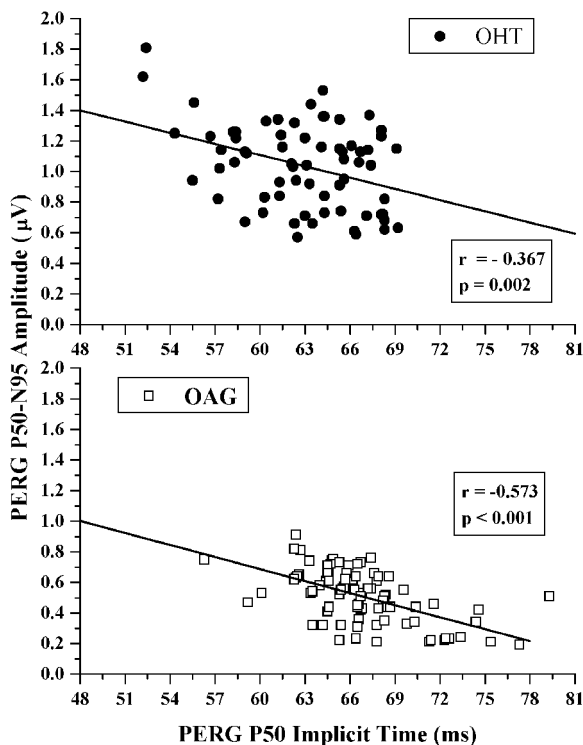


**Figure 3.** Individual electroretinographic signal recording evoked by pattern stimuli (PERG) P50 to N95 amplitude values observed in ocular hypertension (OHT) and open-angle glaucoma (OAG) eyes plotted as a function of the corresponding PERG P50 implicit time values. The Pearson test was used for regression analysis and correlations. ms = milliseconds; μV = microvolts.
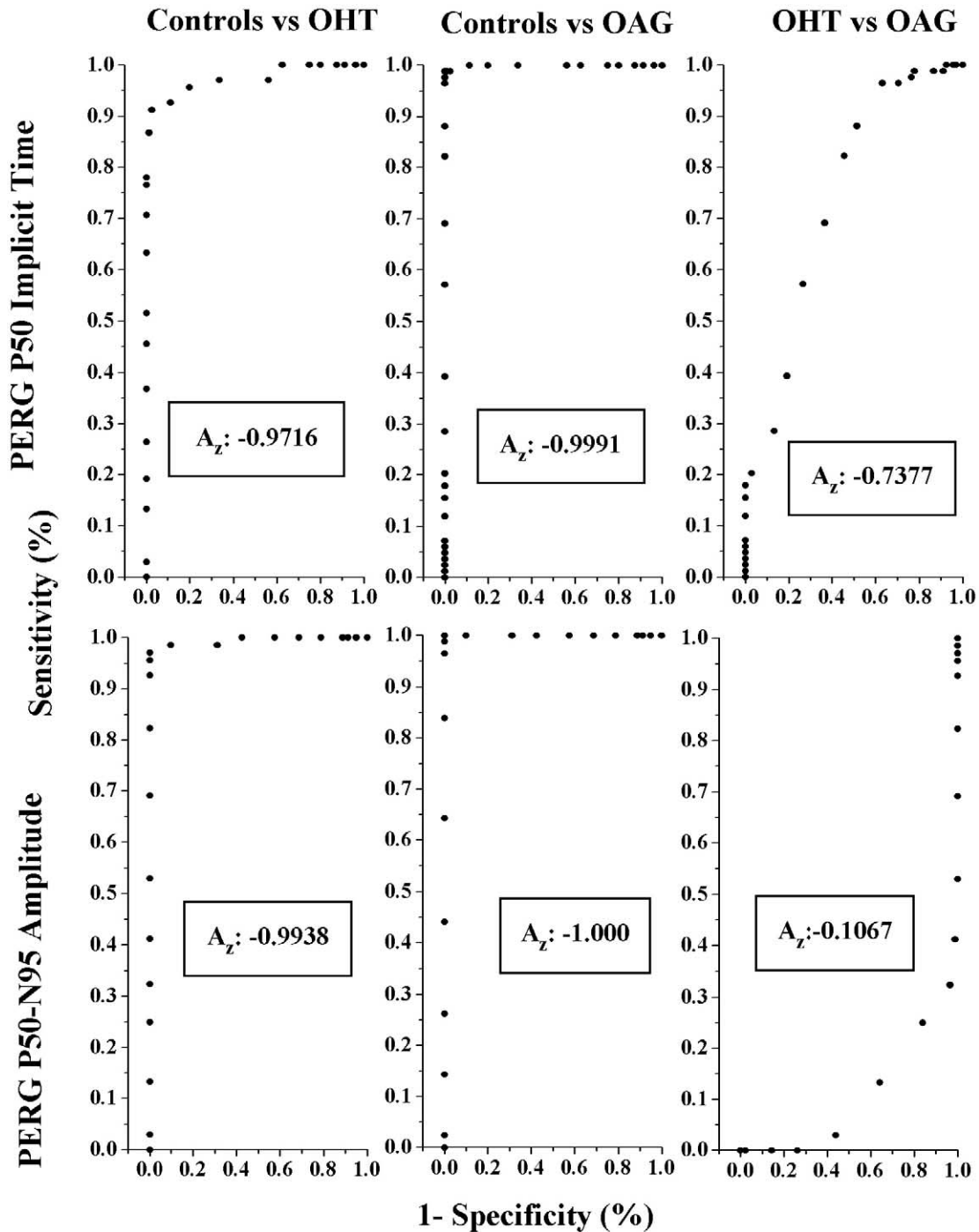
estimated to be 100%. Visual evoked potential N75 to P100 peak amplitudes were within our normal limits in 75 (93.75%) control eyes and abnormally reduced in 5 (6.25%) control eyes. The specificity of the N75 to P100 amplitude was estimated to be 93.75%.

In ocular hypertension eyes, test–retest data for VEP P100 implicit times and N75 to P100 amplitudes were, respectively, mean, 0.049 milliseconds (SD, 0.82; 95% CI, −1.531 to 1.689), and mean, 0.0052 microvolts (SD, 0.115; 95% CI, −0.109 to 0.235).

In ocular hypertension eyes, P100 implicit time was normal in 10 of 68 (14.70%) eyes and delayed in 58 of 68 (85.30%) eyes; N75 to P100 amplitude was normal in 29 of 68 (42.65%) eyes and abnormally reduced in 39 of 68 (57.35%) eyes. On average, P100 implicit time was significantly (*P*<0.01) delayed and N75 to P100 amplitude was significantly (*P*<0.01) reduced with respect to control eyes.

Table 3 reports the correlations between VEP parameters and other clinical characteristics observed in ocular hypertension eyes. No significant correlations (*P*>0.01) were found between P100 implicit time or N75 to P100 amplitude and age, IOP before pharmacological treatment, percentage decrease in IOP under pharmacological treatment with respect to IOP before pharmacological treatment, central corneal thickness, or HFA 24/2 MD or CPSD.

In OAG eyes, test–retest data for VEP P100 implicit times and N75 to P100 amplitudes were, respectively, mean, 0.055 milliseconds (SD, 0.92; 95% CI, −1.785 to 1.895), and mean, 0.0066 microvolts (SD, 0.148; 95% CI, −0.141 to 0.302).

In OAG eyes, P100 implicit time was delayed in all 84 (100%) eyes, and N75 to P100 amplitude was normal in 11 of 68 (13.10%) eyes and abnormally reduced in 73 of 84 (86.90%) eyes. Considering the number of abnormal responses in OAG eyes, the sensitivity of P100 implicit time was estimated to be 100%, and the sensitivity of N75 to P100 amplitude was 86.90%.

On average, P100 implicit time was significantly (*P*<0.01) delayed, and N75 to P100 amplitude was significantly (*P*<0.01) reduced, with respect to corresponding values of control subjects.

Figure 5 reports individual P100 implicit time values and N75 to P100 amplitude values plotted as a function of corresponding values of HFA MD. Significant correlations (*P*<0.01) were found

**Figure 4.** Receiver operating characteristic (ROC) curves for electroretinographic signal recording evoked by pattern stimuli (PERG) P50 implicit time and P50 to N95 amplitude. The area under the ROC curve ($A_z$) score provides a good separation between controls and ocular hypertension (OHT) and open-angle glaucoma (OAG) eyes, whereas there is a weak separation between OHT and OAG eyes. The highest separation can be observed in the PERG P50 to N95 amplitude evaluation between controls and OAG eyes.

between P100 implicit time or N75 to P100 amplitude and HFA 24/2 MD. In addition, CPSD was significantly correlated with P100 implicit time ($r = 0.434$, $P<0.01$) and N75 to P100 amplitude ($r = -0.601$, $P<0.01$).

In both ocular hypertension and OAG eyes, the delay in VEP P100 implicit time was significantly ($P<0.01$) correlated to the increase in PERG P50 implicit time. In Figure 6, individual

ocular hypertension and OAG PERG P50 implicit time values are plotted as a function of corresponding values of VEP P100 implicit times.

Figure 7 reports ROC analyses and $A_z$ scores for VEP P100 implicit times and N75 to P100 amplitudes. The $A_z$ score suggests that VEP P100 implicit times and N75 to P100 amplitudes may allow a good separation between control and ocular hypertension
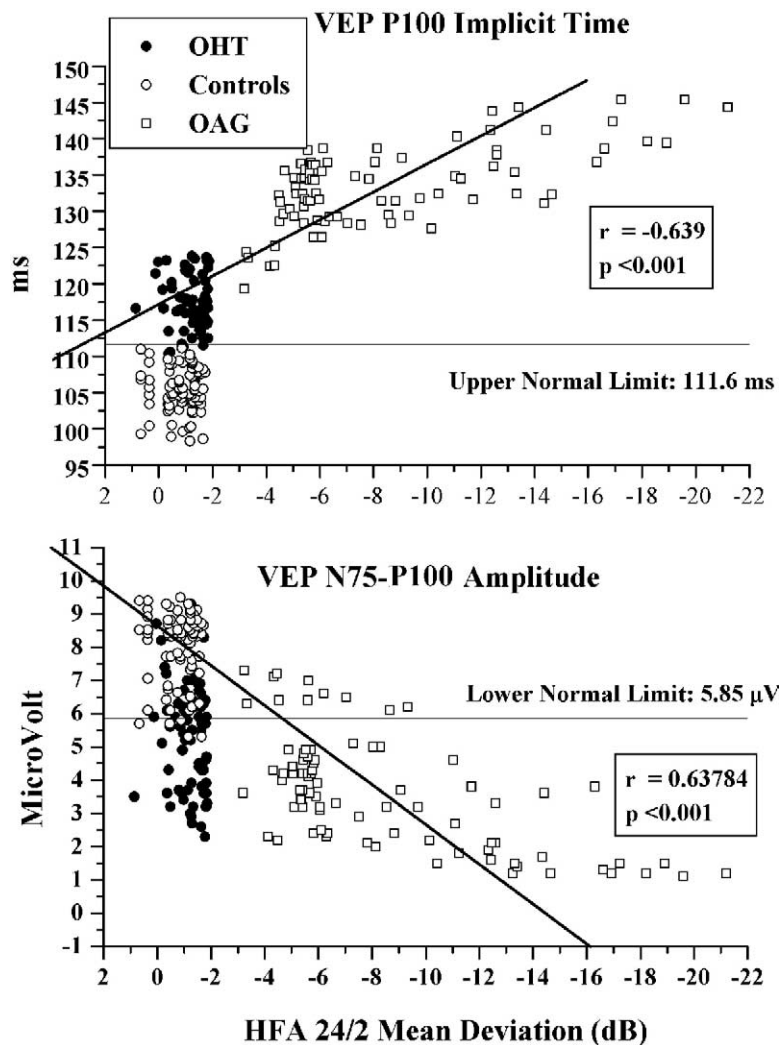
**Figure 5.** Individual visual evoked potential (VEP) P100 implicit time values and VEP N75 to P100 amplitude values plotted against Humphrey 24/2 mean deviation (MD) in control, ocular hypertension (OHT), and open-angle glaucoma (OAG) eyes. For VEP P100 implicit time, the normal upper limit was obtained by calculating the mean value observed in our control subjects plus 2 standard deviations (SDs). For VEP N95 to P100 amplitude, the normal lower limit was obtained by calculating the mean value observed in our control subjects minus 2 SDs. In OAG eyes, VEP P100 implicit time values and VEP N75 to P100 amplitude values also were correlated to the corresponding values of Humphrey 24/2 parameters (MD). The Pearson test was used for regression analysis and correlations. ms = milliseconds; μV = microvolts.

eyes and between control and OAG eyes. A weak separation can be observed when ocular hypertension eyes are compared with OAG eyes.

## Discussion

Our work was designed to evaluate the presence of normal or abnormal PERGs and VEPs in a selected population of patients with increased IOP with (OAG patients) or without (ocular hypertension patients) HFA defects. In our study, patients suffering from normal-tension glaucoma or low-tension glaucoma were not included.

Because it is known that several pathologies affecting photoreceptors (e.g., retinitis pigmentosa[61]), ganglion cells (e.g., diabetes,[62] optic neuritis[9]), the macula,[63] or visual

pathways[63] may induce PERG and VEP abnormalities, our ocular hypertension and OAG patients were selected on the basis of very restricted criteria (see inclusion criteria). Therefore, our data were derived from a nontypical population. On the other hand, many if not all psychophysical testing procedures currently employed for glaucoma detection (e.g., HFA, contrast sensitivity, chromatic testing) can be altered significantly by the concomitance of the above-mentioned pathologies.

The main findings of the present study can be summarized as follows: first, a large population of ocular hypertension patients may show PERG and VEP impairment in the absence of VF defects, and second, in OAG patients the PERG P50 to N95 amplitude and VEP P100 implicit time have a sensitivity of 100% in detecting visual dysfunction. For each PERG and VEP parameter, the analysis of ROC
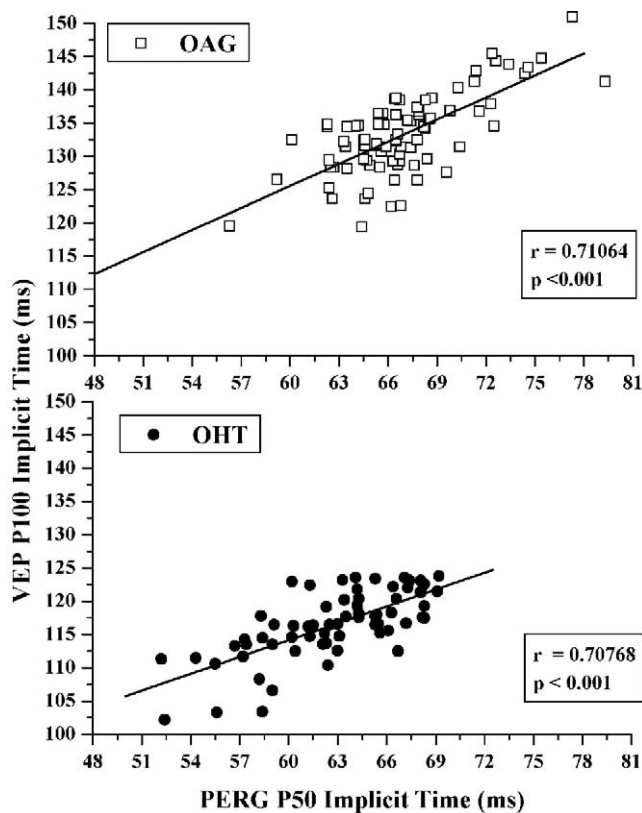
**Figure 6.** Individual visual evoked potential (VEP) P100 implicit time values observed in open-angle glaucoma (OAG) eyes plotted as a function of the corresponding values of electroretinographic signal recording evoked by pattern stimuli (PERG) P50 implicit time values. The Pearson test was used for regression analysis and correlations. ms = milliseconds; OHT = ocular hypertension.

curves provided a good separation between controls and both ocular hypertension and OAG eyes. In contrast, the ability of electrophysiological testing to discriminate between ocular hypertension and OAG eyes was not as good.

Our PERG results are in agreement with other studies in which abnormal PERG responses (P50–N95 amplitude was most frequently the main outcome measure) were detected in large cohorts of ocular hypertension and OAG patients. Our ocular hypertension data are consistent with those of other studies in which patients without VF defects, some disc abnormality, and/or a positive family history were defined as suspected glaucoma, preperimetric glaucoma, or high-risk glaucoma. However, in the current study our ocular hypertension patients had a normal disc on color stereoslide evaluation. In previous studies,[17,18,24,28] it was reported that the percentage of abnormal PERG results ranged from 41% to 73%. In the current study, we found abnormal PERG amplitudes in 69.12% of ocular hypertension eyes. It has been reported that the incidence of PERG abnormalities in OAG eyes ranges from 75% to 94%.[3,17,27–30] In the current study, we observed abnormal PERG amplitudes in 100% of OAG patients. This discrepancy (which is likely to be mainly an effect of statistical variability) could be ascribed to the type of visual stimuli employed in the different

studies. In the present study, the stimuli were high-contrast (80%) 15′ checkerboards reversed at the rate of 2 reversals per second, whereas in other studies different stimulation protocols (e.g., transient 48′[18,27,30] and 30′[3,17] checks, steady-state 1.7 cycles per degree gratings[28]) were used. All this suggests that the present stimulus is at least as sensitive and specific as the others for detecting PERG impairment in both ocular hypertension and OAG eyes. In addition, this discrepancy could be ascribed to the different criteria employed for the selection of patients (e.g., demographics, perimetric MD, optic nerve appearance, IOP history) and, even more relevant, for that of control subjects.

Our VEP findings in ocular hypertension and OAG eyes are in accordance with other studies in which abnormal VEP responses were found (in particular, when P100 implicit time was considered as the main parameter). It should be considered that in several studies[34–36,41,44,48,49] the statistical difference between control and ocular hypertension/ OAG groups is reported only for the average value without defining the ratio of normal to abnormal VEP responses in ocular hypertension or OAG patients. In addition, our results are not comparable to those obtained using multifocal or other types of visual stimuli.[42,44] On the other hand, our OAG results are in full agreement with Horn et al's[45] and Momose et al's,[46] in which abnormal VEP P100 implicit time was observed in all preperimetric or perimetric glaucoma eyes.

Electroretinographic signal recordings evoked by pattern stimuli and VEPs were recorded in ocular hypertension and OAG eyes in the presence of pharmacologically reduced (β-blocker treatment) IOP. This type of treatment was performed on the basis that an increase in PERG amplitude (ranging from 10% to 200%[51,55]) after IOP lowering by using β-blockers[50–54] or acetazolamide[55] has been observed.

In ocular hypertension eyes, no correlations were observed between IOP values without treatment and the presence of abnormal PERG and VEP responses, suggesting that history of elevated IOP may not be the only factor associated with an electrofunctional impairment. This is in agreement with the current opinion[64] that the role of elevated IOP is considered as not exclusive for the onset of the visual dysfunction in glaucoma.

It can also be suggested that some ocular hypertension eyes may have abnormal electrophysiological responses despite IOP lowering, and this could represent a potential risk factor for conversion to glaucoma. Appropriate longitudinal studies are required in our selected population to clarify whether ocular hypertension patients with abnormal PERG and VEP responses may develop VF and optic nerve glaucomatous characteristic defects. On the other hand, those ocular hypertension eyes with PERG and VEP responses within our normal limits cannot definitely be identified as truly normal, as we cannot exclude a treatment-related electrophysiological improvement of PERG and VEP responses with consequent partial functional restoration of ganglion cell function. In those eyes in which abnormal electrophysiological responses were found, it is not possible to exclude that a further reduction of IOP could induce an improvement in both PERG and VEP responses, possibly towards our normal limits.
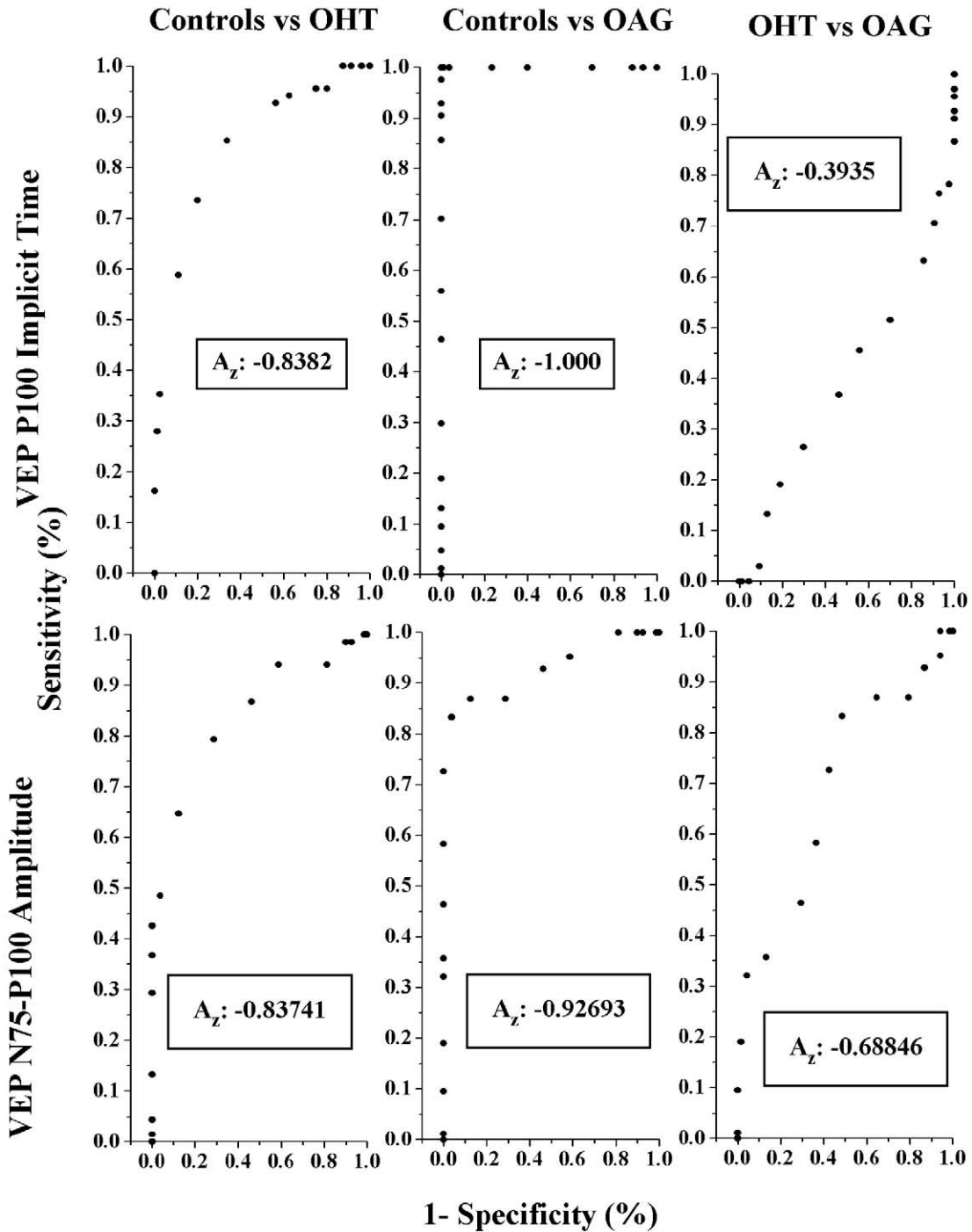
**Figure 7.** Receiver operating characteristic (ROC) curves for visual evoked potential (VEP) P100 implicit time and N75 to P100 amplitude. The area under the ROC curve ($A_z$) score provides a good separation between controls and ocular hypertension (OHT) and open-angle glaucoma (OAG) eyes, whereas there is a weak separation between OHT and OAG eyes. The highest separation can be observed in the VEP P100 implicit time evaluation between controls and OAG eyes.

The lack of correlation between PERG parameters and central corneal thickness (it is known that corneal thickness may represent an important parameter in the estimation of IOP[65,66]) may also indicate that in ocular hypertension eyes with normal PERG and VEP responses there was no overestimation of IOP, whereas in ocular hypertension eyes with abnormal PERG and VEP responses, which overlapped with the range of responses in OAG eyes, there was no underestimation of IOP.

Some considerations should be made regarding the clinical significance of PERG and VEP responses obtained in ocular hypertension and OAG eyes.

## Electroretinographic Signal Recordings Evoked by Pattern Stimuli in Ocular Hypertension and Open-Angle Glaucoma Eyes and Their Clinical Significance

It is known that in humans the integrity of the innermost retinal layers is required to obtain a normal PERG response,[8–11,66–68] and therefore, PERGs may play a clinical role as direct and objective indexes of the function of RGCs and their fibers. The absence of abnormal PERG responses in our control eyes indicates that PERGs may have a specificity of 100%. In both ocular hypertension and OAG eyes, we found a delay in PERG P50 implicit time and a reduction in P50 to N95 amplitude. The delay in the P50 component observed in our ocular hypertension or OAG eyes cannot be ascribed exclusively to a pure RGC dysfunction because a contribution of preganglionic elements has been suggested in the genesis of the P50 component.[69]

The relative contribution of preganglionic and ganglionic dysfunction in the genesis of the P50 delay could also be interpreted in light of the data obtained from the correlations between the increase in P50 implicit time and the decrease in P50 to N95 amplitude. In ocular hypertension eyes, the weak correlation ($r = 0.367$; Fig 3) suggests that there is an early dysfunction of ganglionic elements with a relative preservation of preganglionic elements. In OAG eyes, in which this correlation is tighter ($r = 0.573$; Fig 3), we hypothesize that the delay in P50 implicit time is the result of a combined dysfunction of both ganglionic and preganglionic elements.

That in OAG eyes there is a possible concomitant dysfunction of preganglionic elements is also suggested by other studies in which a functional impairment of the outer retinal layers was documented by electroretinographic signals evoked by flash stimuli[13–15] or by multifocal electroretinogram recordings.[70–74]

The decrease in P50 to N95 amplitude has been reported as an indicator of a dysfunction of the innermost retinal layers (RGCs and their fibers; see Parisi[11] for a review). Thus, in ocular hypertension and OAG eyes the presence of PERGs with reduced P50 to N95 amplitudes may suggest a dysfunction of the innermost retinal layers. This is in agreement with experimental studies in animal models of glaucoma in which RGC degeneration is followed by a reduction in PERG amplitude involving the P50 to N95 complex.[75,76]

The detection of significant PERG amplitude losses in ocular hypertension eyes supports the hypothesis that RGC dysfunctions preceding their death may be reflected in PERG results, whereas HFA sensitivity is still unaltered. Indeed, a loss of at least 20% of ganglion cells is required to induce a reduction of retinal sensitivity evaluated by standard automated perimetry.[77]

## Visual Evoked Potentials in Ocular Hypertension and Open-Angle Glaucoma Eyes and Their Clinical Significance

Visual evoked potentials are derived from the recording of the bioelectrical activity of the visual cortex in response to visual stimuli and represent an electrophysiological method to evaluate the functional integrity of the entire visual pathways (from photoreceptors to occipital visual cortex).[13] The absence of abnormal VEP implicit times in our control eyes may indicate that this VEP parameter may have a specificity of 100%. Ocular hypertension and OAG eyes showed a delay in VEP P100 implicit time and a reduction in N75 to P100 amplitude. These VEP abnormalities can be ascribed to retinal factors, postretinal factors, or both.

In both ocular hypertension and OAG eyes, the concomitant presence of PERG and VEP abnormalities suggests a clear retinal contribution to the delay in visual cortical responses. This also can be derived from the relationship between PERG P50 and VEP P100 implicit times observed in both ocular hypertension and OAG eyes (Fig 6).

Nevertheless, it is interesting to consider whether a concomitant dysfunction in postretinal structures also may contribute to the observed VEP impairment. The VEP delays observed in our OAG patients could be interpreted in light of the available data on the effects of glaucoma at the level of the lateral geniculate nucleus (LGN), a primary site of visual integration. Indeed, histological studies performed in experimental glaucoma showed reduced axonal transport to the LGN in monkeys with chronic IOP elevation and damage, particularly in the magnocellular layers of the LGN.[78] Recent works revealed a morphological involvement of the LGN in monkeys in which experimental glaucoma was induced.[79–82] In humans, a degeneration of the LGN has been observed, by autopsy section, only in 5 glaucomatous patients, and in these patients there was a greater loss of magnocellular tissue, whereas there was no statistical difference in the parvocellular layer compared with controls.[83] Therefore, in our ocular hypertension and OAG eyes VEP abnormalities could be ascribed to retinal factors, but at least for OAG eyes, postretinal factors cannot be ruled out.

In conclusion, by using PERG and VEP recordings it was possible to classify a large percentage of ocular hypertension eyes with early impairment of the innermost retinal layers, notwithstanding a normal optic disc and HFA. In OAG eyes, the PERG P50 to N95 amplitude and VEP P100 implicit time showed the highest sensitivity/specificity in detecting visual dysfunction. The presence of abnormal PERG and VEP responses efficiently discriminated ocular hypertension and OAG eyes from normal eyes, whereas it did not allow a clearcut separation between ocular hypertension and OAG eyes.

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