Visual Electrodiagnosis in Glaucoma Screening: A Clinical Study

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Background: The aim of the present study was to investigate the value of pattern visual-evoked potentials (pVEP) and pattern electroretinograms (pERG) in early glaucoma diagnosis.

Materials and Methods: Thirty-eight eyes of 38 patients were included. Patients were classified into normal control (NC) and glaucoma patient (GP) groups. Patients underwent a detailed clinical ophthalmic examination and an electrodiagnostic examination using steady-state pVEP and pERG. Differences between groups in the amplitudes of the second harmonic of the pVEP and pERG responses to 480′ (A480) and 48′ (A48) check sizes and the ratio of the above amplitudes (A48/A480) were examined.

Results: Differences in the 48′ and 480′ pVEP between groups were not statistically significant. The pVEP A48/A480 ratio was significantly higher in NC than in GP. Differences in pERG between groups were statistically not significant for both 48′ and 480′ check sizes. In contrast, respective differences in pERG A48/A480 ratio were statistically significant.

Conclusions: Steady-state pVEP and pERG A48/A480 ratio may be of value in glaucoma diagnosis.

Key Words: glaucoma, hypertension, visual-evoked potentials, electroretinogram

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Glaucoma-related functional impairment is commonly evaluated in everyday clinical practice by examining visual field defects.[1–4] However, about 20% to 30% of optic nerve fibers may have suffered permanent damage before there is any detectable visual field loss in glaucoma.[5,6] Several previous studies have pointed out that structural loss of retinal ganglion cells (RGC) precedes visual field (functional) impairment.[7–9] Moreover, it has been shown that RGC undergo a prolonged period of dysfunction, that is, reduced neuronal sensitivity, and degeneration before actual anatomic cell loss, whereas detectable anatomic optic disc changes precede visual field defects.[10,11]

On the basis of these findings, methods other than visual field examinations have been proposed for early glaucoma diagnosis. Many are based on recently introduced imaging instrumentation, such as optical coherence tomography, scanning laser polarimetry, and confocal scanning laser ophthalmoscopy.[12–16] Other psychophysical methods, such as frequency-doubling perimetry[17–19] and contrast discrimination,[20] or electrophysiological techniques[21–23] have been used. Electrophysiology includes pattern electroretinograms (pERG) and pattern visually evoked potentials of the occipital lobe (pVEP). The advantages of electrophysiological methods are that they evaluate the reduction in retinal and/or retinocortical function as a result of RGC dysfunction (and not just RGC loss, as assessed by imaging studies) and that they selectively stimulate retinal or postretinal ganglion subgroups with different structural properties, which may be damaged earlier in disease.[24,25] pERG or pVEP are still not commonly used in routine clinical practice for the evaluation of glaucomatous functional defects possibly due to the lack of extensive normative databases and validation studies, which would enable the distinction between glaucomatous patients and normal or borderline subjects.

The purpose of the present study is to evaluate simultaneously recorded steady-state pERG and pVEP responses in glaucoma patients in comparison with an age-matched control group. Findings could prove useful in assessing the clinical role of such electrophysiological methods in early glaucoma diagnosis.

MATERIALS AND METHODS

Participants

Participants were recruited from the outpatient glaucoma service of the University Hospital of Heraklion, in Crete, Greece, between May 2007 and January 2008. Patient recruitment was performed in a prospective consecutive nonrandomized manner. The study conformed to the tenets of the Declaration of Helsinki and followed a research protocol approved by the Institutional Review Board of the University of Crete. All participants were informed verbally about the nature of the study and gave their written informed consent.

Participants were divided into 2 groups: glaucoma patient (GP) and normal control (NC) groups. Overall, 38 participants were recruited (16 men and 22 women). The NC and GP groups included 13 and 25 participants, respectively. The age [mean ± SD (range)] of participants in the groups examined [mean ± SD (range)] was 47 ± 12 (31 to 72) years for NC and 52 ± 12 (26 to 74) years for GP.

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Group allocation was performed by 2 independent glaucoma specialists (E.T.D. and M.K.T.) in a masked manner. The criteria for classification into the GP group, in accordance with the AAO preferred practice patterns glaucoma definitions (http://one.aao.org/CE/PracticeGuidelines/),[26] as suggested, included an appearance of the optic disc or retinal nerve fiber layer that is suspicious for glaucomatous damage (enlarged cup-disc ratio, asymmetric cup-disc ratio, notching or narrowing of the neuroretinal rim, disc hemorrhage, nerve fiber layer defect) or a visual field suspicious for glaucomatous damage in the absence of clinical signs of other optic neuropathies (arcuate bundle defect, nasal step, paracentral scotoma, altitudinal defect, larger mean pattern SD) or consistently elevated intraocular pressure associated with normal appearance of the optic disc and retinal nerve fiber layer and with normal visual field test results. All eyes included had open anterior chamber angles by gonioscopy. Glaucoma severity was evaluated using the Nerve Fiber Index from the GDx Vcc system (Carl Zeiss Meditec Inc., Dublin, CA). The NC group participants did not display any abnormal ocular findings on routine preoperative examination for refractive surgery. For all participants, exclusion criteria were secondary glaucoma (eg, pigment dispersion or pseudoexfoliation syndrome), diabetic retinopathy, major systemic disease, neurological disorders or any other disease able to cause visual field loss or optic disc damage, and any previous ocular surgery. Five participants of the GP group (20%) used assorted topical intraocular pressure-lowering medications.

One eye per patient that fulfilled the criteria cited previously was included in the study. When both eyes from a patient were eligible, the one with the better visual acuity was included. In the case of both eyes having equal visual acuity, the left eye, by convention, was included in the results. Examinations were performed by a medical doctor who was blinded to patients' allocation.

Visual Electrophysiology: Stimulation, Recording, and Analysis

Simultaneous recording of pVEPs and pERGs was performed in a dark, sound-attenuated room. Tests were performed with undilated (natural) pupils and subjects received no anesthetic or other eye drops before examination to avoid any corneal surface changes.

pVEPs and pERGs were elicited using circular onset/offset checkerboards subtending 15 degrees in diameter, with a square wave modulation of 8 Hz (16 reversals/s). Stimuli were presented on a Sony GDM F520 CRT high-resolution display (frame rate: 120 Hz), viewed at a distance of 100 cm, by means of a VSG 2/5 stimulus generator card (CRS, Rochester, UK) and a specially developed software. The mean luminance of the modulated part of the screen was 40 cd/m^2 and was surrounded by a neutral background (chromatic CIE 1931 co-ordinates $x = 0.310$, $y = 0.316$) of the same luminance. The monitor was calibrated using a SpectraScan PR650 spectroradiometer (PhotoResearch Inc., Chatsworth). Subjects viewed the stimulus monocularly. They were corrected for distance and they were instructed to maintain steady fixation during the recordings, on a centrally placed cross, to minimize eye movements. Recordings were performed for check sizes of 480′ (8 degrees) and 48′ (0.8 degrees), whereas the stimulus Michelson contrast was 100%.

pERGs were recorded using a corneal silver-nylon thread (DTLplus, Diagnosis LLC, Lowell) draped across the limbus as an active electrode, and a 9-mm silver-silver chloride (Ag-AgCl) electrode (Biosense Medical, Chelmsford, UK) mounted at the ipsilateral outer canthus as a reference electrode. A similar earth electrode, placed on the forehead, served as a ground. Signals were amplified using a CED 1902 amplifier (Cambridge Electronic Design, UK) with a gain of 20.000x and a bandwidth of 0.5 to 300 Hz. VEPs were recorded using 9-mm Ag-AgCl electrodes. An active electrode was positioned at Oz (10% of the inion-to-nasion distance) and referenced to an electrode placed at Fpz (20% of the nasion-to-inion distance) with a ground electrode placed on the forehead. Trigger synchronization was achieved using a CED "micro" 1401 (Cambridge Electronic Design, UK), whereas the waveforms were amplified using the CED 1902 with a 10.000× gain and a bandwidth of 0.5 to 30 Hz and digitized to a resolution of 16 bits at a sample rate of 500 Hz. Data were recorded and averaged using a CED1401 "micro" inter-face running Signal 2.15 acquisition software (Cambridge Electronic Designs, Cambridge, UK). Signals were acquired at 512 Hz, in epochs of 4 seconds. At least 32 sweeps (2048 data points) were recorded for each condition. Computerized artifact rejection was performed before signal averaging, according to the standard ISCEV guidelines (Brigell and colleagues, 2003), to discard epochs in which deviations in eye position, blinks, or amplifier blocking occurred. Because of the relatively fast alternating stimuli, the response was a steady-state waveform.

After acquisition, the data were subjected to a discrete Fourier transformation to isolate the sinusoidal component at the second harmonic (16 Hz) together with the 15 Hz response as a measure of noise. The data presented are vector averages of individual sweeps.

Data and Statistical Analysis

The indices that entered statistical analysis were as follows: (1) the amplitude of the second harmonic of the pVEP and pERG responses to 480′ (A480) and 48′ (A48) check sizes; and (2) the ratio of the above amplitudes (A48/A480).[27,28] Any statistical difference between the 2 groups (NC, GP) was estimated using 1-way analysis of variance (ANOVA). A 5% significance level was selected. Receiver operator characteristic (ROC) analyses were also performed (MedCalc, version 11.6.1.0, MedCalc Software bvba, Mariakerke, Belgium) to directly compare the discriminative potential of the above-mentioned parameters (A480 and A48 check sizes and A48/A480) between GP and NC groups. On the basis of the ROC results, the sensitivities, specificities, and predictive values for the point on the ROC curve that represents the minimum error score (ie, the point where the product of false positives × false negatives is minimal) were derived. The possible effects of age and sex on the association between glaucoma diagnosis and the pERG and pVEP ratios were examined with multiple regression analysis (MedCalc, version 11.6.1.0, MedCalc Software bvba, Mariakerke, Belgium). The correlations between GDx VFI and electrophysiological parameters (including pERG A48 and A480 amplitudes, pVEP A48 and A480 amplitudes as well as pERG and pVEP A48/A480 ratios) were examined with Pearson bivariate correlation coefficient.

Power calculation, performed using the G*Power version 3.1.3 (Franz Paul, Universität Kiel, Germany),[29]

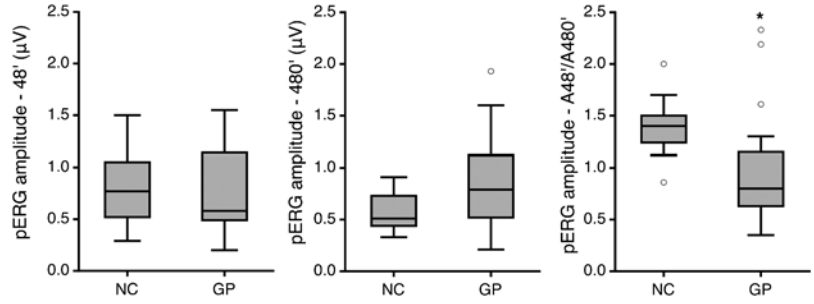

FIGURE 1. Box plots of the electroretinograms (ERG) ratio (amplitude of ERG to 48′ checks/amplitude of ERG to 480′ checks) for the normal control (NC, n = 13) and the glaucoma patient (GP, n = 25) groups. Statistically significant differences were found between all groups. *Significantly different from the NC group. pVEP indicates pattern visual-evoked potentials.

for 1-way ANOVA (2 groups), α-error probability of 0.05, and an effect size of 0.40 rendered a power (1 − β error probability) of 0.67.

RESULTS

pERG response amplitudes for the 48′ check size (mean ± SD) were higher for NC (0.84 ± 0.40 μV) compared with GP (0.74 ± 0.40 μV); in contrast, responses to 480′ checks were lower for the NC (0.58 ± 0.20 μV) compared with the GP (0.85 ± 0.44 μV; Fig. 1). The differences in pERG amplitudes between the 2 groups for both 48′ and the 480′ check sizes were stastistically not significant (1-way ANOVA, F ratio = 0.564, $P = 0.458$ and F ratio = 4.34, $P = 0.054$, respectively). In contrast, the difference in pERG 48/480 ratio between NC (1.39 ± 0.28) and GP (0.97 ± 0.47) was statistical significant (1-way ANOVA, ratio = 7.99, $P = 0.008$).

pVEP response amplitudes for 48′ checks were 1.35 (± 0.81) μV and 1.97 (± 1.41) μV for NC and GP, respectively (Fig. 2). The difference between them was statistically not significant (1-way ANOVA, F ratio = 1.97, $P = 0.17$). pVEP response amplitudes for 480′ checks were 0.78 (± 0.54) μV and 1.92 (± 1.24) μV for NC and GP, respectively. The difference between them was also statistically not significant (1-way ANOVA, F ratio = 4.3, $P = 0.05$). In contrast, the pVEP ratio (A48/A480) was significantly higher in NC (2.09 ± 0.94) than in GP (1.14 ± 0.54; 1-way ANOVA, F ratio = 15.41, $P < 0.001$).

Figure 3 depicts the sensitivity/specificity analysis (ROC analysis). On the basis of the pERG ratio, an ROC area (AUC) of 0.85 was recorded; the sensitivity was 72.0% and the specificity 92.3% at a threshold pERG ratio of 1.07. On the basis of the pVEP ratio, an ROC area (AUC) of 0.80 was recorded; the sensitivity was 84.0% and the specificity 75% at a threshold pVEP ratio of 1.57.

The correlations between GDx VFI and pERG A48 and A480 amplitudes, pVEP A48 and A480 amplitudes, and pERG and pVEP A48/A480 ratios were statistically not significant (Pearson bivariate correlation coefficient). Multiple regression analyses also revealed statistically not significant effects of age and sex on pERG and pVEP ratios (Table 1).

DISCUSSION

The present study examines the diagnostic power of pERG and pVEP steady-state responses in distinguishing healthy individuals (controls) from glaucomatous patients. The findings imply that pERG and VEP ratios, analyzed with the proposed methodology, may be used as clinical markers for clinical glaucoma diagnosis. The methodology used in this study is based on previous data reporting a check-size–specific reduction in ERG responses in early glaucoma.[30] However, to reduce interindividual variability, responses to different check sizes (ie, the ratio between responses to small, 48, and large, 480, check sizes) were compared between groups, using a slightly modified paradigm compared with previous studies.[27,28,30]

Several previous studies have examined the potential value of electrophysiological examinations as a clinical tool in glaucoma diagnosis.[31,32] The transient or steady-state

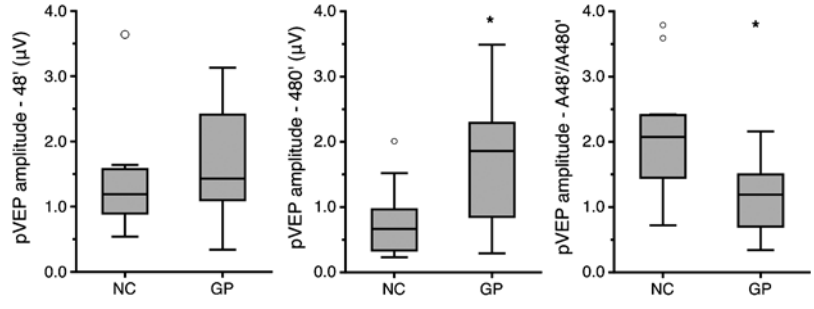

FIGURE 2. Box plots of the visual-evoked potentials (VEP) ratio (amplitude of VEP to 48′ checks/amplitude of VEP to 480′ checks) for the normal control (NC, n = 13) and the glaucoma patient (GP, n = 25) groups. *Significantly different from the NC group.

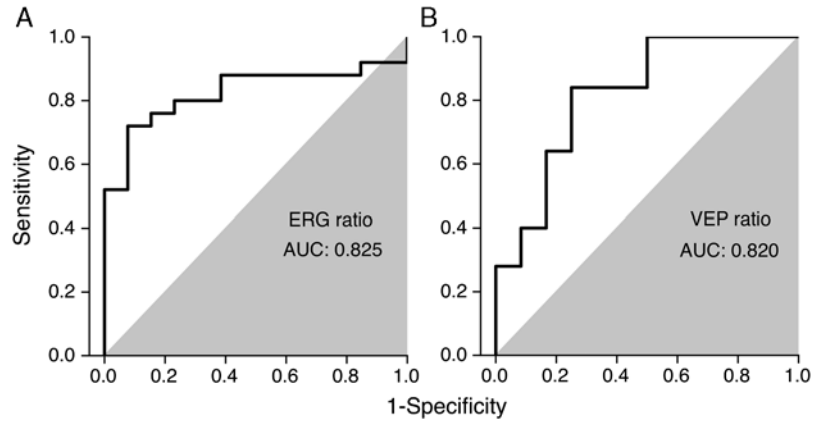

FIGURE 3. Sensitivity/specificity analysis [receiver operator characteristics (ROCs)]. ROCs are based on the pattern electroretinograms (pERG) ratio (A) and the pattern visual-evoked potential (pVEP) ratio (B). The value indicates the area under the ROC curve (AUC).

pERGs have been shown to be significantly affected in advanced glaucoma[33–35] but also attenuated in ocular hypertension (OH) of and in preperimetric glaucoma.[36,37] Furthermore, pERG and pVEP findings have been correlated with Heidelberg retina optic disc analysis to assess the prevalence of normal tension glaucoma in sleep-apnea syndrome patients.[38] Moreover, ERG indices, such as the P50 to N95 amplitude, have been used in the differential diagnosis between normal subjects and ocular hypertensive or open-angle glaucoma patients.[39] According to many previous reports, glaucoma-related pERG abnormalities are mainly characterized by amplitude reduction, without any pronounced effects on latency or phase.[28,39] Bach and Hoffmann[28] reported that the pERG ratio, that is, the ratio between the ERG amplitudes at checks of 0.8- and 8.0-degree size, may be the best marker of early glaucomatous damage. Moreover, prospective studies[40] have suggested that pERG ratio provides an objective clinical tool in defining eyes with a higher risk of developing manifest glaucoma. In contrast, other electrophysiological approaches, such as the conventional VEPs, which are mainly used to evaluate vision deficiencies by analyzing early cortical responses, are less affected by glaucoma than pERGs.[24] This may be explained by the fact that VEP responses reflect postretinal neuronal activity, which is known to mask, perhaps through gain control, changes in the early stages of visual processing.[41,42] In contrast, it has been suggested that the multifocal pattern-reversal visual-evoked potential may be a useful technique for objectively assessing visual field loss in patients with advanced glaucoma.[43]

Findings from the present study, especially the statistically significant difference between NC and GP concerning pVEP and pERG A48/A480 ratios, are in agreement with previous findings and support the role of A48/A480 ratio testing for glaucoma diagnosis. This is also supported by the large ROC areas for both pERG and pVEP A48/A480 ratios. The fact that the 480′ and the 48′ stimuli did not differ significantly between the groups examined also complies with previous studies reporting that pERG and pVEP responses to large stimulus checks may be quite spared in early glaucoma.[27,28,30] The lack of significant correlations between the electrophysiological parameters examined and glaucoma severity may be attributed to the relatively small number of patients included and to the fact that many patients in the GP group had early glaucoma, displaying only a moderate increase in Nerve Fiber Index. The fact that, in the multivariate analysis preformed, the effects of age and sex were statistically not significant implies that the diagnostic potential of the electrophysiological parameters examined are not age or sex related.

In addition to previous studies that have also examined pERG and pVEP changes in glaucoma, this study used a simultaneous recording of steady-state VEP and ERG with pattern stimuli and used discrete fourier transformation, applied at a postacquisition phase. This methodological novelty, together with the head-to-head comparison between NC and GP groups, enhances the validity of the conclusions concerning the use of electrophysiological parameters examined (such as the A48/A480 ratio) as tools for glaucoma diagnosis. A future work may examine whether ratio is the best measure or one involving a power function can lead to more powerful outcomes. In contrast, potential weaknesses of this study are the lack of validation of electrophysiological results by other methodologies, such as visual field testing or optic disc imaging, and the fact that the phase shift analysis was not included in the initial design of the study.

The outcome strongly supports the possibility that the responses in individual stimuli are not a reliable index of

TABLE 1. Multiple Regression Analysis With Age and Sex as Independent Variables, for pERG and pVEP

	pERG			pVEP		
Independent Variables	**Zero-order Correlation Coefficients**	***F* ratio**	***P***	**Zero-order Correlation Coefficients**	***F* ratio**	***P***
Age	−0.1820	1.8127	0.178	−0.07368	0.6635	0.522
Sex	−0.2815			−0.1909		

pERG indicates pattern electroretinograms; pVEP, pattern visual-evoked potentials.

ganglion cell activity and that the ratio of responses to 2 stimuli of different sizes may be a more consistent method to evaluate the functional condition of the RGC's electrical activity in early glaucoma. Therefore, findings could prove useful in assessing the clinical role of such electrophysiological methods in early glaucoma diagnosis.

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