

Pattern ERG as a predictor in ocular hypertensive

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Abstract

Purpose: To report the repeatability of Pattern Electroretinogram (PERG) and its findings in ocular hypertension (OHT) and normal eyes.

Methods: A cross-sectional study where PERG responses were compared between the study group comprising of 80 eyes of 80 patients with intraocular pressure (IOP) > 21 mmHg and the control group with 80 eyes of 80 normal individuals (IOP ≤ 21 mmHg). The optic disc and the visual fields were normal with a visual acuity of ≥ 0.8 in both groups. PERG was recorded twice for each individual in the control group by a single operator on 2 consecutive days to assess the repeatability.

Results: The mean age in the study and control groups was 50.05 ± 10.03 and 54.8 ± 7.66 years ($p=0.44$) respectively. The mean IOP was 26.55 ± 3.9 mmHg for the study group as opposed to 14.45 ± 2.9 mmHg for the controls ($p<0.001$). The central corneal thickness and the cup-disc ratio was similar between the groups ($p>.05$). The P50-N95 amplitude ($p=0.01$) and the P50 latency ($p<0.001$) was statistically significantly different between both the groups. The intra-class correlation coefficient (ICC) showed poor agreement for all parameters except for N35-P50 0.8 to 16 degree check size amplitude ratio (PERG ratio).

Conclusion: Increase in P50 latency emerges as a new candidate for early glaucoma indicator in addition to reduction in P50-N95 amplitude. PERG parameters suffer from high test-retest variability. Deterioration in PERG recordings should be interpreted with caution. The variability is lesser for the PERG ratio which may be more meaningful while monitoring for change over time.

Keywords: Glaucoma, Ocular Hypertension, Pattern Electroretinogram, PERG, Repeatability.

Introduction

Ocular hypertension (OHT) is defined as elevated intraocular pressure (IOP) without any glaucomatous visual field defects or optic disc changes. Elevated IOP is a major modifiable risk factor for glaucoma. Glaucoma is characterized by chronic retinal ganglion cell (RGC) loss. A sizable fraction (25%–35%) of RGCs is already lost when visual field defects become apparent in automated visual field testing.¹

The retinal response to pattern stimulation, the pattern electroretinogram (PERG), predominantly reflects RGC activity.²⁻⁶ Reduction in the PERG amplitude had been reported in patients with OHT.⁷⁻¹⁴ Knowledge of the variability of PERG is extremely important especially when we want to judge its deterioration. This variability has been studied before.^{6,15-16} PERG testing is essentially objective and theoretically more repeatable than subjective testing because it is minimally affected by motor response and learning effects. The aim of our study is to find whether a difference in the PERG recordings between OHT and normal patients exists and also to ascertain

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that this difference is outside the test-retest variability of the PERG machine. To the best of our knowledge both these things together have not been done before.

Materials and methods

This was a cross sectional study and an informed consent was obtained from all subjects. For the study group, we included 80 eyes of 80 consecutive patients diagnosed as ocular hypertension (OHT) from October 2012 to April 2013. Inclusion criteria were: IOP (measured with Goldmann applanation tonometry at two different times) >21 mmHg, open angles on 4-mirror gonioscopy without indentation, normal and reliable visual field test results as described below and normal optic disc at clinical examination and on photographs. Our control group also consisted of 80 eyes of 80 random patients recruited during the same period with similar age range. The inclusion criteria were similar except for the IOP which was ≤ 21 mmHg. Exclusion criteria were visual acuity <0.8 , spherical correction outside $\pm 5.0D$, cylinder correction outside $\pm 3.0D$, secondary glaucoma (e.g., pigment dispersion or pseudoexfoliation syndrome), and diabetic retinopathy or any other condition capable of causing visual field loss or optic disc damage. Pressure lowering treatment was not an exclusion criterion. Treatment was actively recommended only to patients with IOP >28 mmHg which is the standard practice at our institute.

A complete ophthalmic examination including best corrected visual acuity, IOP measurement with Goldmann applanation tonometer, pachymetry, gonioscopy, indirect ophthalmoscopy, slit lamp biomicroscopy, visual fields with Humphrey Visual Field Analyzer II (Carl Zeiss Meditec, Dublin, CA) and PERG recording was done. The PERG was recorded twice for each individual in the control group by a single operator (JJ) on 2 consecutive days at approximately the same time of the day in order to find out the test-retest variability. All other examinations were performed by one of the two authors (PRD and JJ).

Visual field

All the tested eyes had a pupil diameter ≥ 3 mm and corrective lenses were placed on the lens holder to evaluate the visual field. Visual field examination was performed using 24-2 SITA Standard strategy by HVF analyzer. Only patients with reliable visual fields (false positive, false negative $<33\%$, fixation losses $<20\%$) were included. A normal visual field was defined by the absence of each of these responses: a cluster of 3 points lower than $p < 5\%$ or a cluster of 2 points lower than $p < 1\%$ on a pattern deviation plot, or PSD with $p < 5\%$. All visual field examinations were done not more than 1 month prior to doing the first PERG.

PERG Recording

For PERG recording, we followed the International Society for Clinical Electrophysiology of Vision (ISCEV) standard guidelines.¹⁷ RETIport 21 (version: 19-99-04-7.2E; Roland Consult, Brandenburg, Germany) machine was used to perform the PERG under photopic condition at a distance of 1 meter from the 19" monitor. The stimulus

was a high contrast (99%) black and white stimulus with a mean luminance of 80 cd/m^2 and a chequerboard size of 0.8° or 16° . The stimulus frequency was 15.005 Hz, cycle time of 0.6664 seconds and a plot time of 400 milliseconds. Responses from both eyes were measured simultaneously. Before testing, the electrode impedance was monitored automatically and an on-screen indicator signaled an acceptable impedance ($<10 \text{ k}\Omega$). Retinal potentials were recorded with corneal DTL electrodes and gold cup electrodes at the outer ipsilateral canthus served as reference.¹⁸ Signals were amplified and filtered with a 2-channel bio signal amplifier. During each examination, two PERG measurements were taken, and the mean of the traces was used to yield the raw PERG amplitude. The glaucoma program calculated the PERG ratio (response amplitude to 0.8° checks divided by the response amplitude to 16° checks). The spectrum in the software was used for getting the P50-N95 marker. Fig. 1 and Fig. 2 show the representative PERG traces of normal control and ocular hypertensive eyes respectively.

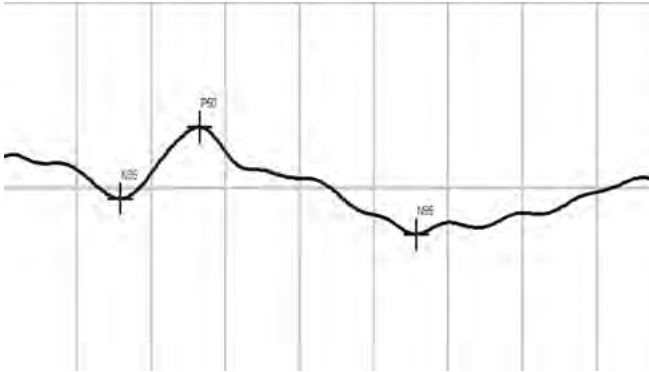


Fig. 1. A representative Pattern Electroretinogram recording of a normal control eye.

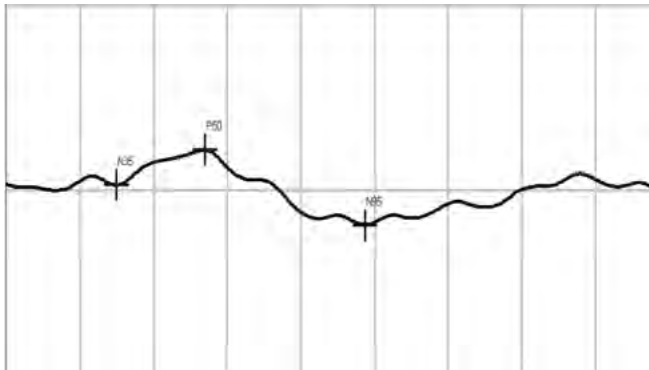


Fig. 2. A representative Pattern Electroretinogram recording of an eye with ocular hypertension.

Statistical Analysis

Descriptive and inferential statistics were performed using STATA version 12 for Windows (StataCorp LP, Texas). Mann-Whitney U test for continuous variables and Chi Square test for categorical variables was used to compare the baseline

parameters between the groups. The 95% confidence limits of variability for all PERG parameters were calculated from the Bland-Altman plot (BAP) method. The intra-class correlation coefficients (ICC) were also calculated for all PERG parameters.

RESULTS

Forty eyes of 80 patients were diagnosed during the study period with ocular hypertension. Twelve patients had a positive family history of glaucoma (1st degree relative having glaucoma). Twenty-two of the 80 eyes were on topical medication. Sixteen of these were on a β-blocker and the remaining 6 on a prostaglandin analogue. Another 80 eyes of 80 patients were recruited as controls during the same period. Table 1 shows the demographic data and PERG parameters of the included patients.

Table 1. Baseline demographics and pattern electroretinogram readings

Parameters	OHT	Controls	p value
Age (years)	50.05±10.03	54.8±7.66	0.44
Male:Female	11:9	8:12	0.34
IOP (mmHg)	26.55±3.9	14.45±2.9	<0.001
CCT	543.95±36.86	530.5±48.9	0.15
CDR	0.45±0.15	0.35±0.07	<0.001
P50-N95amp	2.5±0.82	3.55±1.29	<0.001
P50-N95lat	94.5±9.02	94.8±9.39	0.82
N35lat16	23.62±4.6	22.15±3.4	0.15
N35lat0.8	34.5±3	34.4±8.07	0.17
P50lat16	51.9±5.74	43.35±2.53	<0.001
P50lat0.8	57.7±8.2	52.05±8.52	<0.001
N35-P50amp16	4.7±1.8	5.93±2.87	0.03
N35-P50amp0.8	2.04±1.27	2.2±1.53	0.99
PERG ratio (right)	0.365±0.089	0.284±0.183	0.04
PERG ratio(left)	0.397±0.278	0.49±0.175	0.08

*P50-N95amp =P50-N95 amplitude

†P50-N95lat = P50-N95 latency

‡N35lat16 = N35 latency with 16 degree check size

§N35lat0.8 = N35 latency with 0.8 degree check size

||P50lat16 = P50 latency with 16 degree check size

**P50lat0.8 =P50 latency with 0.8 degree check size

††N35-P50lat16 =N35-P50 latency with 16 degree check size

‡‡N35-P50lat0.8 =N35-P50 latency with 16 degree check size

The age, gender and central corneal thickness was similar between the two groups. The mean IOP in the OHT group was 26.55 ± 3.9 mmHg compared to 14.45 ± 2.9 mmHg in the control group ($p < 0.001$). The P50-N95 latency (P50-N95lat), N35 latency with 16 degree check size (N35lat16), N35 latency with 0.8 degree check size (N35lat0.8) and the N35-P50 amplitude with 0.8 degree check size (N35-P50amp0.8) was similar in both the groups ($p > 0.05$). The P50-N95 amplitude (P50-N95amp), P50 latency with both 16 and 0.8 degree check size (P50lat16, P50lat0.8) and N35-P50 amplitude with 16 degree check size (N35-P50amp16) was statistically significantly different between the groups ($p < 0.05$) as shown in **table 1**.

Table 2 shows the 95% confidence limits of variability for all PERG parameters calculated from Bland-Altman plots. Only P50 latency with 16 degree check size (P50lat16) had a difference beyond the 95% confidence limits between the two groups. Table 2 also shows the ICC for the PERG parameters. The ICC showed poor agreement for all the PERG parameters except for the PERG 0.8 to 16 degree check size amplitude ratio for the right [PERG ratio (right)] and the left eye [PERG ratio (left)] which was 0.69 and 0.68 respectively.

Table 2. Test-retest variability for pattern electroretinogram parameters

Parameters	Control 1 st Run	Control 2 nd Run	p value	Bland-Altman 95% limit	ICC
P50-N95amp	3.55 ± 1.29	3.25 ± 1.22	0.33	-2.835, 3.437	0.184
P50-N95lat	94.8 ± 9.39	90.85 ± 10	0.13	-19.603, 27.503	0.222
N35lat16	22.15 ± 3.4	22.95 ± 3.88	0.24	-11.692, 10.092	-0.16
N35lat0.8	34.4 ± 8.07	29.35 ± 5.75	0.002	-14.081, 24.181	0.024
P50lat16	43.35 ± 2.53	43.8 ± 3.03	0.34	-8.047, 7.047	-0.181
P50lat0.8	52.05 ± 8.52	50.5 ± 9.95	0.16	-24.227, 27.327	-0.009
N35-P50amp16	5.93 ± 2.87	5.87 ± 1.8	0.32	-6.708, 6.826	-0.039
N35-P50amp0.8	2.2 ± 1.53	2.7 ± 2.2	0.35	-5.271, 4.257	0.166
PERG ratio (right)	0.284 ± 0.183	0.466 ± 0.314	0.06	-0.841, 0.713	0.692
PERG ratio (left)	0.49 ± 0.175	0.425 ± 0.255	0.08	-0.553, 0.667	0.676

*P50-N95amp = P50-N95 amplitude

†P50-N95lat = P50-N95 latency

‡N35lat16 = N35 latency with 16 degree check size

§N35lat0.8 = N35 latency with 0.8 degree check size

||P50lat16 = P50 latency with 16 degree check size

**P50lat0.8 = P50 latency with 0.8 degree check size

††N35-P50lat16 = N35-P50 latency with 16 degree check size

‡‡N35-P50lat0.8 = N35-P50 latency with 0.8 degree check size

§§ICC = Intra-class correlation coefficient

Discussion

We already know that the conversion rate from untreated OHT to glaucoma is only ~1% per year.¹⁹ Accordingly, most patients with OHT never have glaucoma and thus do not need treatment. Hence, a method to identify these high risk patients is essential to avoid over treatment. Wanger *et al.*²⁰ reported a significant reduction in the amplitude of PERG in OHT patients. Weinstein GW *et al.*²¹ found a selective reduction in the second negative wave (N-95) in glaucomatous patients and concluded that this wave (N-95) is related to early optic nerve dysfunction. Arai M *et al.*¹² further strengthened this concept when they showed that decrease in the amplitude of the second negative wave (N-95) is a warning sign of development of glaucoma in ocular hypertensives. In our study also we found that the P50-N95 amplitude was statistically significantly less in the OHT group than the controls. However, the difference was not beyond the 95 % limits of test-retest variability of the machine. The previous studies do not mention the test-retest variability of their machines. In addition, the P50lat16 and the P50lat0.8 was more in the OHT group while the N35-P50amp16 was greater in the normal patients. The P50lat16 was the only PERG parameter which had a between group difference greater than the retest variability. This makes it a possible candidate for early indicator of glaucoma. The ICC for all PERG parameters in our study showed poor to fair agreement except for the PERG ratio. Bowd *et al.*²² in their study demonstrated a within-trial and between trial ICC of 0.85 and 0.88 respectively. However, they did not calculate the ICC for each PERG parameter as we have done in our study. Bach M *et al.*²³ described that an individual with a large 0.8° PERG will also have a large 16° PERG and hence it is useful to compute the PERG ratio to reduce the inter-individual variability. Our study finding is in agreement with this. This low variability for the PERG ratio maybe extremely important while monitoring for change over time. Refractive errors decrease the small check size amplitudes more than large check size amplitudes, mainly due to reduction of the visual acuity.²⁴ In our study, we overcame this shortcoming by including only those patients with a best corrected visual acuity ≥ 0.8 . But, this issue somewhat limits the general applicability of the PERG for early glaucoma detection.

This study has its limitations. We had a relatively small sample size and the PERG measurements were all one time measurements. A better way of doing this study would have been to follow-up all these patients and look for PERG changes over time and amongst those who convert to glaucoma. This would throw light on the predictive accuracy of PERG. This study is currently under way. Another confounder was the fact that treatment of OHT eyes was allowed in our study. Ventura LM *et al.*²⁵ have showed that abnormal PERG recorded in the early stages of glaucoma may often improve after IOP reduction. However, treating eyes with OHT is a real life situation that we encounter very often and hence it was not considered as exclusion criteria. Our current study gives us insight into what PERG parameters would have a low variability which could be used for comparison over time. To the best of our knowledge this is the only study which looks into PERG difference between OHT and normal patients with calculation of the retest variability of the PERG

machine. It is extremely important to find parameters with difference outside this range in order to be sure of a real change over time. The increase in the P50 latency has emerged as a new candidate parameter to check for possible conversion of OHT eyes to glaucoma in future. This needs further confirmation by longitudinal studies with larger sample sizes.

Conclusion

Increase in P50 latency emerges as a new candidate for early glaucoma indicator from our study in addition to reduction in P50-N95 amplitude which is already known. PERG parameters suffer from high test-retest variability and hence deterioration in PERG recordings should be interpreted with caution. The changes in the PERG parameters need to be greater than the inherent variability of the machine. The variability is lesser for the PERG ratio which maybe more meaningful while monitoring for change over time.

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