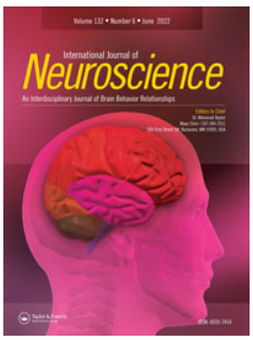

International Journal of Neuroscience

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ines20

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To cite this article: Rasha Zedan, Ayat Allah Farouk, Radwa Azmy, Reem Elhadidy & Eman Attya (2021): Role of pattern electroretinogram in assessment of retinal dysfunction in hypertensive patients, International Journal of Neuroscience, DOI: 10.1080/00207454.2021.1984237

To link to this article: https://doi.org/10.1080/00207454.2021.1984237

INTERNATIONAL JOURNAL OF NEUROSCIENCE
https://doi.org/10.1080/00207454.2021.1984237

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ORIGINAL ARTICLE

Role of pattern electroretinogram in assessment of retinal dysfunction in hypertensive patients

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ABSTRACT

Background: Hypertension is a major health problem in both developing and developed countries. Hypertension causes retinal structural and functional impairment within the ganglion cell layer. Pattern electroretinogram (PERG) offers an objective simple tool for assessment of retinal ganglion cell function.

Aim of the work: To assess retinal dysfunction in hypertensive patients with or without signs of retinopathy using PERG.

Materials and methods: This is a case control study, including ninety-eight eyes. Twenty-eight eyes of healthy subjects served as a control group (group I) and seventy eyes of patients with systemic hypertension, who were further subdivided into group II including 39 eyes of hypertensive patients with normal fundus and group III including 31 eyes of patients with signs of hypertensive retinopathy. All subjects were subjected to ophthalmological examination and electrophysiological assessment using PERG.

Results: PERG implicit times were significantly prolonged and amplitudes were significantly reduced in patients with established hypertensive retinopathy. PERG abnormalities were detected in 96.8% of hypertensive retinopathy patients and 79.5% of hypertensive patients with normal fundus.

Conclusions: PERG can objectively assess retinal dysfunction in hypertensive patients and may be considered a promising tool for early detection of hypertensive retinopathy.

ARTICLE HISTORY
Received 6 July 2020
Revised 4 October 2020
Accepted 16 September 2021

KEYWORDS
Hypertension; hypertensive retinopathy; retinal ganglion cells; pattern electroretinogram

Introduction

Hypertension is a major health problem worldwide. It is the most common chronic disorder in Egypt, having a prevalence rate of 26.3% among the adult population [1]. Hypertension is classified as either primary (essential) hypertension which represents about 90–95% of cases, or secondary hypertension which represents the remaining 5–10% of cases [2].

Hypertension causes retinal structural and functional impairment within the ganglion cell layer. Researchers detected degenerative changes along axonal and dendritic extensions [3]. Systemic hypertension is linked to signs of hypertensive retinopathy rather than other risk factors of atherosclerosis. Hypertensive retinopathy varies from arteriovenous nicking and focal retinal arteriolar narrowing to hemorrhagic and cotton-wool lesions [4].

Full field flash ERG shows reduced amplitude responses only when large areas of the retina are functionally impaired, therefore ERG amplitude is not usually compromised the until the disease becomes advanced [5,6]. The pattern electroretinogram PERG is well-established objective measure of retinal ganglion cell function [7]. PERG is a retinal biopotential that arises mainly in the ganglion cells and is affected in dysfunction confined to the macula or to the retinal ganglion cells. Such dysfunction is not usually detected by conventional flash electroretinogram [8], being a non-localizing mass potential, that reflects combined electrical activity of different cells of the retina [9].

Researchers have investigated retinopathy in several systemic and ocular disorders, however, to the best our knowledge, there was no previous research investigating the role of PERG in systemic hypertensive patients.

The aim of the current study is to spot light on the value of PERG in diagnosis of retinal dysfunction in hypertensive patients and its early detection before it becomes evident by fundus examination. Early

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detection of retinopathy could prevent other atherosclerotic complications of hypertension.

Subjects and methods

This case control study was carried out on hypertensive patients recruited from the outpatient clinic, at Kasr Alainy Hospital, Cairo University. Neurophysiological and ophthalmological assessment were carried out at Clinical Neurophysiology Unit of Kasr Alainy Hospital & Ophthalmology outpatient Clinic of Kasr Alainy Hospital respectively.

Ninety eight eyes from 54 subjects were included in this study as per sample size estimation. Twenty-eight eyes were of age and sex matching, normotensive, healthy subjects with no prior antihypertensive medication and seventy eyes were of patients who are known to have essential hypertension. 10 eyes were excluded from the study due to: increased intraocular pressure (6 eyes) (nasal shift of vessels at the optic disc and confirmed by applanation tonometry), anterior ischemic optic neuropathy (3 eyes) and traumatic eye injury (1 eye). All patients were known to be controlled on oral antihypertensive medications. Informed consent was obtained from all subjects involved in the study. The protocol was approved by the ethics Committee, Faculty of medicine, Cairo University.

Opthalmological examination was performed for all participants by a single ophthalmologist, who was blinded to the PERG results. Fundoscopy and slit-lamp biomicroscopy of anterior and posterior segment were done. Patients with diabetes, renal disease, significant anterior segment diseases e.g. cataract or glaucoma, significant posterior segment diseases or surgery were excluded from the study. Hypertensive retinopathy was evaluated according to a simple three-grade classification system suggested by Wong and McIntosh in 2005 [4].

Electroretinogram was performed using ISCEV PERG standards [10], before dilatation of the pupil for fundus examination. PERG was carried out, using the METROVISION scan version 8000 F (Metrovision, France). Retinal potentials were recorded using HK-loop corneal electrodes placed in the lower bulbar conjunctiva, and gold cup electrodes at the outer ipsilateral canthus served as reference which their impedance should be less than 10 kOhm. The stimulus was presented on a video monitor covering a field of 60 degrees at a distance of 0.3 m. The checkerboards had a mean luminance of 100 cd/m2, a contrast of 93.3% and a check size of 50″ and were counterphased at 4 reversals per second. Signals were amplified and filtered with an analog band-pass of 1.0 – 100 Hz. Sweeps are averaged up to 230 trials and displayed online; traces exceeding 100 micro-volts were rejected as artifacts. After correction of vision, subjects were instructed to fixate both eyes on a small red cross in the center of the stimulating screen. The amplitude and peak time of P50 and N95 waves were analyzed. P50 amplitude was measured from the trough of N35 to the peak of P50. The N95 amplitude is measured from the peak of P50 to the trough of N95. Implicit time or peak time of P50 and N95 were designated.

Data was analyzed using Microsoft Excel 2010 (Microsoft Corporation, New York, USA) and IBM SPSS version 21.0 (IBM corp., USA). Comparison was done using One-way ANOVA with Bonferroni correction for post-hoc analysis as the data was normally distributed. Categorical data was described with Chi-square. Correlations were done by Pearson correlation coefficient (*r*). *P-value* less than or equal 0.05 was considered statistically significant.

Results

This is a case-control study, conducted on 98 eyes, divided into three groups, control group (group I) including 28 eyes and study group consisting of 70 eyes of essential hypertensive patients who were further subdivided according to fundus findings into group II including 39 eyes of hypertensive patients with normal fundus, and group III including 31 eyes of patients with signs of hypertensive retinopathy. Mean age of subjects in group I was 46.0 ± 11 years, while in group II it was 47.0 ± 8 years, and 51.0 ± 8 years for group III patients. No significant difference was noted among the three groups as regards age ($p = 0.08$), gender ($p = 0.67$) or laterality of eyes examined (OD/OS) ($p = 0.812$). Duration of hypertension was significantly longer in group III patients (4.1 ± 4 and 10.2 ± 5.4 years for groups II and III respectively; $p < 0.001$).

PERG parameters in the three study groups are shown in Table 1, Figures 1 and 2. P50 and N95 implicit times (peak latencies) were measured in milliseconds (msec), while amplitudes were measured in microvolt (μV).

The correlation of age of the subjects in the 3 study groups to the PERG parameters is shown in Table 2, while correlation of the duration of hypertension to PERG parameters is shown in Table 3. No significant correlation was found between both eyes in groups II and III regarding P50 &N95 amplitude or IT (Table 4).

PERG P50 and N95 amplitude reduction was detected in 96.8% of hypertensive retinopathy patients

Table 1. PERG parameters in the three study groups.

	Group I		Group II		Group III		
	Mean	SD	Mean	SD	Mean	SD	P value
P50 implicit time (msec)	50.2a	3.9	50.6b	3.9	53.2a-b	5.1	0.014
P50 amplitude (μv)	7.1a	2.5	5.8b	2.2	4.2a-b	1.9	<0.001
N95 implicit time (msec)	94.5a	6.2	96.1	6.7	100.1a	8.5	0.010
N95 amplitude (μv)	−9.5	4.1	−9.2	12.3	−5.3	2.4	0.074

*Similar letters in the same row are statistically significant by post hoc analysis; a-b (a & b).

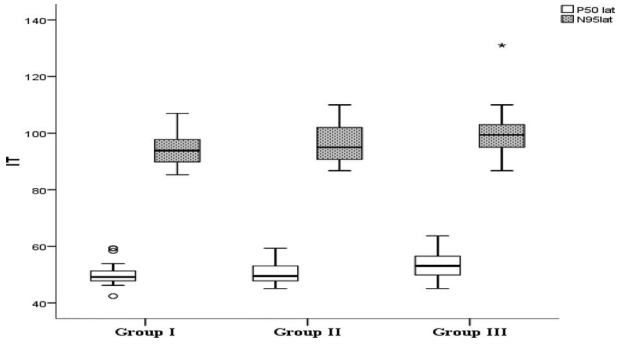

Figure 1. Comparison between groups regarding the average implicit time of P50 & N95 waves.

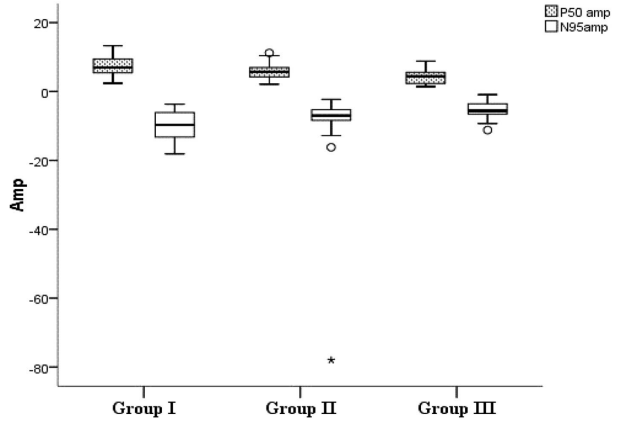

Figure 2. Comparison between groups regarding the average amplitude of P50 & N95 waves.

(30 out of 31 examined eyes of hypertensive retinopathy patients) and 79.5% of hypertensive patients with normal fundus (31 out of 39 examined eyes of hypertensive patients with no apparent retinopathy signs).

Examples of PERG responses in groups II and III are shown in Figures 3 and 4.

Discussion

Hypertension is a serious, mostly asymptomatic disorder, often called the 'silent killer' [11]. Hypertensive patients have higher risk for atherosclerosis rendering them more prone to cardiac failure, myocardial infarction, stroke, retinopathy, renal insufficiency and premature death [2,12].

Elevated blood pressure causes serious retinal pathophysiological changes, referred to as hypertensive retinopathy [13]. Hypertension is the second systemic condition associated with retinopathy after diabetes [4,13].

The ganglion cell origin of the N95 component of PERG allows electrophysiological evaluation of ganglion cell function both in primary and secondary dysfunction. On the other hand, the P50 component of PERG appears to reflect dysfunctions in the internal retinal layers anterior to the ganglion cells which are altered in macular diseases [14] The macula being highly populated by ganglion cells, a concomitant

Table 2. Correlation between the age of the patients and PERG parameters in the three study groups.

	P50 wave				N95 wave			
	Amplitude (μv)		Implicit time (msec)		Amplitude (μv)		Implicit time (msec)	
	r	P	r	P	r	P	r	P
Group I	0.137	0.486	−0.152	0.440	−0.085	0.668	−0.083	0.674
Group II	−0.357*	0.035*	0.378*	0.025*	0.104	0.550	0.004	0.981
Group III	−0.173	0.351	0.353	0.052	0.170	0.361	0.241	0.191

*Significant.

Table 3. Correlation between the duration of hypertension and PERG parameters in groups II and III.

	P50 wave				N95 wave			
	Amplitude (μv)		Implicit time (msec)		Amplitude (μv)		Implicit time (msec)	
	r	P	r	P	r	P	r	P
Group II	0.040	0.819	0.556*	0.001*	0.000	1.000	0.352*	0.038*
Group III	−0.116	0.533	.445*	0.012*	0.382	0.034	0.069	0.711

*Significant.

Table 4. Comparison of PERG parameters between both eyes.

	Mean	SD	P value
RtP50lat	52	4.9	0.231
LtP50lat	51.3	4.6	
RtP50 amp	4.9	2.3	0.987
LtP50amp	4.9	2.3	
RtN95lat	97.1	7.5	0.437
LtN95lat	98	8.7	
RtN95amp	−8.2	12.6	0.378
LtN95amp	−6.4	3	

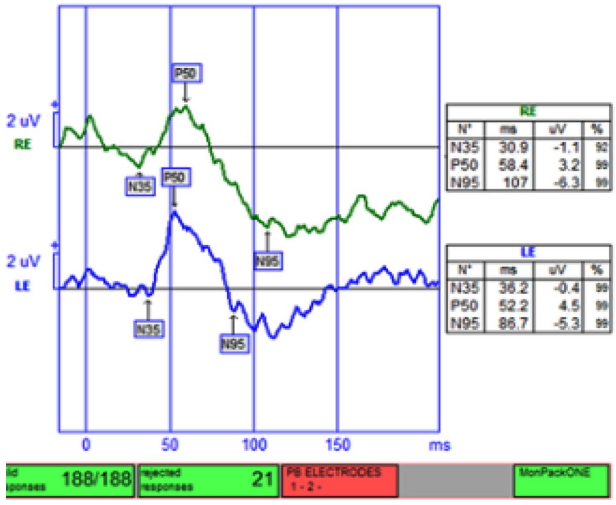

Figure 3. PERG of a hypertensive patient with normal fundus showing reduced amplitude of P50 over the right side and borderline amplitude value over the left side.

reduction in N95 and P50 [15] and can be used to quantify retinal ganglion cell dysfunction [16].

In the present study, the authors investigated PERG in 98 eyes assigned into 3 groups, group I: 28 eyes of control subjects, group II: 39 eyes of hypertensive patients with no signs of retinopathy and group III: 31 of hypertensive patients with retinopathy, with no significant difference among the study groups as regards age nor gender. The authors found that P50 wave showed amplitude reduction and implicit time prolongation in Group III (with retinopathy signs) compared to controls and Group II respectively, in addition to significant delay in N95 wave implicit time in Group III compared to normal controls. These changes are likely due to direct microvascular damage caused by high blood pressure which impairs the blood flow to the optic nerve. In addition, the breakdown of the blood retinal barrier results in hemorrhage and exudate with subsequent ischemia of the nerve fiber layer [17]. It is worth noting that, mean implicit times of P50 and N95 were prolonged and their mean amplitudes were reduced in group II compared to controls, though they were not statistically significant probably due to dilution of data of borderline values.

By reviewing literature, researchers have investigated PERG in diabetic retinopathy, ocular hypertension, and glaucoma [18]. N95 amplitude was significantly reduced in diabetics [19], and in diabetic

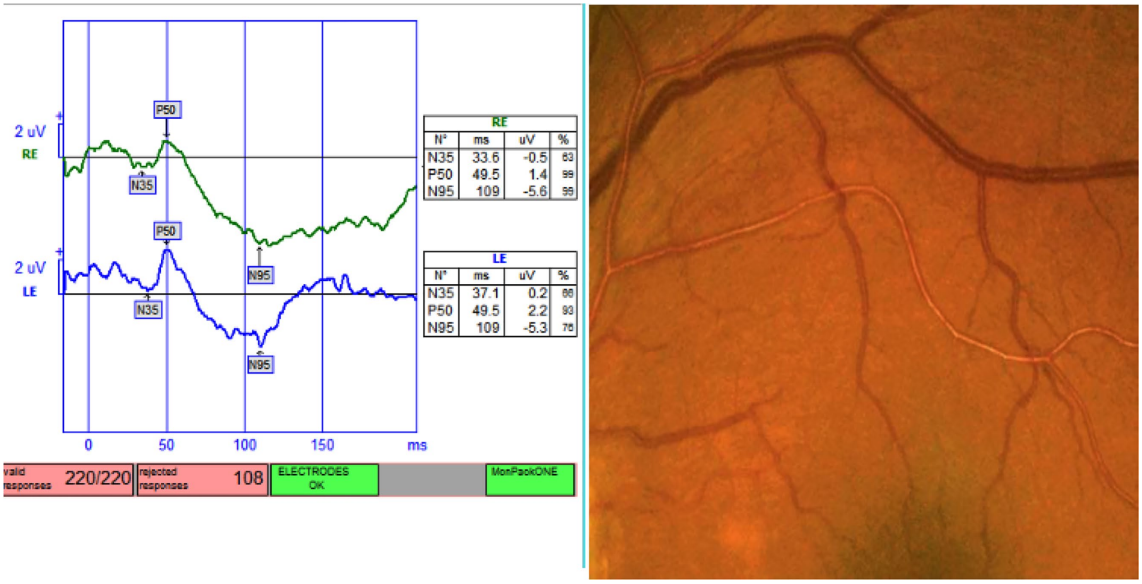

Figure 4. PERG showing markedly reduced amplitudes of P50 in hypertensive patient with grade II retinopathy. Fundus photography shows copper wiring.

subjects with suspected glaucoma or ocular hypertension [20].

In the current study, the age of the patient was not correlated with PERG parameters in group I. P50 amplitude in group II patients was negatively correlated with the amplitude and positively correlated with the implicit time, denoting P50 amplitude reduction and implicit time delay with aging, while in group III there was a near significance positive correlation with the implicit time of P50. This near significance could be attributed to borderline or mildly affected PERG parameters which may vary with increasing the sample size. Amplitude changes with aging in the present study are in accordance with reported PERG amplitude drop with aging in glaucoma [20], and diabetes [18].

Duration of hypertension was positively correlated to implicit times of P50 and N95 in group II, and P50 in group III, noting that the duration was significantly longer in group III compared to group II. However, authors stated that, PERG amplitude is reduced with increased disease duration in ocular hypertension and glaucoma [8,21]. Authors also suggested that in non-retinopathic diabetics the PERG signal is significantly correlated with the duration of disease [22]. The difference in PERG parameters correlated is probably due to different pathophysiology in each disorder.

The present study revealed PERG abnormalities in 79.5% of hypertensive patients with normal fundus. In previous studies, researchers found that PERG amplitude is reduced before signs of glaucomatous damage becomes evident by perimetry and concluded that PERG can detect early retinal dysfunction preceding glaucoma [8,23]. Turkey et al. [24] reported prolonged peak latencies and reduced amplitudes of P50 and N95 in patients with ocular hypertension and open angle glaucoma and concluded that PERG allows detection of retinal dysfunction earlier than optical coherent tomography in ocular hypertension.

In conclusion, PERG allows objective assessment of the retinal function in hypertensive patients, and may be considered a promising tool to detect early dysfunction in hypertensive patients with normal fundus. Longitudinal follow up of these patients is recommended to assess clinical progression.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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