



# Investigating the effects of glaucomatous damage on the multifocal visual evoked potential parameters

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## Abstract

**Purpose** To investigate the effects of glaucomatous damage on the mfVEP parameters of patients suffering from primary open-angle glaucoma (POAG).

**Methods** Fifteen healthy subjects and 15 patients with unilateral POAG participated in this study. In addition, routine ophthalmological examinations including visual acuity, anterior segment examination, posterior segment examination, intraocular pressure, mfVEP with electrophysiological system, RETI-port/Scan 21, and visual field test with automated Humphrey ZEISS HFA II 750i Perimeter were also performed.

**Results** The results show that there was a strong correlation between the  $\Delta$ MDs and the number of abnormal points with the  $\Delta$ amplitudes more than 256 nV, in patients ( $n = 15$ ,  $r = 0.802$ ,  $p < 0.05$ ), but

no correlations were found between the mean sensitivity differences ( $\Delta$ PSDs) and mfVEP parameters.

**Conclusions** Comparing the monocular mfVEP responses from both eyes is an appropriate method to detect unilateral damage. Achievement of more development and making the mfVEP test more functional can be a solution for early diagnosis in most of the eye diseases.

**Keywords** Multifocal visual evoked potential · Mean deviation · Pattern standard deviation · Visual field

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## Introduction

Glaucoma is considered as a major cause of irreversible vision loss including a diverse ophthalmopathies characterized by attenuating the neural and connective tissue segments and eventually progression of specific patterns of visual dysfunction. One of the primary risk factors is high intraocular pressure (IOP); however, it is not the main reason of this disease. Currently, perimetry is known as the most accurate method for diagnosis and following up of glaucoma [1]. A variety of techniques are used to carry out perimetry, including Goldmann perimeter, tangent screen, confrontation technique, and automated perimeters. The automated perimeter is the most applicable method [2].

Regardless of the unreliability of automated perimeters (HFA) for visual field defects, this method provides a rapid screening [3]. Some disadvantages of this technique are time-consuming, subjective nature, and inherent inaccuracies, especially in patients who are unable to cooperate properly [4].

Electrodiagnosis could be considered as an optional method in ophthalmology [5]. Two important and distinctive aspects of this method are its functionality and objectivity [6]. Nowadays, in the case of unreliable visual field test results obtained with subjective techniques, the multifocal visual evoked potential (mfVEP), an electrophysiological technique, has been adopted as an objective measure of visual fields [3]. The two most important parameters in the mfVEP are amplitude and latency [7].

The Humphrey visual field losses were in compatibility with defects in mfVEP responses in patients with ganglion cell damage [8].

The main purpose of this study is to investigate the effects of glaucomatous damage on the mfVEP parameters of patients suffering from primary open-angle glaucoma (POAG). According to different responses of the mfVEP among normal subjects due to the intersubject variability [7] and as a result of study by Randall et al., sensitivities of both eyes in a normal subject are nearly symmetrical [9], and comparing the monocular mfVEP responses from both eyes is an appropriate method to detect unilateral damage and to resolve the problem of intersubject variability [7].

## Materials and methods

### Subjects

The study was conducted at the Ophthalmology Clinic of Imam Khomeini Hospital of Ahvaz. Fifteen healthy subjects (age: 22–51 years; mean 35.7 years) and 15 patients with POAG (age: 45–70 years; mean 63 years) participated in this study. Ophthalmological examinations including visual acuity, anterior segment examination, posterior segment examination, intraocular pressure, mfVEP, and visual field test with automated perimeter were performed. All patients were categorized as unilateral POAG. The  $\bar{X}_{MD}$  (mean of mean deviation) and  $\bar{X}_{PSD}$  (mean of pattern standard

deviation) in more involved eyes in POAG patients were  $-6.72$  ( $SD = \pm -5.61$ ) and  $5.6$  ( $SD = \pm 4.95$ ), respectively.

The exclusion criteria were patients with best correction visual acuity (BCVA)  $< 20/70$ , severe opacity of the cornea and lens, and diseases involving retina or visual pathway

### Stimulus

In this study, the electrophysiological system, RETI-port/Scan 21, was used. The stimulus in a 21-inch screen was displayed. It consisted of 61 sectors in a dartboard pattern, and each sector contained 16 checks, eight white ( $200 \text{ cd/m}^2$ ) and eight black ( $< 1 \text{ cd/m}^2$ ). Each check alternatively was flashing black and white at a frame rate of 60 Hz. The contrast between black and white checks was kept nearly 98%. In the middle of the screen, there was a red cross in order to maintain fixation. The dartboard pattern had a diameter of  $24^\circ$ . The sectors of mfVEP stimulus were scaled in accordance with Fig. 1 [11, 12].

### Recording

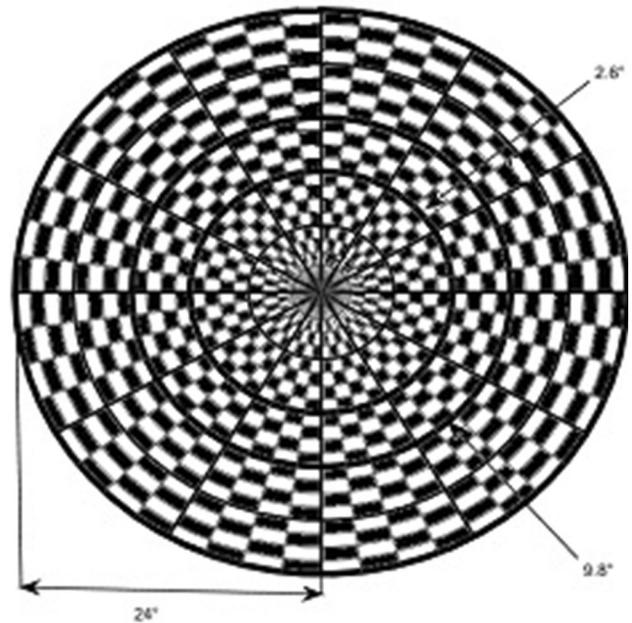
It is necessary that pupil had normal size during mfVEP recording. Electrode resistance in contact with the skin was less than  $10 \text{ K}\Omega$ . The recording was detected from one channel. In the mfVEP recording, gold cup electrodes were placed at a distance of 4 cm above the inion (active electrode), at the inion (reference electrode), and on the forehead (ground electrode).

The patients underwent near refractive correction. The test time was approximately 7 min for each eye. To obtain an mfVEP, the low- and high-frequency cutoff of recording was amplified at 1 and 100 Hz, respectively. The sample rate was set at about 1020 times per second.

### Visual field

The Humphrey visual fields (HVF) can be evaluated using the 24-2 SITA Standard program by means of Humphrey ZEISS HFA II 750i Perimeter. The interpolated visual fields were calculated to estimate the sensitivity within a stimulus sector in the mfVEP.

**Fig. 1** mfVEP display. Dart pattern of mfVEP stimulation and the scale of mfVEP stimulation



## Analysis

The intersubject variability lies in two major anatomical diversities: first, the relative position of calcarine fissure to the external landmarks; second, the difference in the way that cortex is folded and the position in which the primary visual area is located [10]. In this study, visual field assessing using mfVEP was applied to diagnose glaucomatous damage and also to determine the correlation of the mfVEP parameters with the global indices (MD and PSD) and local thresholds by the three following approaches. Firstly, the correlations between the mean differences in global indices in all 61 stimulated regions in the interpolated field were compared with the  $\bar{X}_{\Delta\text{amplitudes}}$  (mean differences in the amplitudes) and  $\bar{X}_{\Delta\text{latencies}}$  (mean differences in the latencies) between the two eyes in each patient. Secondly, the correlations of the sensitivity in each location of the interpolated visual field (MD and PSD) with the  $\Delta\text{amplitudes}$  and  $\Delta\text{latencies}$  between the two eyes in same locations of mfVEP in two patients with low-defect POAG were determined. Thirdly, the correlations of the number of points in each sector of mfVEP with the  $\Delta\text{amplitudes}$  and  $\Delta\text{latencies}$  between the two eyes of each patient ( $> \text{mean} \pm 2\text{SD}$ ) were determined. Moreover, the correlation of those points with the  $\Delta\text{global}$  indices in interpolated visual field of patients was clarified. In the present study, Pearson's

correlation of coefficient (for normal data) and Spearman's correlation of coefficient (for abnormal data) were calculated considering the significant level of  $p < 0.05$  using the SPSS software (v.22). Signal analysis was run using a software programmed in the Roland device, and the other statistical calculations were done by MATLAB software (R2015a version), as well. To access more information on the interpolated technique, see Ref. [12].

## Results

The  $\bar{X}_{\Delta\text{amplitudes}}$  and  $\bar{X}_{\Delta\text{latencies}}$  in all 61 stimulated locations of mfVEP in each patient were determined; thereafter, the averages of these values in each patient were compared with the same values in control group. As given in Table 1, the  $\bar{X}_{\Delta\text{amplitudes}}$  and  $\bar{X}_{\Delta\text{latencies}}$  in POAG patients were significantly higher than the control group (Mann–Whitney,  $p < 0.05$ ).

In the first method of analysis, the correlations between the  $\bar{X}_{\Delta\text{amplitudes}}$  and  $\bar{X}_{\Delta\text{latencies}}$  with the  $\bar{X}_{\Delta\text{MDs}}$  and  $\bar{X}_{\Delta\text{PSDs}}$  between the two eyes in each patient were determined; however, no correlations were observed. In this aspect of intersubject study, only the mathematical absolute values of the mean sensitivity, the  $\bar{X}_{\Delta\text{amplitudes}}$ , and  $\bar{X}_{\Delta\text{latencies}}$  among patients were considered (Table 2).

**Table 1** Means and standard deviations of interocular amplitude and latency differences

Group	$\bar{X} \pm SD(n_{\text{subjects}} = 15)$ (interocular amplitude differences)	$\bar{X} \pm SD(n_{\text{subjects}} = 15)$ (interocular latency differences)
Control	14.750 ± 17.984	0.44 ± 0.55
POAG	74.57 ± 66.30	1.74 ± 0.79

**Table 2** Correlation of calculated average of interocular mean sensitivity differences (MD and PSD) with the differences in mfVEP parameters in POAG

Parameters	$\bar{X} \pm SD(n_{\text{patient}} = 15)$	<i>r</i>	<i>p</i>
$\Delta MD_{\text{POAG}}$	6.8507 ± 5.4501		
$\Delta \text{amplitude (nV)}_{\text{POAG}}$	74.578 ± 66.305	− 0.086*	0.761
$\Delta \text{implicit time (ms)}_{\text{POAG}}$	1.700 ± 0.8	0.086**	0.761
$\Delta \text{PSD}_{\text{POAG}}$	1.7053 ± 1.360		
$\Delta \text{amplitude (nV)}_{\text{POAG}}$	74.578 ± 66.305	− 0.108*	0.703
$\Delta \text{implicit time (ms)}_{\text{POAG}}$	1.700 ± 0.8	0.335**	0.222

\*Spearman's correlation of coefficient

\*\*Pearson's correlation of coefficient

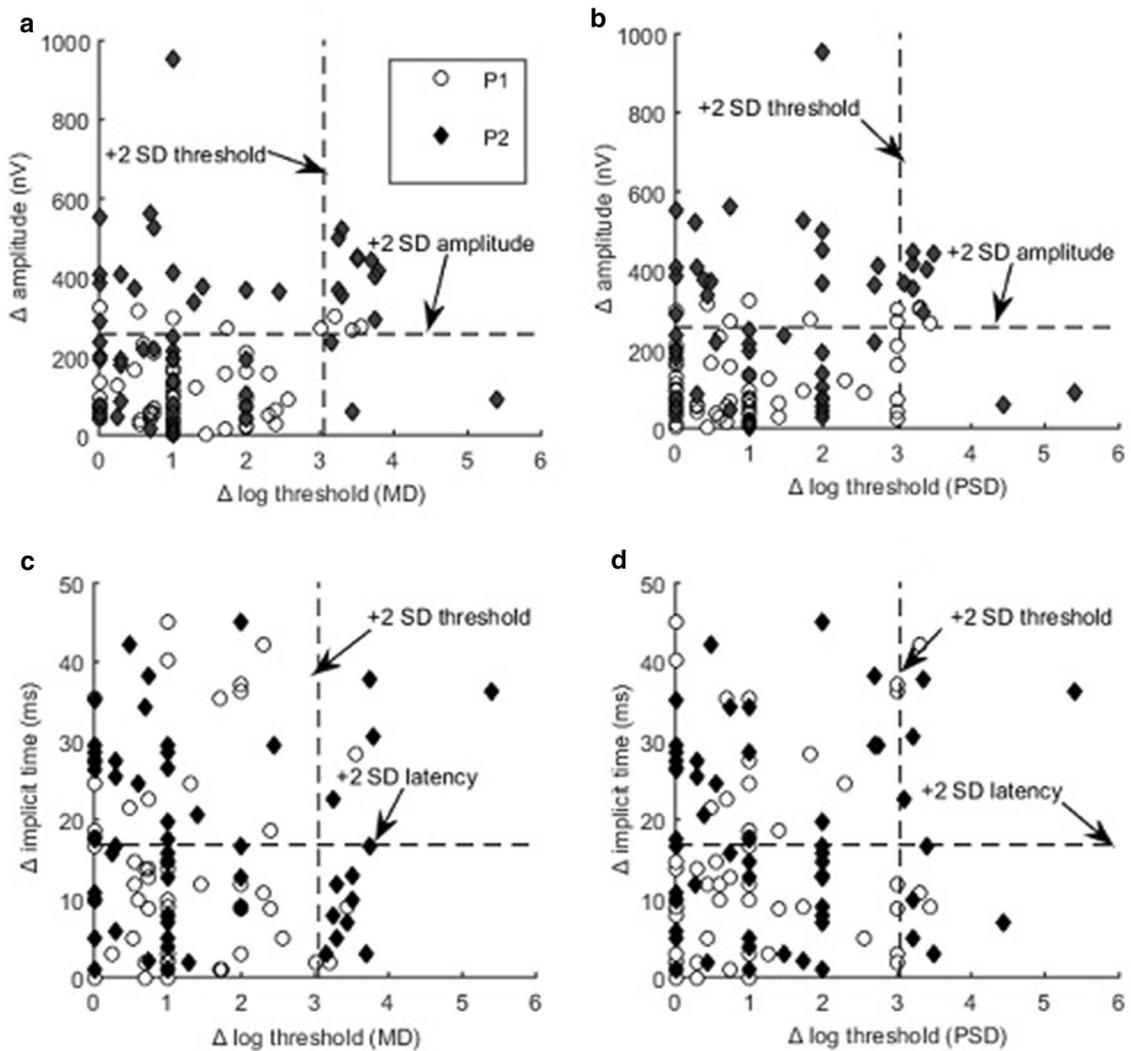
In the second method of analysis, in Fig. 2, scatter plots show the  $\Delta$ amplitudes (Fig. 2a, b) and  $\Delta$ latencies (Fig. 2c, d) against the  $\Delta$ MDs and  $\Delta$ PSDs in each of 61 locations, in patients P<sub>1</sub> and P<sub>2</sub>. Two dashed lines represent two standard deviations (+ 2 SD) from the control group, which is the mean standard deviation of each sector. In control group, the value of + 2 SD from the  $\bar{X}_{\Delta \text{amplitudes}}$  is 256 nV and the value of + 2 SD from the  $\bar{X}_{\Delta \text{latencies}}$  is 16.8 ms. As inferred from the scatter plots in Fig. 2, there are no statistical correlations of the  $\Delta$ amplitudes and  $\Delta$ latencies with visual field defects (Tables 3 and 4), and Fig. 2a, b shows that the points have abnormal  $\Delta$ MDs and  $\Delta$ PSDs, however mostly located above the horizontal lines and in the upper right quarter of the plots. Furthermore, the points that their  $\Delta$ amplitudes are abnormal are seen in the areas of normal  $\Delta$ MDs and  $\Delta$ PSDs, as well as in the regions with abnormal  $\Delta$ MDs and  $\Delta$ PSDs (the points that fall into the left side of the vertical lines). As illustrated in Fig. 2a, b, there has been less scattering compared to the  $\Delta$ latencies against the mean sensitivity plots (Fig. 2c, d). The calculations in this section are regardless of the magnitude of defects in each of 61 locations.

In the third method of analysis (Table 5), no significant correlation was observed between the mean sensitivity differences ( $\Delta$ MD and  $\Delta$ PSD) and the number of abnormal points with the  $\Delta$ latencies more than 16.8 ms. Similarly, no correlation was found between the mean sensitivity differences ( $\Delta$ PSDs) and the number of abnormal points with the  $\Delta$ amplitudes more than 256 nV. However, there was a strong correlation between the  $\Delta$ MDs and the number of abnormal points with the  $\Delta$ amplitudes more than 256 nV, in POAG subjects ( $n = 15$ ,  $r = 0.802$ ,  $p < 0.05$ ), (Fig. 3).

## Discussion

The results of the present study showed that there is a significant correlation of MD global parameter with the number of sectors with abnormal amplitude (Fig. 3).

Based on the results, asymmetry in the sensitivity of the visual pathway between the two eyes can be used in POAG subjects as an indicator in recognizing the abnormal visual field.



**Fig. 2** Differences in the amplitude and latency against the differences in the log threshold for patients P<sub>1</sub> and P<sub>2</sub>

**Table 3** Correlation of the interocular MD with the interocular differences in mfVEP parameters in POAG eyes in P<sub>1</sub> and P<sub>2</sub> (in each location of interpolated field)

Parameters	$\bar{X} \pm SD(n_{\text{location}} = 60)$	<i>r</i>	<i>p</i>
$\Delta MD_{P_1}$	$1.2350 \pm 0.8994$		
$\Delta \text{amplitude (nV)}_{P_1}$	$114.98 \pm 95.611$	0.103*	0.432
$\Delta \text{implicit time (ms)}_{P_1}$	$13 \pm 11.9$	- 0.089*	0.497
$\Delta MD_{P_2}$	$1.3096 \pm 1.2093$		
$\Delta \text{amplitude (nV)}_{P_2}$	$244.47 \pm 190.47$	0.147*	0.261
$\Delta \text{implicit time (ms)}_{P_2}$	$16.8 \pm 11.5$	- 0.178*	0.173

\*Spearman’s correlation of coefficient

**Table 4** Correlation of the interocular PSD with the interocular differences in mfVEP parameters in POAG eyes in P<sub>1</sub> and P<sub>2</sub> (in each location of interpolated field)

Parameters	$\bar{X} \pm SD(n_{\text{location}} = 60)$	<i>r</i>	<i>p</i>
$\Delta PSD_{P_1}$	1.0360 ± 1.1005		
$\Delta \text{amplitude (nv)}_{P_1}$	114.98 ± 95.611	0.253*	0.051
$\Delta \text{implicit time (ms)}_{P_1}$	13 ± 11.9	0.198*	0.130
$\Delta PSD_{P_2}$	1.4224 ± 1.2711		
$\Delta \text{amplitude (nv)}_{P_2}$	244.47 ± 190.47	0.094*	0.473
$\Delta \text{implicit time (ms)}_{P_2}$	16.8 ± 11.5	− 0.103*	0.432

\*Spearman’s correlation of coefficient

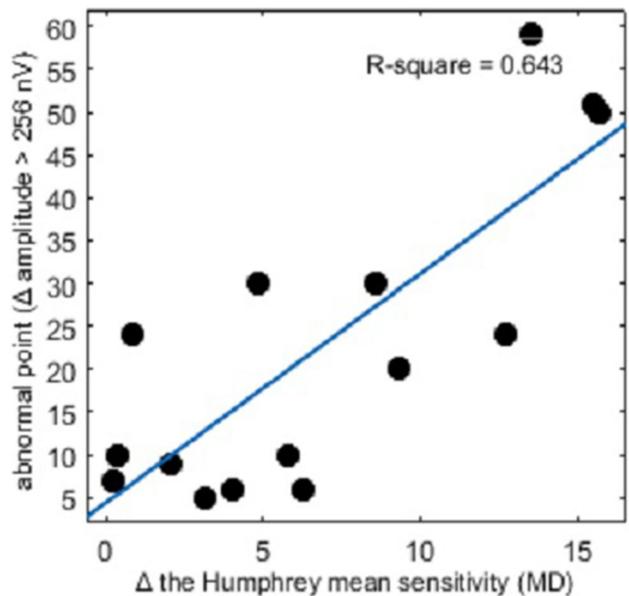
**Table 5** Correlation of the number of abnormal points ( $\Delta \text{amplitude} > 256 \text{ nm}$ ,  $\Delta \text{implicit time} > 16.8 \text{ ms}$ ) on mfVEP perimetry with the Humphrey interocular mean sensitivity differences (MD and PSD) in POAG eyes

Parameters	$\bar{X} \pm SD(n_{\text{patient}} = 15)$	<i>r</i>	<i>p</i>
$\Delta MD_{\text{patient}}$	6.8507 ± 5.45008		
Number of abnormal points <sub>patient</sub> ( $\Delta \text{amplitude} > 256 \text{ nm}$ )	22.7333 ± 18.14413	0.802**	0.00
Number of abnormal points <sub>patient</sub> ( $\Delta \text{implicit time} > 16.8 \text{ ms}$ )	13.7333 ± 3.82598	− 0.220*	0.430
$\Delta PSD_{\text{patient}}$	1.7053 ± 1.36065		
Number of abnormal points <sub>patient</sub> ( $\Delta \text{amplitude} > 256 \text{ nm}$ )	22.7333 ± 18.14413	0.170*	0.544
Number of abnormal points <sub>patient</sub> ( $\Delta \text{implicit time} > 16.8 \text{ ms}$ )	13.7333 ± 3.82598	− 0.437*	0.103

\*Spearman’s correlation of coefficient

\*\*Pearson’s correlation of coefficient

**Fig. 3** Correlation of the number of abnormal points ( $\Delta \text{amplitude} > 256 \text{ nV}$ ) on mfVEP with the  $\Delta \text{Humphrey}$  mean deviations for all 15 POAG patients



According to the current findings, electrophysiological tests such as mfVEP can be considered as a suitable method for measuring the visual field through the examination of visual pathway. The severity of defect in the mfVEP perimeter is estimated based on the extent of damage to the ganglion cells [8]. In the other words, it is possible to use the mfVEP test to confirm the healthy visual field in subjects who are not able to perform other subjective tests through inter-subject comparisons (children, the elderly, some mentally or physically disabled subjects, and some specific physiological conditions such as inaccuracy, fatigue, and malingering) [3, 4].

Donald Hood and colleagues showed that in patients with glaucoma and ischemic optic neuropathy suffering from unilateral visual field defects, calculating the ratio of the response amplitude in each eye is more accurate than the response  $\Delta$ amplitudes in mfVEP between the two eyes [13]. In the case of the latency of mfVEP responses with the MD global index in glaucoma, the results reported by Roodart et al. [14] were in agreement with the present study.

Kothari et al. compared the variations in VEP test parameters with the PSD in HVF. The amplitude response in POAG patients with moderate to severe glaucomatous defect showed a significant decrease compared with normal eyes ( $r = 0.434$ ,  $p < 0.01$ ) [15]. Other studies confirmed the results of Kothari. Another study on POAG patients showed that the latency period increases in POAG patients in comparison with control group [16]. But in our study, the mfVEP stimulus was used instead of VEP stimulus. No correlation was found between the mfVEP response amplitude and the PSD index. Similarly, no correlation was found between the mfVEP response latency and either MD or PSD index in HVF. It may be due to more received signals from a wide area of visual pathway and anatomical differences in visual pathway in different subjects, as well.

In this study, due to the time-consuming process of applying the multi-channel method, we were inevitably used only one channel. However, using more channels would enable us to receive more signals from a wide area of visual pathway, resulting in more accurate information [7]. Optimizing the time of the stimulation provides more accurate information. In this study, about seven minutes were allocated to stimulate each eye, in accordance with previous studies [17].

In conclusion, since the HVF responses are threshold values and the electrophysiological tests such as mfVEP are suprathreshold measures [10], achievement of more development and making the mfVEP test more functional can be a solution for early diagnosis in a considerable number of the eye diseases.

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#### Compliance with ethical standards

**Conflict of interest** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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