MULTIFOCAL ELECTRORETINOGRAPHY IN THE ASSESSMENT OF EYES WITH CENTRAL RETINAL VEIN OCCLUSION

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Abstract- Data suggest that the multifocal electroretinography (mfERG) may have a role in the assessment of patients with central retinal vein occlusion (CRVO). To explore the mfERG responses in patients with CRVO. mfERG responses were recorded at 61 discrete retinal locations from both eyes of 25 patients diagnosed with retinal vein occlusions within 3 weeks of onset. The latencies and amplitudes of average responses of 5 eccentric rings from 0 to 26 degrees relative to fixation, and grouped central and peripheral rings of involved eyes were compared with values obtained from 13 normal fellow eyes of these subjects. The mfERG responses obtained from eyes with CRVO were significantly different from those derived from the fellow eye, especially when the rings are grouped as central and peripheral. mfERG is a new, safe, non-invasive, and quick investigative tool to assess retinal function. Our results suggest that mfERG could be a useful electrophysiologic test in clinical evaluation and determination of the severity of underlying ischemia in patients with retinal vein occlusion. Further studies are needed to evaluate its role as a prognostic method to determine which eyes are prone to serious complications. This is the first report of mfERG results in Iran.

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INTRODUCTION

Retinal vein occlusion (RVO) is the second most common vascular disease of the retina only to the diabetic retinopathy (1, 2). As one of the most common vascular diseases of the retina, central retinal vein occlusion (CRVO), particularly the ischemic type, can lead to a severe loss of vision. Eyes with extensive capillary nonperfusion are at significant risk of neovascular complications (3).

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The prognosis is usually poor, especially in the ischemic type. Although visual acuity at baseline is a strong predictor of final vision, visual improvement does not differ significantly between the ischemic and non-ischemic types (1, 4).

Multifocal electroretinogram technique, which developed by Sutter *et al.*, allows quick simultaneous recording of many local electroretinogram from the posterior pole (5-7). The stimulation of the different areas during examination occurs in a pseudo- random manner and each focal ERG is calculated from the raw data by a cross correlation technique which extracts linear and non-linear components. The linear component, the so called first order kernel, has been shown to provide information from the outer retinal layers. The technique is quite novel with

respect to other techniques of focal electroretinography. The origins of the waveforms recorded with mfERG are still poorly understood. An animal study suggested that the mfERG has large contribution from the ON- and OFF-bipolar cells, in addition to a smaller contribution from the inner retinal components and the photoreceptors (8).

These data suggest that the mfERG may have a role in the assessment of patients with CRVO. mfERG is more susceptible than the standard ERG to changes in the nonlinear dynamics of the eye because of the multiple frequencies of stimulation used to obtain mfERG responses. Therefore, the mfERG could be a more sensitive indicator of the underlying disease affecting the layers of the retina in eyes with vein occlusion. mfERG also has the advantage of taking 8 minutes to perform once the pupils have been dilated, as opposed to the 40 minutes required to obtain a full standard ERG, possibly making the mfERG a more efficient and better-tolerated investigative tool than standard ERG in a busy clinical setting (9).

This is the first experience with mfERG in Iran. In this study, the effects of CRVO on the components of ERG responses were evaluated in our patients in Farabi Eye Hospital.

MATERIALS AND METHODS

We recorded mfERG responses simultaneously from both eyes of 25 patients diagnosed with CRVO. All of patients were recruited from the Retina Clinic at Farabi Eye Hospital of Tehran University of Medical Sciences. The age range of patients was 22–87 years (mean=56.3). The diagnosis of CRVO was on the basis of results of clinical findings by funduscopy, slit lamp biomicroscopy, color fundus photographs, and fluorescein angiography. Patients were excluded if there was clinical evidence of any other retinal disease or media opacity in the affected eye. Informed consent was obtained from all subjects before their participation. Procedures followed the tenets of the Declaration of Helsinki, and the protocol was approved by the review board and ethical committee of Eye Research Center of Tehran University of Medical Sciences. All patients were assessed within 3 weeks of the onset of symptoms.

The results of affected eyes compared with the 13 apparently normal unaffected eyes of the patients. The clinical data of the subjects are shown in Table 1. Affected eyes had mean corrected vision of 0.16, clear refractive medium or only aging change of the lens and no ocular disease unrelated to CRVO.

The Metrovision system was used for the measurement. The stimulus, consisting of 61 hexagons covering a visual field of 26 degrees horizontally and 20 degrees vertically, was presented on a 20 inches black-white monitor with a frame rate of 120 Hz and resolution of 1024 × 768 at a distance of 40 cm from the subject's eye. The first-order mfERG responses, namely the P1 RMS (root mean square) amplitude, P1 latency, and N1 RMS amplitude and latency were analyzed. The N1 amplitude was measured from the baseline to the N1 trough. The P1 amplitude was measured from N1 trough to P1 peak. The latencies of the N1 and P1 were the difference between the N1, P1 and the beginning of the stimulation.

After the pupil was dilated to more than 7 mm with tropicamide drop, the cornea was anesthetised with 1% tetracaine drop. The ERG jet disposable unipolar contact electrode was used to record the mfERG. The reference and natural electrodes were large size disposable electrodes. The fellow eye was occluded, and the subject's vision was corrected for best acuity for the viewing distance after insertion of the contact lens. The eye's position was monitored in the screen of the computer. The subjects made focus to satisfy their view to the screen. The first-order component was used in this study for analysis.

Data were analyzed using SPSS software. Mann-Whitney non-parametric test and *t* test was used to compare the results from the affected and fellow eyes. The RMS amplitudes and latencies were evaluated in 5 ring retinal regions according to the eccentricities. Also, for more evaluation the results were grouped into two central and peripheral group rings. Central group ring comprised two inner rings and peripheral ring comprised the remaining three outer rings. The location and focus of the stimulation image were controlled with an infrared fundus video system and monitored in the screen of the computer. The subjects were asked to fix in the central cross. The patients with low vision were asked to fix steadily to the center of the screen.

Table 1. The clinical data of subjects*

	Subject	Age	Visual acuity
Affected Eye	25	22-87(56.5)	HM-0.8 (0.16)
Fellow Eyes	13	22-67(56.3)	0.9-1 (0.99)

*Data are given as range (mean).

RESULTS

mfERG were recorded and analyzed from both eyes of each patient, except in 12 cases, in which the results from the fellow eye were excluded because of preexisting ocular disease. Firstly, the latencies and average RMS amplitudes of the 5 rings were measured. The comparisons of the latencies and average RMS amplitudes of 5 ring retinal regions between two groups are shown in Tables 2-5. In patients with CRVO the N1 and P1 average RMS amplitudes of 1-2 rings were decreased significantly. Also the N1 and P1 average latencies of rings 1 and 5 were delayed significantly.

Figure 1 shows the trace array from a patient's right eye with CRVO and visual acuity of Cf/1.5 m, and the fellow unaffected eye subject with visual acuity of 20/30. Most of the elements showed reduced amplitude and the greater amplitude at the center was correspondent to the good vision of the patient. Figure 2 shows the trace array and 2-dimension plots of P1 and N1 wave amplitudes of a patient with CRVO with visual acuity of Cf/0.5 m.

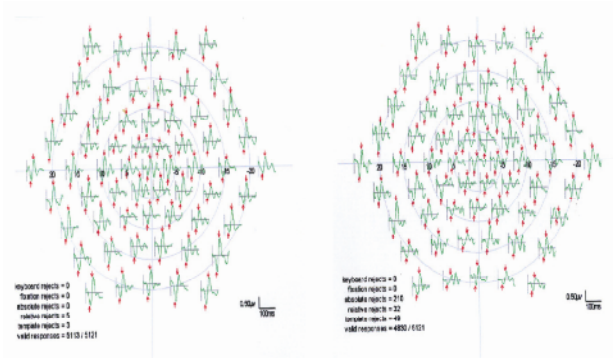

Fig. 1. Trace array from a patient's right eye with CRVO and visual acuity of Cf/1.5 m, and the fellow unaffected eye with visual acuity of 20/30.

Secondly, the results were grouped into two central and peripheral group rings. Central group ring comprised two inner rings and peripheral ring comprised the remaining three outer rings. Table 6 shows the results from the two group rings of mfERG recordings of the affected and the fellow eyes. A typical example of mfERG trace arrays from a patient's affected eye and the fellow eye is shown in Figure 2.

The distribution of mfERG responses was not normal, nonparametric statistical analysis, comparing the mfERG responses from the affected and the fellow eyes were performed. The differences in all the mfERG parameters assessed, except peripheral N1 amplitude, reached statistical significance ($P < 0.01$) between the affected and unaffected eyes, as shown in Table 6.

Table 2. The N1 RMS amplitudes (nv) of multifocal ERG in central retinal vein occlusion

Ring	Range of Responses		Mean ± SD		*P* value
	Affected Eye	Fellow Eyes	Affected Eye	Fellow Eyes	
1	6.70-33.10	4.80-60.70	18.10 ± 7.94	32.47 ± 14.65	0.002
2	2.50-31.10	11.80-35.40	15.87 ± 7.40	21.46 ± 6.52	0.035
3	3.50-22.90	10.00-17.00	12.20 ± 5.15	13.59 ± 2.46	0.380
4	2.80-19.80	7.70 -15.70	10.19 ± 4.85	11.53 ± 2.50	0.317
5	3.20 -15.90	6.80 -12.70	8.84 ± 4.03	9.57 ± 1.97	0.518

Table 3. The P1 RMS amplitudes (nv) of multifocal ERG in central retinal vein occlusion

Ring	Range of Responses		Mean ± SD		*P* value
	Affected Eye	Fellow Eyes	Affected Eye	Fellow Eyes	
1	10.00-70.00	24.60-149.00	33.64 ± 17.30	79.58 ± 37.90	0.000
2	9.60-56.60	33.30-73.40	32.77 ± 13.29	45.91 ± 11.94	0.004
3	6.20-45.90	23.50-41.40	25.22 ± 10.71	30.60 ± 4.73	0.074
4	6.50-41.20	16.30-35.60	21.88 ± 9.49	25.22 ± 5.99	0.157
5	6.50-31.70	14.20-27.70	19.00 ± 7.86	20.54 ± 4.82	0.415

Table 4. The N1 Latencies (ms) of multifocal ERG in central retinal vein occlusion

Ring	Range of Responses		Mean ± SD		*P* value
	Affected Eye	Fellow Eyes	Affected Eye	Fellow Eyes	
1	21.30-50.00	24.40-29.80	33.14 ± 6.78	27.16 ± 1.68	0.003
2	12.50-41.00	13.30-26.70	25.35 ± 6.92	21.26 ± 3.74	0.079
3	10.00-39.30	15.20-26.30	24.05 ± 7.10	21.40 ± 3.00	0.091
4	14.20-34.10	15.70-26.70	25.37 ± 6.40	21.96 ± 3.40	0.113
5	12.80-35.00	9.30- 25.60	25.12 ± 5.78	21.31 ± 4.12	0.035

Table 5. The P1 latencies (ms) of multifocal ERG in central retinal vein occlusion

Ring	Range of Responses		Mean ± SD		*P* value
	Affected Eye	Fellow Eyes	Affected Eye	Fellow Eyes	
1	38.20-70.20	38.20-51.70	53.46 ± 7.71	45.32 ± 3.37	0.001
2	25.10-58.20	34.90-48.60	44.49 ± 8.43	40.79 ± 4.23	0.067
3	24.10-57.00	36.90-44.10	41.93 ± 9.20	41.22 ± 2.30	0.340
4	34.60-51.70	32.60-46.90	44.46 ± 5.73	40.89 ± 4.23	0.051
5	34.60-55.10	33.80-45.10	44.24 ± 5.24	40.52 ± 2.89	0.024

Table 6. N1 and P1 RMS amplitudes (nv) and implicit times (ms) in different group rings

Parameters of central and peripheral group rings	Range of responses		Mean (SD)		*P* value
	Affected eyes	Fellow eyes	Affected eyes	Fellow eyes	
Central P1 amplitude (nv)	9.60-70.00	24.60-149	33.21(15.28)	62.75(32.44)	000*
Peripheral P1 amplitude (nv)	6.20-45.90	14.20-41.40	22.03(9.64)	25.45(6.56)	0.028†
Central N1 amplitude (nv)	2.50-33.10	4.80-60.70	16.99(7.68)	26.96(12.45)	0.000*
Peripheral N1 amplitude (nv)	2.80-22.90	6.80-17.00	10.41(4.84)	11.56(2.80)	0.111†
Central P1 implicit time (ms)	25.10-70.20	34.90-51.70	48.97(9.19)	43.05(4.40)	0.000†
Peripheral P1 implicit time (ms)	24.1-57	32.6-46.9	43.54(6.95)	40.87(3.17)	0.006†
Central N1 implicit time (ms)	12.5-50	13.3-29.8	29.25(7.84)	24.21(4.13)	0.002*
Peripheral N1 implicit time (ms)	10-39.3	9.3-26.7	24.84(6.39)	21.56(3.45)	0.002*

* nonparametric statistical analysis.
†*t* test.

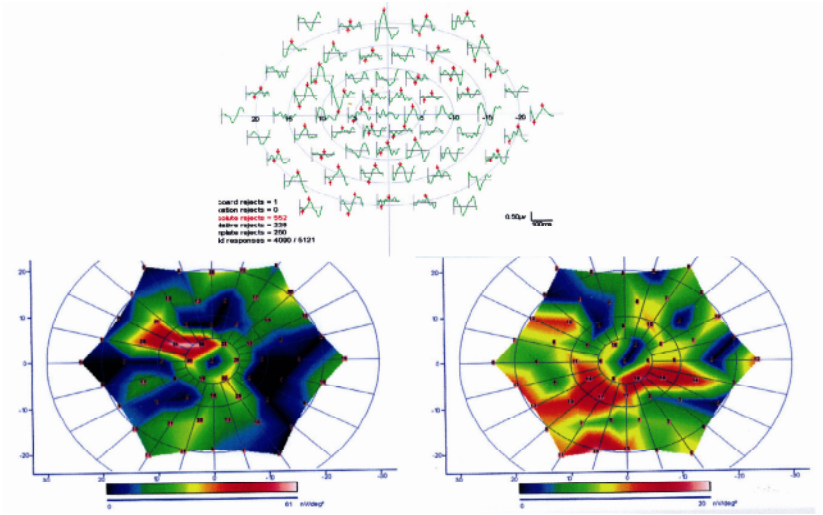

Fig. 2. Trace array and 2-dimensional plots of a patient with CRVO with visual acuity of Cf/0.5m.

DISCUSSION

The posterior pole involvement significantly damages the cone system, which makes the mfERG to be a sensitive test for quantifying the visual function. Tables 2 and 3 and Figure 1 show that the amplitude was the greatest in the fovea and decreases gradually with eccentricity in fellow eyes. In data analysis, the 2-dimension and 3-dimension plots may exactly show the location of normal and abnormal responses in every individual. But for the comparison between the control and patient groups, the comparison of average response may be of more value. (10) Palmowski *et al.* who used the mfERG technique averaged across all 103 local responses and found that mean implicit times in the first-order component were significantly increased in eyes with NPDR and peak amplitudes were reduced (11). In agreement with the mentioned studies, we also found that implicit times were significantly increased. Increased delays of the local ERG responses were associated with increased severity of local signs. Responses were also delayed in areas without retinopathy. The widespread nature of these timing delays may reflect retinal thickening and/or the effects of retinal hypoxia.

The amplitudes of N1 and P1 in 1–2 rings, central and peripheral P1 group rings, and central N1 group ring were decreased dramatically. The dramatic decrease of visual function was shown by the reduced visual acuity subjectively and the decrease average amplitudes of mfERG objectively. It is suggested that the slight damage of outer retina may cause decreased amplitude and that the more severe damage of the full-thick retina may lead to more amplitude decrease (12, 13). Seeliger showed that the longer latencies appear in the blind spot, the upper and lower margin of the stimulation field and the fovea and third rings and prolong toward the 1st ring and 5th ring. (7) These characteristics were preserved in CRVO. In addition, the prolong N1 and P1 latencies of rings 1 and 5, and all central and peripheral group rings were found. The results suggested that the latencies might be influenced when the lesion is dramatic. It has been shown that in the fellow eyes of patients with CRVO, mfERG may be abnormal, which may reflect abnormal retinal function in patients with underlying systemic disease.

We found that CRVO markedly affected P1 and N1 amplitudes and implicit times of mfERG. We observed subnormal P1 amplitudes and P1 implicit time delays in eyes with CRVO. This observation is in keeping with a previous report of mfERG responses in a subgroup of five patients with CRVO, (14) in whom the P1 amplitudes and implicit times were reduced and delayed in the affected eyes. Significant differences between the ERG responses of the affected and unaffected eyes have been reported (15-17). Fortune *et al.* reported that in patients with early diabetic retinopathy, it was common to find ERG responses that were severely delayed, yet these responses were among those with the larger amplitudes (18). Functional changes in the inner retina were also implicated by Palmowski *et al.* (11) to explain the differences between waveforms obtained from control subjects and diabetics when second order responses were analyzed.

The purpose of this study was to evaluate the nature and extent of retinal dysfunction in our patients with CRVO by mfERG. We have shown that local responses were significantly delayed and decreased in amplitude, and more severely affected eyes tended to have more abnormal mfERG responses. We are studying the sensitivity of mfERG in predicting neovascular complications in patients with CRVO.

Acknowledgments

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Conflict of interests

The authors declare that they have no competing interests.

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