Arch Iranian Med 2006; 9 (3): 261 – 265

Original Article

MULTIFOCAL ELECTRORETINOGRAM IN CLINICALLY SIGNIFICANT DIABETIC MACULAR EDEMA

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Objective: To explore the multifocal electroretinogram in patients with nonproliferative diabetic retinopathy with clinically-significant macular edema.

Methods: Forty-one eyes with clinically significant macular edema were tested. The latencies and amplitudes of average responses of 5 eccentric rings from 0 to 26 degrees relative to the fixation point were compared with normal values obtained from 13 nondiabetic subjects.

Results: Local electroretinogram responses were significantly delayed and decreased in amplitude in patients with clinically-significant macular edema.

Conclusion: Multifocal electroretinogram can be used to quantify the visual function in clinically significant macular edema.

Archives of Iranian Medicine, Volume 9, Number 3, 2006: 261 – 265.

Keywords: Clinically-significant macular edema • diabetic retinopathy • multifocal electroretinogram

Introduction

It has been shown that in diabetic retinopathy, full-field electroretinography (ERG) shows abnormalities including reductions in the amplitudes of the components and delay in implicit times, which appear to be related to the severity of the retinopathy.[1 – 5] The problem with full-field ERG techniques is that they are of little value for assessing the effects of clinically-significant macular edema (CSME) on central retinal function. The development of focal ERG techniques has allowed the examiner to study local retinal areas. Focal ERG results obtained from patients with diabetic retinopathy with and without CSME show reduction in amplitudes, delay in implicit times, and reduction in oscillatory potential (OP) amplitudes.[6 – 8]

Multifocal electroretinogram (mfERG) technique, which developed by Sutter and his colleagues allows quick simultaneous recording of many local ERG from the posterior pole.[9 – 11] Some studies have shown the effect of diabetic retinopathy on mfERG.[12 – 15]

In this study, the effects of CSME on the components of ERG responses were evaluated in our patients in Farabi Eye Hospital, Tehran, Iran.

Patients and Methods

Forty-one eyes with CSME from 22 patients with noninsulin-dependent diabetes mellitus were tested. Both eyes of each subject were tested. All patients were recruited from the Retina Clinic of Farabi Eye Hospital affiliated to Tehran University of Medical Sciences, between September 2003 and February 2005. The level of retinopathy and degree of macular edema were determined for each patient on the basis of results of slit lamp biomicroscopy, color fundus photographs, and fluorescein angiography. The exclusion criteria included poor central or unsteady fixation of eyes, poor cooperation, and any other ocular diseases including fundal problems. Thirteen control volunteers aged between 27 and 62 (mean of 43) years with no abnormalities of the visual system also participated in the study. Matching was not possible, because of the low number of cooperative

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Accepted for publication: 2 November 2005

volunteers in the control group. It should be mentioned that during the test, most of patients and normal controls did not cooperate enough or refuse to do so. Those who took part in this study had been selected from a large population. All subjects had corrected vision equal or better than 20/200, clear refractive medium or only senile changes of the lens, and no ocular disease unrelated to diabetes. Because of differences in methods used, the previously-reported normal results have not been used for comparison. All subjects had central fixation.

Informed written 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 the Ethical Committee of the Eye Research Center of Tehran University of Medical Sciences.

The Metrovision system was used for the measurements. The stimulus, consisting of 61 hexagons covering a visual field of 26 degrees horizontally and 20 degrees vertically, was presented on a 20-inch black and white monitor with a frame rate of 120 Hz and a resolution of 1024 × 768 pixels, at a distance of 40 cm from the subject's eye. The amplitudes and latencies were evaluated in five-ring retinal regions, according to the eccentricities. The location and focus of the stimulation image were controlled with an infrared fundus video system and monitored on the screen of the computer. The subjects were asked to fix at the central cross. The patients with low vision were asked to fix steadily to the center of the screen.

After the pupil was dilated to more than 7 mm with tropicamine, the cornea was anesthetized with 1% tetracaine ophthalmic drop. The ERG jet disposable unipolar contact electrode was used to record the mfERG. The reference and neutral electrodes were large disposable electrodes. The fellow eye was occluded, and the subject's vision was corrected for the best acuity for viewing distance after insertion of the contact lens. The eye position was monitored in the screen of the computer. The subjects focused till satisfied with the vision on screen.

Table 1. The clinical data of subjects.

Group	*N*	Age (yr) (mean)	Visual acuity (mean)
Control	13	27 – 67 (43)	0.9 – 1 (9.92)
CSME*	41	48 – 70 (56.3)	0.1 – 1 (5.18)

*CSME = clinically-significant macular edema.

The latencies and average response densities of the five rings were measured. The N1 amplitude was measured from the baseline to the N1 trough. The P1 amplitude was measured from the N1 trough to the P1 peak. The latencies of the N1 and P1 were the differences between the N1, P1, and the beginning of the stimulation.

The first-order component was used in this study for analysis. Mann-Whitney U test was used to compare the data obtained between groups. Data were analyzed using SPSS.

Results

The mean age of patients with CSME was 56.3 (range: 48 – 70) years. The clinical data of the subjects are shown in Table 1.

The comparisons of the latencies and average response densities of five-ring retinal regions between the two groups are shown in Tables 2 – 5.

Table 2. The N1 amplitudes of multifocal ERG in those with clinically significant macular edema.

Rings	Control		DR* with CSME#		*P* value
	Range	Mean ± SD	Range	Mean ± SD	
1	4.80 – 60.70	32.47 ± 14.65	1.30 – 61.20	20.56 ± 13.37	0.005
2	11.80 – 35.40	21.46 ± 6.52	2.20 – 34.00	15.24 ± 7.47	0.009
3	10.00 – 17.00	13.59 ± 2.46	3.50 – 24.60	12.66 ± 4.92	0.312
4	7.70 – 15.70	11.53 ± 2.50	2.70 – 19.00	10.12 ± 3.60	0.145
5	6.80 – 12.70	9.57 ± 1.97	2.70 – 15.30	8.81 ± 3.20	0.430

* = diabetic retinopathy; # = clinically-significant macular edema.

Table 3. The N1 latencies of multifocal ERG in those with clinically significant macular edema.

Rings	Control		DR* with CSME#		*P* value
	Range	Mean ± SD	Range	Mean ± SD	
1	24.40 – 29.80	27.16 ± 1.68	16.30 – 50.00	29.14 ± 7.33	0.221
2	13.30 – 26.70	21.26 ± 3.74	7.30 – 33.70	22.41 ± 5.93	0.241
3	15.20 – 26.30	21.40 ± 3.00	7.20 – 29.90	23.25 ± 5.16	0.042
4	15.70 – 26.70	21.96 ± 3.40	12.60 – 31.70	24.04 ± 4.74	0.072
5	9.30 – 25.60	21.31 ± 4.12	13.90 – 30.00	24.31 ± 4.42	0.004

* = diabetic retinopathy; # = clinically-significant macular edema.

Table 4. The P1 amplitudes of multifocal ERG in those with clinically significant macular edema.

Rings	Control		DR* with CSME#		*P* value
	Range	Mean ± SD	Range	Mean ± SD	
1	30.60 – 124	78.27 ± 30.62	8.40 –146	43.23 ± 1.40	0.002
2	33.30 – 73.40	46.90 ± 12.65	12.40 – 69.60	34.24 ± 14.10	0.004
3	25.90 – 41.40	31.03 ± 4.58	10.50 – 52.30	29.02 ± 9.67	0.424
4	17.10 – 35.60	26.40 ± 5.65	7.30 – 39.00	22.85 ± 7.98	0.424
5	14.70 – 27.70	20.59 ± 4.52	6.50 – 31.90	19.33 ± 6.55	0.571

* = diabetic retinopathy; # = clinically-significant macular edema.

In patients with CSME, the N1 and P1 average amplitudes of 1 – 2 rings were decreased significantly. Moreover, the N1 and P1 average latencies of rings 3 and 5 were delayed significantly. In diabetic patients without CSME, the N1 and P1 average amplitudes of 1 – 2 rings were decreased significantly. Moreover, the N1 and P1 average latencies of rings 4 were delayed. Figure 1 shows the trace array and 3-dimensional plot in a control subject with a visual acuity of 20/20. All the 61 elements showed good response

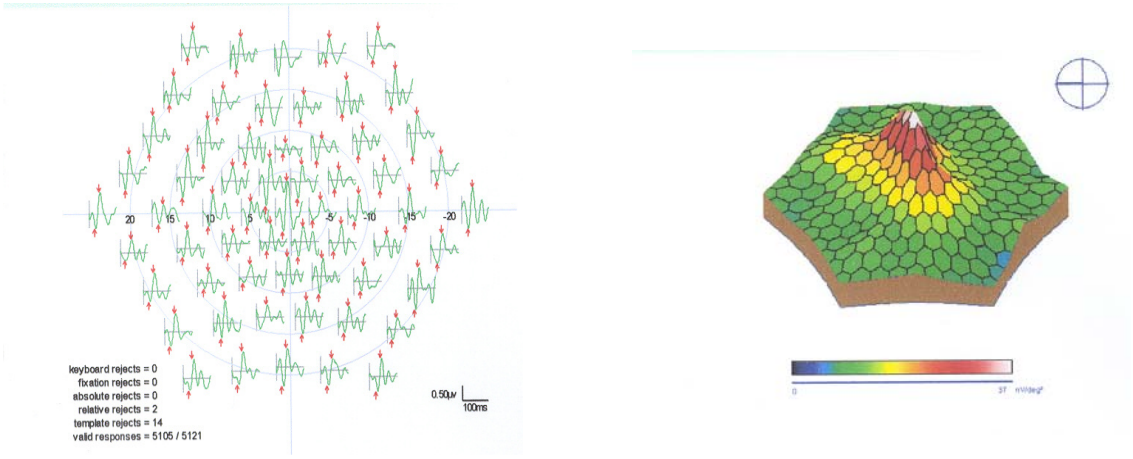

Figure 1. Trace array and 3-dimensional plot of a control subject with a visual acuity of 20/20.

in the trace array. The plot showed a typical shape, with the greatest average response density in the center. Figure 2 shows the trace array and 2-dimensional plot of N1 wave amplitudes and latencies in a patient with CSME with a visual acuity of 20/70. Most of the elements showed a reduction in amplitude. The greater amplitude at the center corresponds to the good vision of the patient.

There was no significant difference between sex- and age-related differences with the patient groups chosen in this study.

Discussion

The objective of this study was to evaluate the nature and extent of retinal dysfunction in the posterior pole of retina in patients with CSME. There are numerous studies on the effects of diabetic retinopathy on the full-field cone ERG.[1, 3, 4] Recently, focal ERG techniques have been used to assess localized central retinal function. Studies using focal ERG techniques have reported reductions in amplitude and delay in the implicit time in eyes with nonproliferative diabetic retinopathy with and without CSME.[7, 8] In one study, the mean amplitude was lower in

Table 5. The P1 latencies of multifocal ERG in those with clinically significant macular edema.

Rings	Control		DR* with CSME#		*P* value
	Range	Mean ± SD	Range	Mean ± SD	
1	38.20 – 51.70	45.84 ± 3.4	33.10 – 70.20	47.79 ± 6.95	0.403
2	34.90 – 48.60	41.04 ± 4.43	22.10 – 53.40	42.22 ± 7.18	0.221
3	36.90 – 43.80	41.10 ± 2.29	20.80 – 48.20	42.37 ± 5.22	0.025
4	32.60 – 46.90	41.80 ± 3.68	25.60 – 50.80	42.49 ± 5.26	0.127
5	33.80 – 45.10	40.52 ± 2.89	31.50 – 49.20	43.21 ± 4.23	0.006

*diabetic retinopathy; #clinically-significant macular edema.

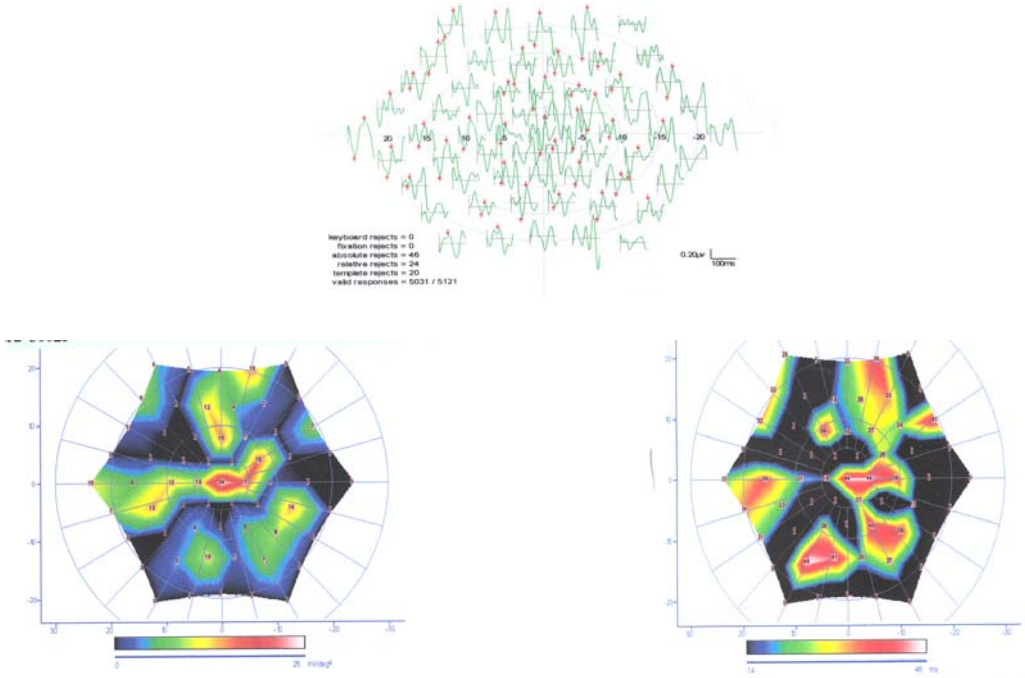

Figure 2. Trace array, 2-dimensional plot of N1 wave amplitudes and latencies of a patient with clinically significant macular edema and a visual acuity of 20/70.

proliferative diabetic retinopathy without CSME, as compared with that of the normal eyes. It was lower in eyes with CSME. The mean implicit time was significantly delayed in eyes with CSME.[14]

The macular diseases mainly damage the cone system, which make the mfERG as a sensitive test for quantifying the visual function of maculopathies. Tables 2 and 3, and Figure 1 show that the amplitude, with its peak in the fovea, decreases gradually with eccentricity in the control subjects. During data analyses, the 2- and 3-dimensional plots may exactly show the location of normal and abnormal responses in every individual. But for the purpose of comparison between the control and patient groups, the comparison of average response could be of greater value.[16] Palmowski et al[13] have used the mfERG technique, averaged across all 103 local responses, and found that the mean implicit times in the first-order component were significantly increased in the eyes with nonproliferative diabetic retinopathy and that the peak amplitudes had been reduced. In agreement with the above-mentioned studies, we also found that implicit times were significantly increased. Although increased delays of the local ERG responses were associated with increased severity of the local retinopathy signs, responses were also delayed in areas without retinopathy. The widespread nature of these timing delays may reflect upon the retinal thickening and/or the effects of retinal hypoxia. The amplitudes of N1 and P1 in 1 – 2 rings were decreased dramatically in patients with CSME. The dramatic decrease of visual function was shown by the reduced visual acuity, subjectively, and the decreased average amplitudes of mfERG, objectively. It is suggested that the slight damage of outer retina may cause the decreased amplitude and that the more severe damage of the full-thickness retina could lead to further decrease in the amplitude.[14, 15]

Seeliger et al showed that the longer latencies appear in the blind spot, the upper and lower margin of the stimulation field and the fovea and the third rings and prolong towards the first and the fifth rings. These characteristics were preserved in CSME. In addition, the prolonged N1 and P1 latencies of rings 3 and 5 in CSME were found. The results suggested that the latencies might be influenced, when the lesion is dramatic.[16]

We found that the effects of CSME on local ERG response amplitudes were more variable. Fortune et al[12] 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. Functional changes in the inner retina were also implicated by Palmowski et al[13] to explain the differences between waveforms obtained from the control subjects and diabetics, when the second-order responses were analyzed. Despite the similarities between the sensitivity and timing changes, other researchers have found that in diabetic patients with CSME, the implicit time is not a good predictor for the degree of sensitivity loss.[15]

With the mfERG technique, we have shown that the local responses were significantly delayed and decreased in amplitude, and that timing changes affected a larger area of the retina than amplitude changes.

Acknowledgment

This study was supported by grants from Deputy of Research of Tehran University of Medical Sciences and Eye Research Center of Farabi Eye Hospital.

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