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A preliminary assessment of macular function by MF-ERG in myopic eyes with CNV with complete response to photodynamic therapy

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PURPOSE. To evaluate by multifocal electroretinogram (MF-ERG) macular function before and after photodynamic therapy (PDT) in myopic eyes with choroidal neovascularization (CNV).

PATIENTS AND METHODS. Ten eyes with classic subfoveal CNV due to pathologic myopia were studied with MF-ERG before and after PDT in order to evaluate the results of PDT with verteporfin. The post-treatment follow-up was 6 months.

Visual acuity testing, ophthalmic examinations, fluorescein and indocyanine green angiograms, and MF-ERG recordings were used to evaluate the results of PDT with verteporfin. The post-treatment period was 6 months.

RESULTS. Before treatment, the electrical response densities in the foveal and perifoveal areas were apparently decreased in all patients. Six months after treatment, the mean retinal response densities in the same areas were found to be higher than before treatment.

CONCLUSIONS. MF-ERG evaluates objectively the macular function in myopic eyes with CNV. After successful PDT, the electrical activity of the foveal and parafoveal areas is higher than before treatment. This finding postulates the efficacy of PDT in the treatment of CNV. (Eur J Ophthalmol 2003; 13: 461-7)

KEY WORDS. Verteporfin, Choroidal neovascularization, Myopia, Photodynamic therapy, Multifocal electroretinogram

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INTRODUCTION

Choroidal neovascularization (CNV) is a leading cause of loss of central vision in developed countries (1). Pathologic myopia has also been reported to be a major cause of blindness in the United States (2). Many of these cases of visual loss result from the development of CNV.

The potentially poor natural history of many subfoveal CNV lesions and the limitations of thermal laser photocoagulation for these lesions have prompted the search for alternative treatment modalities, including photodynamic therapy (PDT) (3-9). PDT involves intravenous injection of a photosensitizer followed by irradiation of the neovascular tissue to be treated by nonthermal light at one of the red, or near infrared, absorption peaks of the dye. In neovascular tissue, cellular damage to the endothelium can lead to throm-

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bosis within the vessels. Experiments in normal monkey eyes demonstrated minimal damage to photoreceptors and verteporfin dose-dependent recovery of the retinal pigment epithelium (RPE) and choriocapillaris (10, 11).

Visual function before and after PDT is assessed by visual acuity (VA) measurement. However, the VA represents only a part of the impaired visual function resulting from CNV. Visual field testing and contrast sensitivity are other methods to estimate the results of PDT.

The purpose of this study is to record the electroretinographic changes of the foveal and parafoveal area by means of the multifocal electroretinogram (MF-ERG) in myopic eyes with CNV before and after PDT and to assess its efficacy objectively. The MF-ERG introduced by Sutter and Tran (12) allows the simultaneous derivation of 61 or 103 focal ERG signals in a central visual field of 30° diameter around the fovea. This technique allows functional mapping of the retina and contributes to detailed evaluation of the retinal function, especially in regional disorders of the inner retinal layers.

PATIENTS AND METHODS

Ten eyes of 10 patients with classic subfoveal CNV due to myopia were studied. These cases were selected from 45 patients in whom PDT was applied during the period 2000–2002. None of the eyes included in this study showed a remission of CNV leakage 6 months after treatment. All the other cases with remaining leakage were excluded from the study.

Pathologic myopia was defined in eyes requiring a distance correction of at least –6.0 diopters (D; spherical equivalent). An eye with a spherical equivalent less than –6.0 D was eligible if there were retinal abnormalities consistent with pathologic myopia (such as lacquer cracks) and if the axial length of the eye was at least 26.5 mm. The refractive error of the cases studied ranged between 6.0 and 10.0 D (mean 8.05; SD 1.321) (Tab. I).

Six men and four women were included (age range 32–55 years; mean 45.7; SD 7.303). Best VA at preoperative screening ranged between 30 and 52 Early Treatment Diabetic Retinopathy Study (Tab. I).

The study protocol was approved by the local institutional review board of our hospital. Each patient signed a written consent statement before entering the study.

Best-corrected VA was measured on a Bailey-Lovie chart using a standardized refraction protocol at baseline and at 1 week, 3 months, and 6 months . Patients were included when fluorescein angiography showed specific characteristics of CNV. The CNV lesion had to show a pattern of classic CNV, without any evi-

TABLE I - CLINICAL DATA OF THE PATIENTS WITH CLASSIC SUBFOVEAL CHOROIDAL NEOVASCULARIZATION DUE TO PATHOLOGIC MYOPIA

No.	Age, years	Preoperative VA	Refractive error, D	Lesion size, μ	Postoperative VA
1	32	48	7.0	1200	60
2	40	52	9.0	500	60
3	45	52	6.0	750	50
4	50	48	10.0	1100	52
5	55	40	9.5	1500	32
6	48	46	8.0	1600	55
7	39	36	6.5	1750	48
8	51	50	7.5	700	52
9	43	30	9.0	1050	48
10	54	48	8.0	1150	59
Average	45.7	45.00	8.05	1031	51.60
SD	7.303	7.318	1.321	518.8	8.302

VA = Visual acuity

TABLE II - RETINAL RESPONSE DENSITIES OF AREAS 1 AND 2 OF MULTIFOCAL ELECTRORETINOGRAM BEFORE AND AFTER PHOTODYNAMIC THERAPY (PDT) IN MYOPIC EYES WITH CHOROIDAL NEOVASCULARIZATION

	Before treatment		**A week after PDT**		**3 months after PDT**		**6 months after PDT**	
No.	Area 1	Area 2	Area 1	Area 2	Area 1	Area 2	Area 1	Area 2
1	4.14	2.14	3.75	1.97	0.25	1.50	0.45	1.75
2	2.63	2.90	0.96	3.12	11.0	6.00	12.50	3.00
3	7.00	5.97	3.71	4.21	4.00	4.50	5.00	6.50
4	1.04	2.90	-7.10	4.05	2.80	6.80	2.30	6.30
5	2.57	-046	3.58	-0.88	-3.73	0.86	4.23	0.93
6	5.28	1.45	2.33	0.87	2.55	0.95	5.88	1.02
7	3.22	1.25	-0.37	-0.73	2.44	0.70	4.56	1.20
8	2.33	0.56	-1.88	-3.20	1.57	0.23	3.90	0.88
9	5.60	1.20	-0.74	-0.56	4.20	0.53	6.20	0.35
10	7.40	2.06	1.34	-0.40	4.70	0.79	10.60	3.10
Average	4.121	1.997	0.558	0.845	2.978	2.286	5.562	2.503
SD	2.126	1.793	3.338	2.435	3.723	2.484	3.600	2.241

dence of occult CNV, and have a size of 500 to 1750 μ (mean 1031; SD 518.8).

All patients received verteporfin therapy at a dose of 6 mg/m^2 of body surface, administered via intravenous infusion of 30 ml over 10 minutes. Fifteen minutes after the infusion was started, a nonthermal (diode) laser light at 689 nm was delivered using a total of 50 J/cm^2 at an intensity of 600 mW/cm^2 over 83 seconds, using a spot size with a diameter 1000 μm larger than the greatest linear dimension of the CNV.

All patients were examined by MF-ERG on the same day before PDT treatment and 1 week and 3 and 6 months after PDT treatment. Patients with other ocular diseases such as glaucoma, generalized retinal degeneration, and cataract were excluded from our study, so that the first order responses of MF-ERG recording would not be influenced by the above mentioned diseases.

Statistical analysis was performed with the paired t-test. Because of the small number of cases in our study, the nonparametric Wilcoxon signed-rank test was also performed.

Multifocal ERG recording

For the recording of the multifocal ERG, the VERIS III (Visual Evoked Response Imaging System, Tomey, Nagoya, Japan) was used. The stimulus matrix consisted of 61 hexagon elements displayed on a cathode ray tube color monitor driven at a frame of 75 Hz. These hexagons elicit approximately equal signal amplitude at all locations on a normal retina.

Each hexagon was independently alternated between black and white at a rate of 75 Hz and this stimulation technique allowed a retinal response from each stimulus. The luminance of the stimulus for white was 200 cd/m^2 and the contrast 99.3%. The radius of the stimulus array subtended approximately 20° high and 25° wide. The bandwidth of the amplifier was 10–300 Hz and the amplification x10,000.

Subject pupils were dilated by means of tropicamide 0.5% and phenylephrine 5% and the eyes were optically corrected for near vision. Because all patients had poor central vision a spoke-shaped (filled cross) fixation aid was used and the patients were instructed to fixate at the intersection of the spokes. For signal derivation a bipolar contact lens was used in which the reactive and the reference electrodes are incorporated in the contact lens. The ground electrode was attached at the earlobe. The opposite eye was closed and the duration of data acquisition was 4 minutes divided into eight sessions of 30 seconds. The response density (amplitude per unit retinal area, nV/deg^2) of each local response was estimated as the dot product between normalized response template and each local response. Figure 1 shows a multifo-

cal ERG recorded from a normal case. The normal ranges for these amplitudes were defined by calculation of the median and 95% confidence interval of 30 normal volunteers (one eye each; i.e., 30 eyes) aged 35–50 years (mean age 38.8 years). Multifocal ERG stimuli location and anatomic areas correspond roughly as follows: ring 1 to the fovea, ring 2 to the parafovea, ring 3 to the parafovea, ring 4 to the near periphery, and ring 5 to the central part of the middle periphery. The amplitude of each group is scaled to reflect the angular size of the stimulus hexagons, which produce the response. These averages give a more accurate view of the relative response density for each group. The average relative response density of the retinal area corresponding to ring 1 is roughly 20.03 nV/deg^2, to ring 2 is 15.04 nV/deg^2, to ring 3 is 12.8 nV/deg^2, to ring 4 is 10.1 nV/deg^2, and to ring 5 is roughly 10.0 nV/deg^2. The retinal response density (RRD) decreases with eccentricity, although there is no further decrease from ring 4 to ring 5.

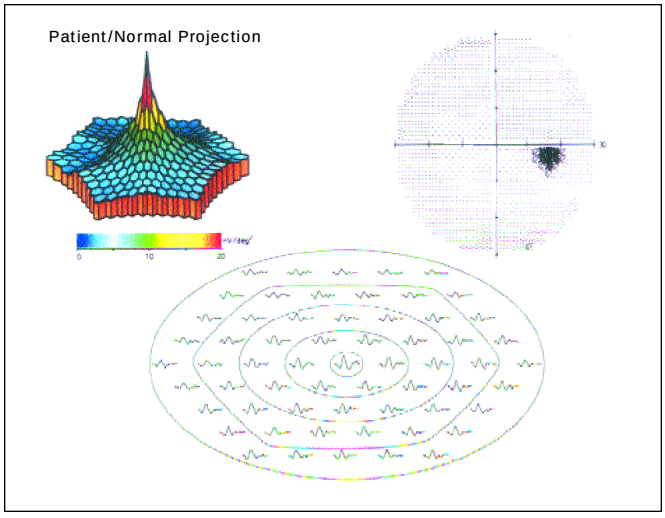

Fig. 1 - Normal multifocal electroretinogram with the five rings of electroretinogram traces corresponding to the different retinal areas around the fovea.

RESULTS

One week after treatment, fluorescein angiography showed the same decrease of CNV leakage in all patients. Three months after PDT, minimal leakage was still observed in five cases and the PDT was repeated. Six months after photocoagulation, an absence of CNV leakage was realized in all cases included in the study (Fig. 2).

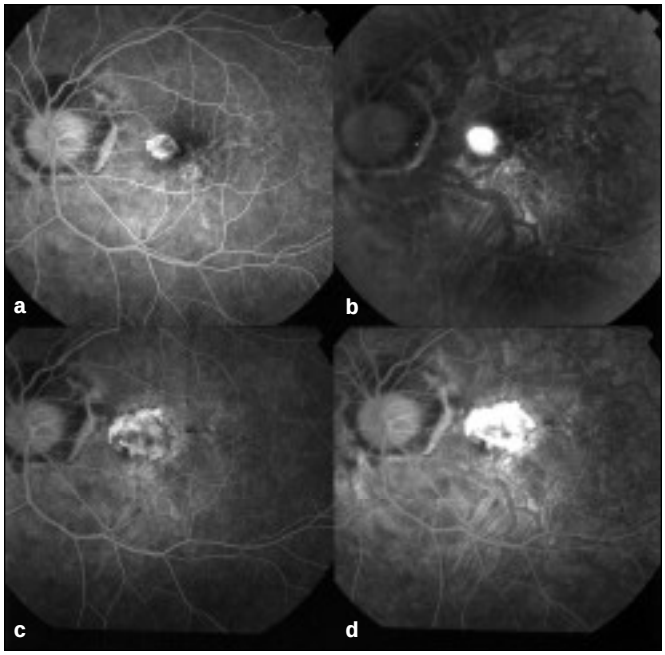

Fig. 2 - Case 8. Fluorescein angiography in the early **a)** and late phase **b)** before treatment. The size of the choroidal neovascularization lesion is about 1050 μ. Six months after photodynamic therapy there is only staining of the lesion without leakage in the early phase **c)** and the late phase **d)**.

The initial VA at screening before treatment was 50–42 in 8 eyes (80%) and 39-40 in 2 eyes (20%). The mean VA before PDT was 45.0 (SD 7.318). The final VA 6 months after treatment was 60–50 in 6 eyes (60%) and 49–42 in 4 eyes (40%). The mean VA after PDT was 51.6 (SD 8.302) (Tab. I).

According to the statistical analysis (paired t-test), there was a statistically significant difference between the mean VA before and after PDT. More specifically, there was a statistically significant improvement in the mean VA after the PDT ($p = 0.00118$). Nonparametric tests were also performed, with the same results ($p = 0.0281$).

Figure 3 shows the distribution of eyes with improvement, stability, or impairment of VA after treatment. In four eyes (40%), the final VA was higher than before treatment, and in six cases (60%), VA remained the same as before treatment. In no eye did the VA worsen after treatment. Figure 4 also shows that the mean VA postoperatively is higher than before treatment.

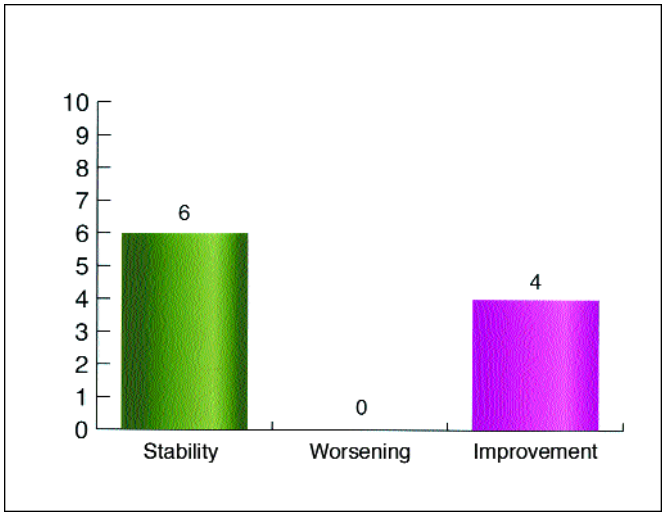

Fig. 3 - Schematic representation of the distribution of eyes with improvement, stability, or impairment of visual acuity after photodynamic therapy.

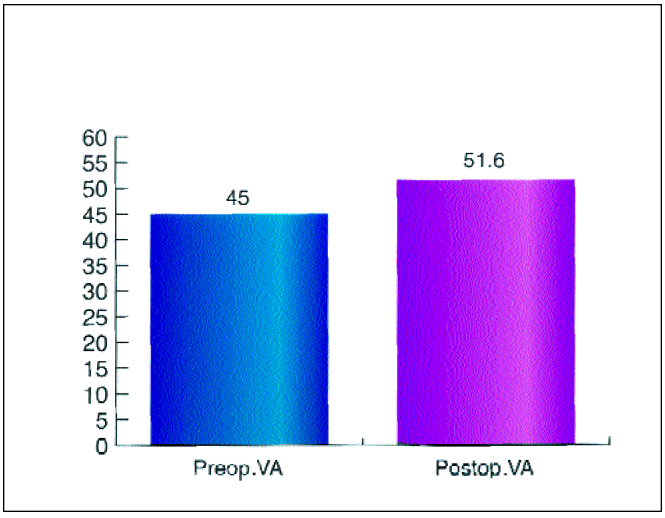

Fig. 4 - Schematic representation showing that the mean visual acuity after photodynamic therapy is higher than before.

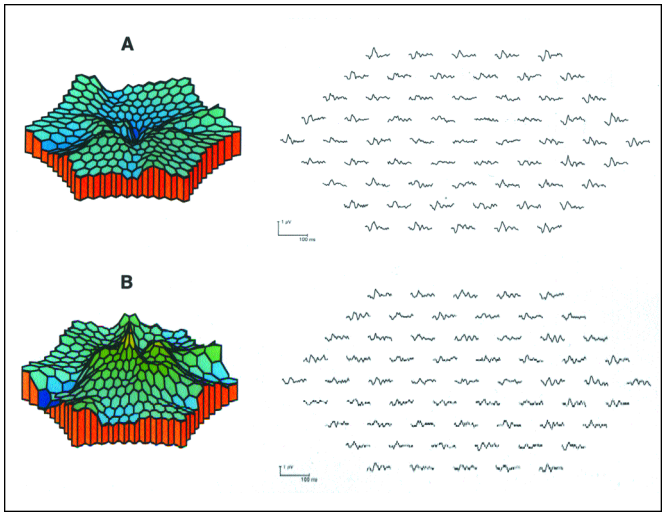

Fig. 5 - Multifocal electroretinogram of Case 8 before and 6 months after photodynamic therapy (PDT). The electroretinogram traces of areas 1 and 2 show an increase in their values after PDT.

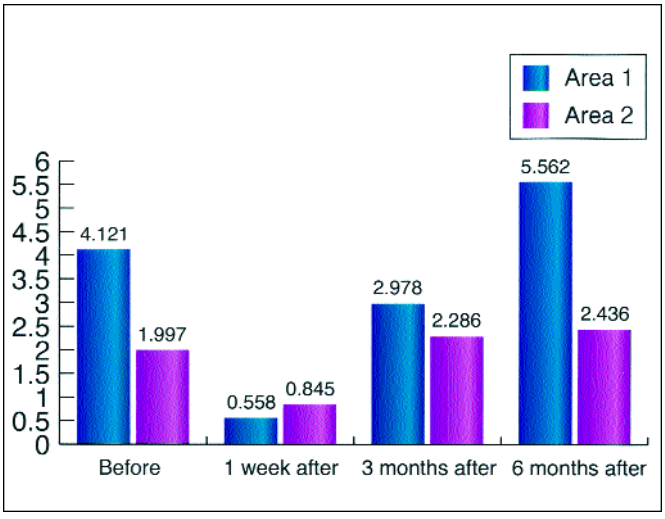

Fig. 6 - Schematic representation of the changes in the mean value of retinal response densities in areas 1 and 2 of multifocal electroretinogram during the 6 month period following photodynamic therapy. At the end of the 6 month period, the electrophysiologic values are higher than before treatment.

MF-ERG results

The results of MF-ERG are summarized in Table II. Analysis of the Table shows that before treatment the mean RRD in area 1, which represents the fovea, was 4.121 nV/deg^2 (SD 2.126), and in area 2, which represents the parafoveal area, 1.997 nV/deg^2 (SD 1.733). One week after PDT, these values decreased to 0.558 nV/deg^2 (SD 3.338) for area 1 and 0.845 nV/deg^2 (SD 2.345) for area 2. This decrease in mean RRD in areas 1 and 2 1 week after PDT was statistically significant ($p = 0.0015$ for area 1 and 0.0166 for area 2). Nonparametric tests were also performed with the same results ($p = 0.0093$ for area 1 and 0.0367 for area 2).

Three months after PDT, the mean RRD in area 1 was 2.978 nV/deg^2 (SD 2.723) and in area 2 it was 2.286 nV/deg^2 (SD 2.484). These differences between the mean RRD before and after PDT in areas 1 and 2 were statistically significant ($p = 0.3862$ for area 1 and 0.06343 for area 2). Nonparametric tests confirmed these results ($p = 0.1688$ for area 1 and 0.8785 for area 2).

At the end of the follow-up, 6 months after PDT, the mean value of RRD in area 1 was 5.262 nV/deg^2 (SD 3.600) and in area 2 it was 2.503 nV/deg^2 (SD 2.241) (Fig. 5). These differences between the mean RRD before and 6 months after PDT in areas 1 and 2 were found to be statistically significant ($p = 0.02321$ for area 1 and 0.2233 for area 2). Nonparametric tests confirmed these results ($p = 0.2408$ for area 1 and 0.2845 for area 2).

Figure 6 shows schematically that a week after the PDT, the RRD decreased. Three months after PDT although there is an increase of the electrophysiologic values. At the end of the follow-up, 6 months after PDT, the electrophysiologic values are higher than before treatment.

DISCUSSION

Although several studies have noted the VA benefits of verteporfin therapy in myopic eyes with classic subfoveal CNV (3, 4, 6, 8, 9), questions remain concerning the efficacy of the method in these cases.

The overall beneficial outcomes with verteporfin therapy have been based on VA, visual fields, contrast sensitivity, and fluoroangiography (8, 9). The first two parameters are subjective and the third provides anatomic support of the VA results based on the extent of the RPE and its atrophy (5, 7, 8). Therefore, other types of visual function tests must be adopted for the interpretation of macular function.

In our study, the first order response of MF-ERG was recorded before and after successful PDT in eyes with CNV due to pathologic myopia. With this method, the electrical activity of the photoreceptors and bipolar cells of the foveal and parafoveal region is objectively assessed and a picture of the function of these areas is offered.

Our results show that in pathologic myopia the VA improves in 40% of cases. In the other 60% of cases, VA remains the same as before treatment. The mean value of VA after treatment is also better than before PDT.

Electrophysiologic study of the fovea and parafoveal region with MF-ERG 6 months after treatment revealed an improvement of the mean retinal densities of these areas. These findings support objectively the benefits of PDT in CNV due to pathologic myopia. The good prognosis and the satisfactory efficacy of verteporfin therapy are possibly due to the small CNV lesions at the initial screening or to the young age of the patients and the healthy RPE-photoreceptors complex surrounding the lesions (5, 7, 8). Table I shows that the mean age of our patients with pathologic myopia was 45.7, which is lower than the mean age of patients with age-related macular degeneration.

In conclusion, MF-ERG provides an objective measure of electroretinal dysfunction and is a reliable method to evaluate the efficacy of PDT on CNV due to pathologic myopia. MF-ERG findings also support other studies showing the good prognosis of CNV in myopic eyes. Our findings must be confirmed by other studies based on a greater number of patients with a longer follow-up.

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