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Multifocal Electroretinograms in Patients with Branch Retinal Artery Occlusion

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Purpose: We recorded multifocal electroretinograms (M-ERG) in patients with branch retinal artery occlusion (BRAO) and compared the waveforms in the area of retinal artery occlusion with those in the normal area, to evaluate the influence of the damage to the inner retina shown by M-ERG responses.

Methods: Three patients who had normal visual acuity and visual field loss of more than one quadrant due to BRAO were examined. The central 50° of ocular fundus was stimulated through dilated pupils by an array of 103 hexagonal elements for 4 minutes. The waveforms of the first order and second order kernel responses of M-ERG in the area of the retinal artery occlusion were compared with those of the vertically symmetrical, normally perfused area of the same eye.

Results: The amplitude of the averaged tracing decreased in the first negative wave (N1), first positive wave (P1), and second negative wave (N2) in the first order kernel responses in the area of retinal artery occlusion in comparison with the normally perfused area. Furthermore, prolongation of latency was noted for N1, P1, and N2 in the same area. Second order kernel responses were not detected in the area of the retinal artery occlusion.

Conclusions: The damage to the inner retina affected parts of N1, P1, and N2 of the first order kernel responses, with N2 being the most seriously affected. Furthermore, second order kernel responses clearly reflected the condition of the inner retina. **Jpn J Ophthalmol 2001;45:516–522** © 2001 Japanese Ophthalmological Society

Key Words: Branch retinal artery occlusion, electroretinogram, inner retina, multifocal, second order kernel.

Introduction

Recently multifocal electroretinography (M-ERG)[1] has been increasingly applied to the detection of retinal dysfunction in various ophthalmic disorders.[2–10] M-ERGs have been reported to be useful in retinitis pigmentosa, occult macular dystrophy, retinal detachment, diabetic retinopathy, myopia, and glaucoma.

Hood et al[11] suggested in their report that the M-ERG and photopic ERG resemble each other in waveforms. However, the origin of M-ERG waves is still unknown.[12] It is generally thought that the first negative wave (a-wave) and the first positive wave (b-wave) of bright-flash ERG originate from the photoreceptor and inner retina of bipolar (and/or Müller) cells, respectively. In central retinal artery occlusion (CRAO), electroretinographic studies have shown a relatively normal a-wave and a diminished b-wave in bright-flash ERG[13,14] when mainly inner retinas are damaged. In M-ERG, many local retinal areas are stimulated according to a binary m-sequence. The first order kernel of the M-ERG (F-MERG) is the difference between the response to all white frames in the sequence and the response to all black frames. The second order kernel of the M-ERG (S-MERG) represents the temporal interaction between two focal flashes separated by an integral number of stimulus base intervals, suggesting that these kernels may originate from different

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retinal layers.[15] Recently, it has been suggested that S-MERG may be useful in evaluating the function of the ganglion cell.[3,4] However, there have been few reports on the use of S-MERG to date, and one of the purposes of the current study was to evaluate the waveform changes of the F-MERG and S-MERG in patients with branch retinal artery occlusion (BRAO).

Materials and Methods

The characteristics of subjects in this study are shown in Table 1. Three patients with BRAO were examined and informed consent was obtained from all subjects before M-ERG recordings. All 3 patients were male and had a corrected visual acuity better than 1.0 but they had visual field loss of one or more quadrants due to BRAO. They had no neurologic or ophthalmologic disorders other than BRAO. The patients were 13, 64, and 64 years of age. Time intervals from the initial onset of BRAO to the recording of the M-ERG were 11 days to 18 months.

Case 1

A 64-year-old man exhibited a sudden visual field loss. His corrected visual acuity was 1.2 in both eyes. Goldmann perimetry revealed an inferonasal visual field loss in the left eye (Figure 1A). Fundus examination revealed a branch occlusion in the superotemporal retinal artery of the left eye and the sensory retina was edematous at the superotemporal area of the posterior pole. M-ERG was performed 11 days after onset (Figures 1B, 1C, 2).

Case 2

A 13-year-old boy exhibited a superonasal visual field loss in the right eye. Visual acuity in his right eye was 1.5. Fundus examination revealed a branch occlusion in the inferotemporal retinal artery. Goldmann perimetry revealed a superonasal visual field loss in the right eye (Figure 3A). M-ERG was performed 2 months after onset (Figures 3B, 3C, 4).

Table 1. Characteristics of Subjects of This Study

Case No.	Age	Sex	Visual Acuity	Visual Field Defect	Time Interval
1	64	Male	1.2	Inferonasal	11 days
2	13	Male	1.5	Superonasal	2 months
3	64	Male	1.2	Inferior	18 months

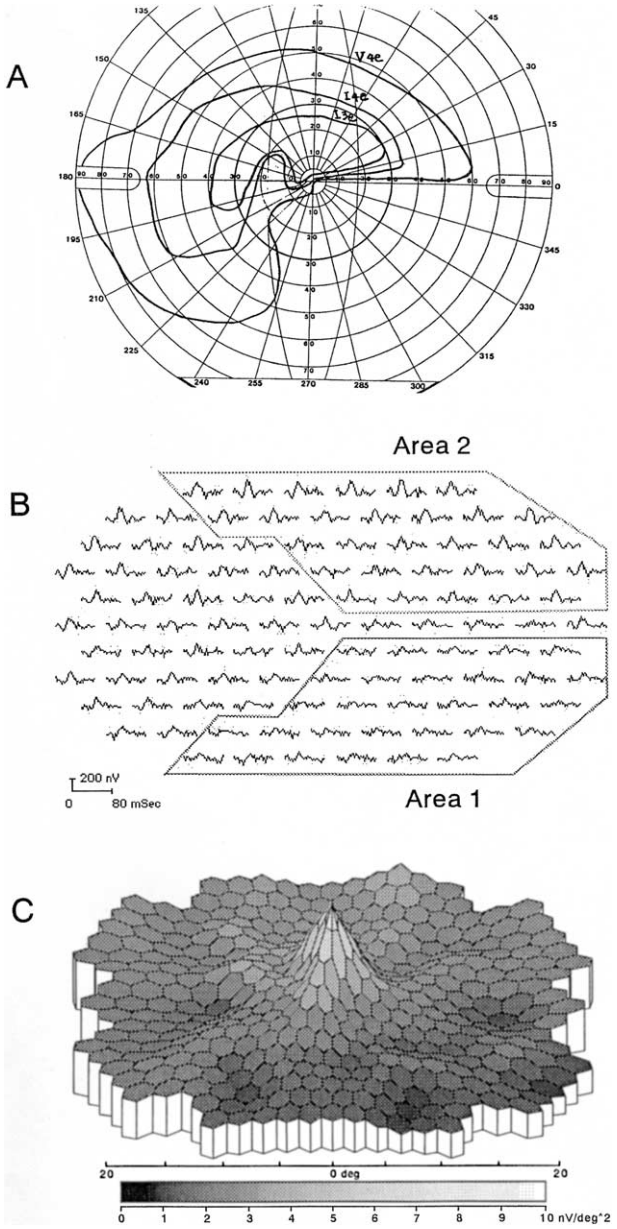

Figure 1. (**A**) Goldmann perimetry in the left eye in case 1. (**B**) 103 local first order responses of multifocal electroretinogram (M-ERG) obtained from left eye in case 1. (**C**) Three-dimensional representation of M-ERG from left eye in case 1.

Case 3

A 63-year-old man had been treated for angina. He noticed blurred vision in his left eye during cardiac catheterization.[16] Fundus examination showed that superonasal and superotemporal branches of the central retinal artery were occluded, and marked retinal edema was observed at the superior area of the

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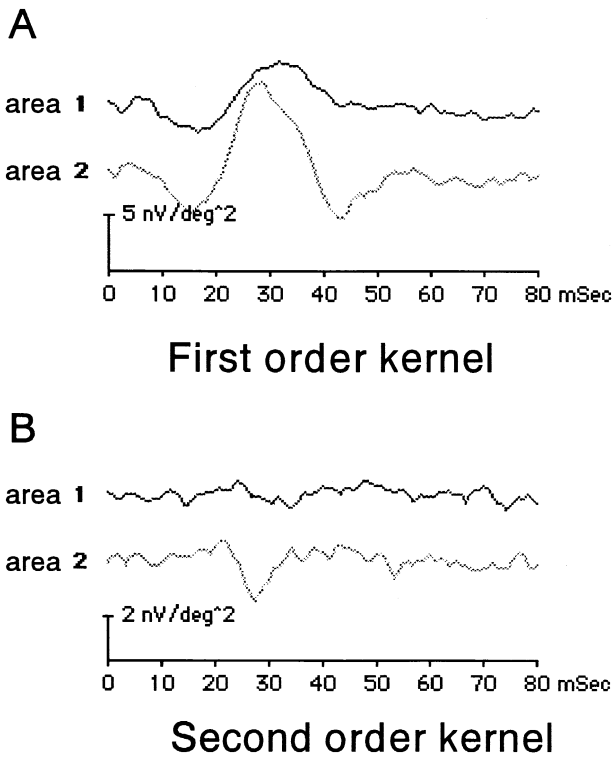

Figure 2. (**A**) Averages of local first order responses of multifocal electroretinogram (M-ERG) in case 1. (**B**) Averages of local second order responses of M-ERG in case 1.

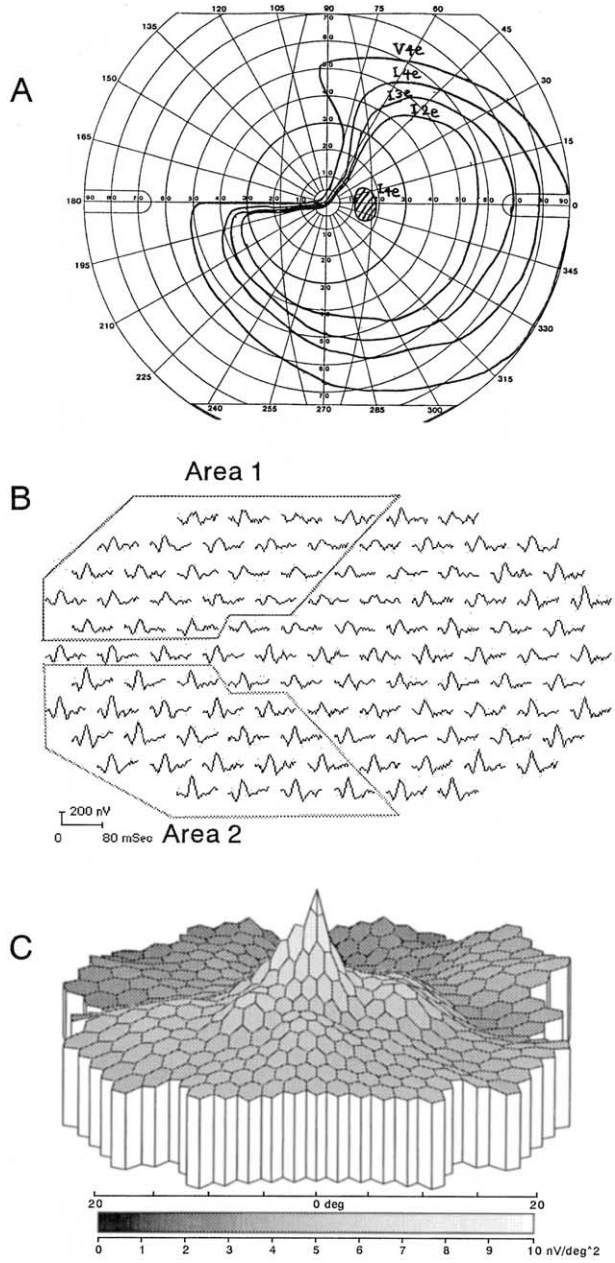

Figure 3. (**A**) Goldmann perimetry in right eye in case 2. (**B**) 103 local first order responses of multifocal electroretinogram (M-ERG) obtained from right eye in case 2. (**C**) Three-dimensional representation of M-ERG from right eye in case 2.

posterior pole. Visual acuity in his left eye was 1.2. Examination by Humphrey visual field analyzer showed an altitudinal lower visual field defect (Figure 5A). There was no change in the visual acuity and visual field of his left eye after onset. M-ERG was performed 18 months after onset (Figures 5B, 5C, 6).

Methods

Multifocal ERG recording was obtained using the VERIS system (Tomey, Nagoya). The central 50° of ocular fundus was stimulated by an array of 103 hexagonal elements that were displayed on a monochromatic monitor (MD-B1700, Chu-ou Musen, Tokyo). The color of each hexagon was alternated between black and white according to a pseudorandom sequence called a binary m-sequence at a rate of 75 Hz. A small fixation spot was placed at the center of the monitor. Good fixations were maintained during recordings in these patients.

The pupil size was fully dilated to a diameter greater than 7 mm using a mixture of 0.5% tropicamide and 0.5% phenylephrine. A bipolar contact lens electrode (Kyoto Contact Lens, Kyoto) was used to record the ERG and a ground electrode was attached to the earlobe. The other eye was occluded. The vision of the patients was corrected to the best visual acuity after insertion of the contact lens. The CRT monitor was set to project an image on the retina of the same size as normal emmetropic

subjects can receive at 30 cm distance. The total recording time was 7 minutes and was divided into eight segments with a resting time. The signal amplification was 100,000 and the bandpass filter was set from 10 to 300 HZ (RPS-107; Grass, West Warwick, RI, USA).

Data were analyzed using a VERIS Science 3.0.1 analysis program (Electro Diagnostic Imaging, San Mateo, CA, USA). Averaged local F-MERG and S-MERG responses from the area of retinal artery occlusion (area 1) were obtained using a multi-input analysis technique. Area 2 was defined as symmetrical to area 1 against a horizontal meridian, and its average was comparable to a normal control. Area 3 was defined as the corresponding area of the contralateral normal eye. In F-MERG, the amplitude from the baseline to the first negative wave (N1) trough was referred to as the N1 amplitude; from the N1 trough to the first positive wave (P1) peak was referred to as the P1 amplitude; and from the P1 peak to the second negative wave (N2) trough was referred to as the N2 amplitude. The first slice of S-MERG was obtained by analysis and showed the averaged waveform in areas 1 and 2. The artifact removal procedure and the spacial averaging procedure were not used in this study.

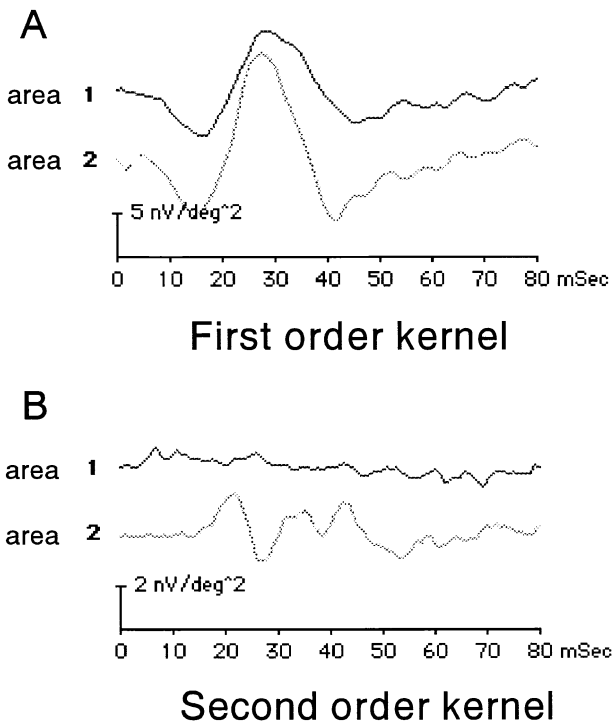

Figure 4. (**A**) Averages of local first order responses of multifocal electroretinogram (M-ERG) in case 2. (**B**) Averages of local second order responses of M-ERG in case 2.

Results

F-MERGs from Patients with BRAO

Trace array and three-dimensional (3D) mapping of the F-MERG from the affected eye were compared with the visual field loss in BRAO patients (Figures 1B, 1C, 3B, 3C, 5B, 5C). In the 103 trace array of normal subjects, the F-MERG responses are almost the same in size in all areas except for a portion of the optic disc. However, F-MERG responses from area 1 were diminished in all 3 of our patients. On the other hand, F-MERG responses from area 2 were normal in amplitude. In our BRAO patients, 3D mapping showed that the height of the plots decreased in the area of visual field loss. However, although the responses were decreased, substantial responses of the F-MERG were still noted where the psychophysically measured perimetry revealed no sensitivity.

Averaged F-MERGs from Affected and Unaffected Areas in BRAO Patients

M-ERGs were averaged as described above for areas 1 and 2 (Figures 2A, 4A, 6A). The mean amplitudes of the averaged F-MERG in area 1 were 3.3 nV/deg^2 for N1, 7.9 nV/deg^2 for P1, and 6.1 nV/deg^2 for N2 (Table 2). The amplitudes of the averaged F-MERG in area 1 were diminished for N1 (51–73%), P1 (48–65%), and N2 (33–56%). In patient 2, although a relatively strong response was noted, the F-MERG amplitude of area 1 was still smaller than that of area 2. The mean implicit time in area 1 was 17.0 milliseconds for N1, 31.1 milliseconds for P1, and 48.6 milliseconds for N2. The implicit times for N1, P1, and N2 were delayed in all cases (N1: 11-17%, P1: 3–18%, N2: 8–22%).

Averaged S-MERG from the Affected and Unaffected Areas in BRAO Patients

In the averaged S-MERG for area 1, no significant responses were found in any patients (Figures 2B, 4B, 6B). It was noted that although a clear response was recorded in the F-MERG, no significant S-MERG was recorded in area 1 of patient 2. However, a strong response with a peak at 20 milliseconds and a trough at 30 milliseconds was detected in all patients in area 2.

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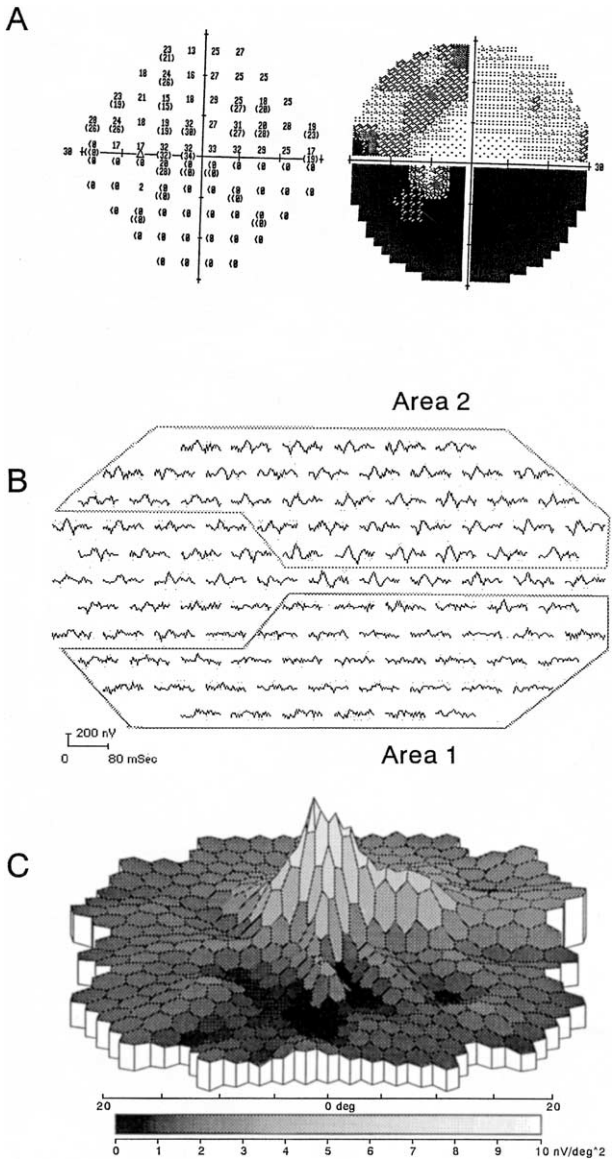

Figure 5. (**A**) Goldmann perimetry in left eye in case 3. (**B**) 103 local first order responses of multifocal electroretinogram (M-ERG) obtained from left eye in case 3. (**C**) Three-dimensional representation of M-ERG from left eye in case 3.

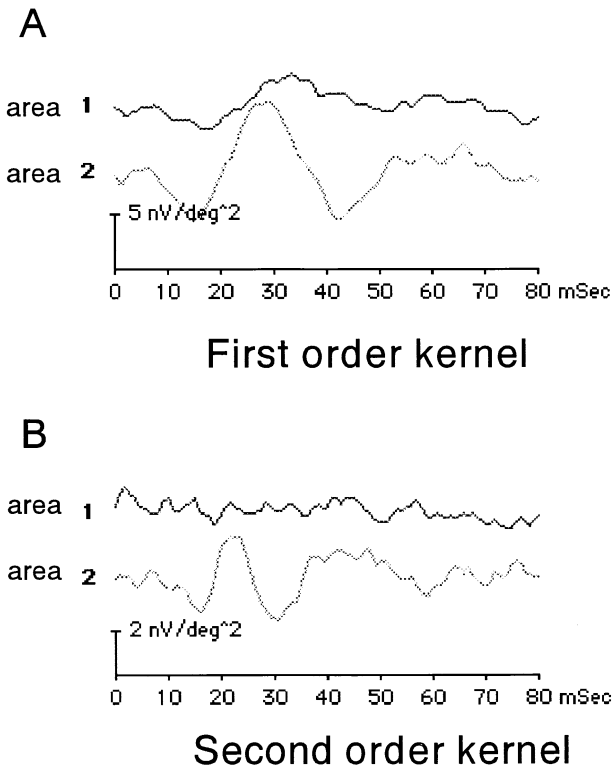

Figure 6. (**A**) Averages of local first order responses of multifocal electroretinogram (M-ERG) in case 3. (**B**) Averages of local second order responses of M-ERG in case 3.

Inter-ocular Ratio (Area 1/Area 3) of F-MERG for Amplitude and Latency

Table 3 shows the inter-ocular ratio for amplitudes and latencies. The inter-ocular ratios for the amplitudes were reduced in N1 (40–75%), P1 (32–66%), and N2 (20–55%). The inter-ocular ratios for latencies were increased in N1 (11–18%), P1 (3–14%), and N2 (10–17%). The inter-area ratios of area 1 to area 2 for the N1, P1, and N2 latencies were almost equal to the inter-ocular ratios in all cases, and in case 2, the inter-area ratios were nearly equal to inter-ocular ratios for the N1, P1, and N2 amplitudes. However, in cases 1 and 3 inter-area ratios for N1, P1, and N2 amplitudes were larger than the inter-ocular ratios.

Discussion

The central retinal artery and its branches supply the inner retinal layers, including the nerve fiber layer, ganglion cells, inner plexiform layer, and the inner portion of the inner nuclear layer. In contrast, the outer retinal layers are supplied by the arteries of the choroid. Thus, because CRAO mainly affects the inner retina, bright-flash ERG in patients with CRAO shows a normal a-wave that has inputs from the photoreceptor, and a diminished b-wave that has inputs from the inner retina of bipolar (and/or Müller) cells. This waveform is called a negative ERG.[13,14] On the other hand, new evidence suggests that the a- and b-waves of photopic ERG are derived, in part, from the inner retina.[17,18] Qahtani et al[19] reported that in CRAO patients, photopic on/off-ERGs showed a significant decrease in ampli-

Table 2. Amplitude and Latency of First Order Kernel of Multifocal Electroretinograms in Areas 1 and 2*

	Amplitude (nV/deg^2)			Latency (msec)		
	N1	P1	N2	N1	P1	N2
Case No.	Area 1/Area 2	Area 1/Area 2	Area 1/Area 2	Area 1/Area 2	Area 1/ Area 2	Area 1/Area 2
1	2.7/3.9 (69)	6.5/11.9 (55)	4.2/12.3 (34)	16.7/15.0 (111)	31.7/28.3 (112)	49.2/43.3 (113)
2	4.8/6.6 (73)	12.2/18.9 (65)	10.7/19.2 (56)	16.7/15.0 (111)	28.3/27.5 (103)	45.0/41.7 (108)
3	2.3/4.5 (51)	5.1/10.7 (48)	3.5/10.6 (33)	17.5/15.0 (117)	33.3/28.3 (118)	51.7/42.5 (122)

*Area 1: area of retinal artery occlusion, area 2: area symmetrical to area 1 of horizontal meridian, N1: first negative wave, P1: first positive wave, N2: second negative wave. Values in parentheses are percentages.

tude and a significant increase in latency for the a-, b-, and d-wave components.

In our present study, the F-MERG from the affected area of BRAO patients showed a decreased amplitude and a delayed latency in the N1, P1, and N2 components, but did not show a negative configuration. Kondo et al[2] also reported that focal ERG shows a negative configuration but that M-ERG shows decreased responses, although it does not show a negative configuration in the affected areas in BRAO patients. Hood et al[11] have recently suggested that the N1 and P1 of M-ERG are generated by the same cells that generate the a-wave and the positive peaks of the full-field photopic ERG, confirming the findings in this study. N1 and P1 are thought to be generated, in part, from the inner retina and it is thought that the latter portion of the F-MERG reflects the condition of the inner retina, because N2 is the most seriously affected.

S-MERG responses were detected in area 2, but no significant waves were detected in area 1, and because the S-MERG responses are markedly decreased and histologically inner retinal layers are damaged in patients with BRAO, our finding suggested that the S-MERG is more sensitive than F-MERG in detecting the damage of inner retinal layers. The retinas of BRAO patients initially become edematous with a gradual loss of the inner retinal layers over time and, although these M-ERGs were recorded at different phases of the disease, the results were consistent in all 3 cases.

In the present study, vertically symmetrical areas of the affected area were selected as normal control, because recording conditions are supposed to be consistent between these regions. Kondo et al[20] reported that no significant supero-inferior asymmetry was observed along the vertical meridian in normal subjects. We also compared the response in area 1 with the response in the corresponding area of the contralateral normal eye (area 3). The inter-ocular ratios of the M-ERG amplitude were reduced for N1, P1, and N2, and the inter-ocular ratios of the F-MERG latency were increased for the N1, P1, and N2. Although the inter-area ratio was nearly equal to the inter-ocular ratio for amplitudes in case 2, the inter-area ratios for amplitudes were larger than the inter-ocular ratios in cases 1 and 3. It has been suggested that the amplitudes are larger in the upper retina.[21]

In conclusion, the F-MERG components decreased in amplitude and increased in latency, and the S-MERG markedly decreased in the affected area in patients with BRAO. It was concluded that the S-MERG may clearly reflect the condition of the inner retina. The measurements of S-MERG may be a very sensitive tool to detect slight inner retinal damage due to various retinal diseases.

Table 3. Amplitude and Latency of First Order Kernel of Multifocal Electroretinograms in Areas 1 and 3*

	Amplitude (nV/deg^2)			Latency (msec)		
	N1	P1	N2	N1	P1	N2
Case No.	Area 1/Area 3	Area 1/Area 3	Area 1/Area 3	Area 1/Area 3	Area 1/Area 3	Area 1/Area 3
1	2.7/5.9 (46)	6.5/17.9 (36)	4.2/19.4 (22)	16.7/15.0 (111)	31.7/29.2 (109)	49.2/43.3 (114)
2	4.8/6.4 (75)	12.2/18.5 (66)	10.7/19.2 (55)	16.7/14.2 (118)	28.3/27.5 (103)	45.0/40.8 (110)
3	2.3/5.7 (40)	5.1/15.7 (32)	3.5/17.5 (20)	17.5/15.0 (117)	33.3/29.2 (114)	51.7/44.2 (117)

*Area 3: area corresponding to area 1 in contralateral normal eye. Values in parentheses are percentages.

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