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Differentiation of Neovascular Maculopathies by Nonphotic Electrooculogram Responses

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Abstract: Four kinds of electrooculographic (EOG) responses for the retinal pigment epithelium (RPE) were studied to assess RPE integrity in neovascular macular diseases. In 20 eyes with age-related macular degeneration (ARMD), 13 fellow eyes of ARMD patients, eight eyes with central exudative chorioretinopathy (CECR), and seven unaffected eyes of CECR patients, we evaluated the light peak/dark trough ratio, and the hyperosmolarity, Diamox, and bicarbonate responses. We found no abnormalities in any ARMD eyes or fellow eyes of ARMD patients. In both the CECR eyes and unaffected eyes of CECR patients, however, the Diamox response was subnormal whereas the other three EOG responses remained normal. There was no significant difference in Diamox response between the CECR eyes and unaffected eyes of CECR patients. The selective deterioration of the Diamox response in CECR, but not in ARMD, can serve as a new index for differentiating between these similar conditions. **Jpn J Ophthalmol 1997;41:174–179** © 1997 Japanese Ophthalmological Society

Key Words: Age-related macular degeneration, central exudative chorioretinopathy, electrooculogram, nonphotic response, retinal pigment epithelium.

Introduction

Neovascular maculopathy is typically described as destruction of the retinal pigment epithelium (RPE) and Bruch's membrane underlying the macular area, intrusion of neovascular tissue into the submacular space, subsequent extravasation from the neovascular tissue, and eventual cicatricial changes.[1–4] Although neovascular maculopathy, especially age-related macular degeneration (ARMD), is the major threat to sight in the elderly populations of developed countries,[5,6] its pathogenesis is not yet clearly understood.

Recent histological studies have revealed that the RPE is a significant factor in the development and healing of this disease,[5,7–12] therefore, it is reasonable to speculate that histological breakdown of the RPE is preceded, accompanied, or followed by functional changes. Some reports do note RPE dysfunction in neovascular maculopathy[13–15] but they consider only one type, or only one of the several RPE parameters. Thus electrophysiological testing has not yet been adequately utilized in attempting to understand this condition.

In the present study, we investigated the RPE function in diseases predisposed to neovascular maculopathy, using electrophysiological evaluation of three nonphotic electrooculogram (EOG) responses.[16] We focused on ARMD and central exudative chorioretinopathy (CECR) with the aim of differentiating the pathogenesis of these similar conditions. We successfully defined one characteristic difference in the RPE function parameters that potentially can be useful for differential diagnosis.

Subjects and Methods

Subjects

Subjects with ARMD or CECR were chosen from outpatients seen in our macula service from 1991 to 1993. All subjects were fully informed of the purpose and the potential risks of the tests, and gave their written consent. Selection criteria for both the ARMD[1] and CECR[17] groups included: (1) one or more of the following signs in the macular area—

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angiographic subretinal neovascular tissue, subretinal hematoma, angiographic RPE detachment associated or unassociated with serous retinal detachment, or subretinal cicatricial tissue; and (2) no systemic or other ocular diseases that could lead to neovascular maculopathy. Qualified subjects were then subclassified into ARMD and CECR groups. The ARMD group included those with at least one of the following lesions in the macular area: subretinal or sub-RPE hematoma of at least 2 disc diameters (DD), subretinal cicatricial or fibrous tissue of at least 2 DD, or serous retinal detachment of at least 2 DD associated with RPE detachment. The CECR group included subjects with exudates no longer than 2 DD in the macular area. Subjects who qualified for the initial selection, but did not fit either subgroup, were excluded. Subjects who were seropositive for toxoplasma or other parasitic infections were excluded from the ARMD, but not the CECR, group.

In the ARMD group, we examined 34 eyes of 17 subjects (11 men, 6 women; ages 56–85; mean ± SD = 66.4 ± 7.9). Data reliably recorded from 33 eyes of these subjects were analyzed statistically. Data from one fellow eye of a unilaterally-affected subject were excluded because of excessive electrode contact noise. Fourteen subjects had unilateral involvement; three had bilateral. The final study group included 20 ARMD eyes and 13 fellow eyes of ARMD patients.

In the CECR group, 28 eyes of 14 subjects (women, ages 20–57; mean ± SD = 34.3 ± 10.6) were examined. Data reliably recorded from 15 eyes of 8 subjects were analyzed statistically. All CECR subjects were unilaterally affected. Data from one unaffected eye was excluded because of a mechanical problem in the recording system. The final study included eight CECR eyes and seven unaffected eyes of the CECR patients.

EOG Recording and Measurement of Responses

Silver–silver chloride plate electrodes (NT-6164U, Nihon-Koden, Tokyo) were placed on the skin near the inner and outer canthi. The potentials were dc-amplified (RDU-5, Nihon-Kohden; high-cut, 10 Hz) and recorded on a chart recorder (SP-G6P, Riken Denshi, Tokyo). Intermittent horizontal saccades were induced by requesting subjects to gaze at two dim red light-emitting diodes (LEDs) attached to the inner surface of the integrating hemisphere with an angular distance of 15 degrees from the center in each direction. The LEDs were turned on at 1.0 Hz for 5 seconds each minute.

The light peak/dark trough ratio (L/D ratio) was obtained by dividing the maximum EOG amplitude in response to full-field illumination (1250 cd/m^2, 12 minutes) by the minimum EOG amplitude recorded during a 36-minute dark period preceding illumination. In our previous study, the lower limit of the normal L/D ratio at the present settings was 1.43.[16]

The hyperosmolarity, Diamox, and bicarbonate responses were recorded as nonphotic responses of the RPE. For the hyperosmolarity response, a hyperosmotic solution (10% fructose with 15% mannitol, 1330 mOsm; Fructmanit®, Taiho Pharmaceutical, Tokyo) was intravenously infused for 20 minutes at a flow rate of 11% of the subjects' circulating blood volume[18] per hour. For the Diamox response, 500 mg of acetazolamide (Diamox®, Takeda Pharmaceutical, Osaka) was injected intravenously. For the bicarbonate response, 7% sodium bicarbonate solution (Meylon®, Otsuka Pharmaceutical, Tokyo) was intravenously infused at a rate of 0.83 mL/kg per minute for 5 minutes. A stable EOG was confirmed in the dark for at least 30 minutes before each administration of nonphotic stimulus.

The amplitudes of all nonphotic RPE responses were defined as the ratio of the maximum EOG decrease, in response to the nonphotic stimulus, to the stable EOG amplitude recorded in the dark, before the stimulus. No lights, except the saccade-stimulating red LEDs, were permitted during any nonphotic response procedures. The normal ranges of the hyperosmolarity, bicarbonate, and Diamox responses (mean ± 2 SD in normal subjects) were 22.9–44.9%,[16] 15.2–28.6%,[16] and 32.1–52.9%,[16,19] respectively.

In each subject, each EOG session was recorded at approximately the same time of day, with minimum 1-week intervals, except for the first session in which the L/D ratio and one nonphotic response were recorded on the same day. Each eye was statistically analyzed separately; statistical significance was determined with the Student's unpaired *t*-test.

Results

The ages of the ARMD and CECR patient groups differed significantly ($P < 0.001$). When each eye was considered individually, the mean and standard deviations of ages in the four groups (ARMD eyes, fellow eyes of ARMD patients, CECR eyes, unaffected eyes of CECR patients) were 66.6 ± 8.2, 66.0 ± 8.3, 34.3 ± 11.3, and 33.7 ± 12.1 years, respectively. The ARMD eyes, and the fellow eyes of ARMD patients, were significantly older than the CECR eyes and the unaffected eyes of CECR patients ($P <$

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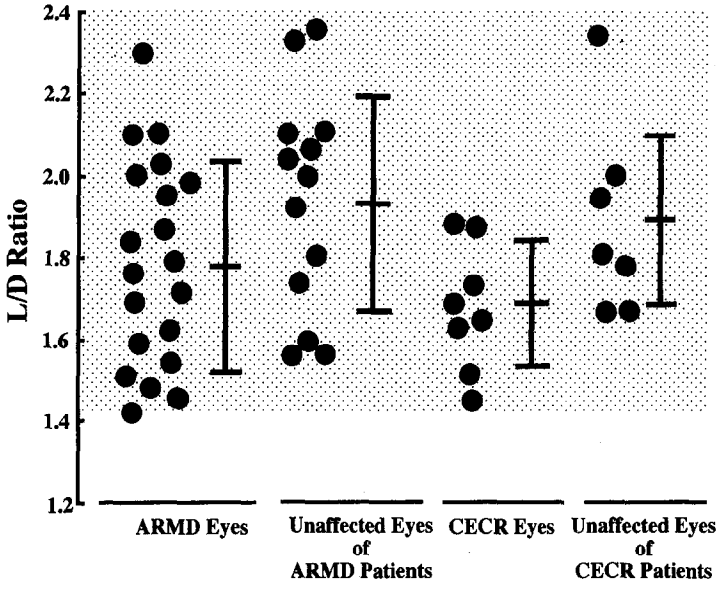

Figure 1. Scattergram of the L/D ratio in the four groups. Shaded area and vertical bars designate normal range for the response determined at our clinic and the mean ± standard deviation in each group.

0.001). The four EOG responses (L/D ratio and hyperosmolarity, Diamox, and bicarbonate responses) for each eye of the four groups are shown in Figures 1–4; the means and standard deviations of the four EOG responses in each of the four groups are shown in Table 1. No statistically significant difference in L/D ratio was found in any two groups. A subnormal L/D ratio was seen only in one of the ARMD eyes, but in no others (Figure 1). Similar analysis was done for the hyperosmolarity response (Figure 2) and the bicarbonate response (Figure 3). The hyperosmolarity response was subnormal in three of the ARMD eyes, in one of the fellow eyes of ARMD patients, in two of the CECR eyes, but not in any of the unaffected eyes of CECR patients (Figure 2); the amplitude did not differ significantly in any two of the four groups (Table 1). Similarly, the bicarbonate response was subnormal in eight of the ARMD eyes, in two of the fellow eyes of ARMD patients, in four of the CECR eyes, and in two of the unaffected eyes of CECR patients (Figure 3); the amplitude did not differ significantly in any two of the four groups (Table 1).

In contrast, the Diamox response was frequently reduced in CECR, although not in ARMD. Figure 4 illustrates typical patterns of the Diamox response in an ARMD eye, its fellow eye, a CECR eye, and its unaffected fellow eye. The Diamox response amplitudes were all significantly lower in the CECR eyes than in ARMD eyes, in unaffected eyes of CECR patients compared to ARMD eyes, in CECR eyes

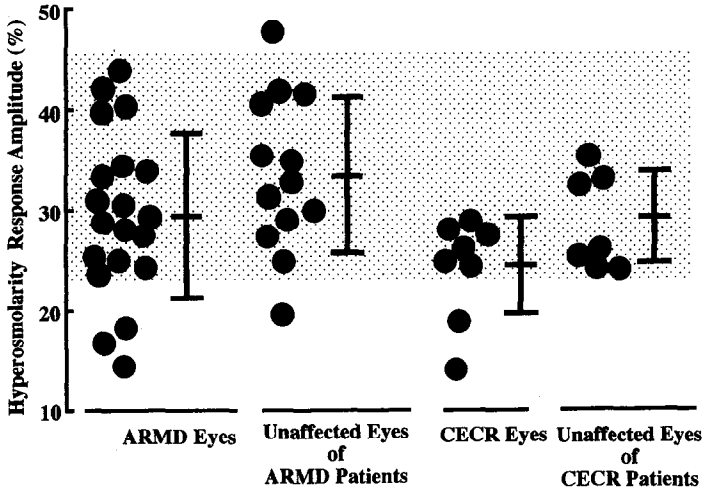

Figure 2. Scattergram of hyperosmolarity amplitude in the four groups.

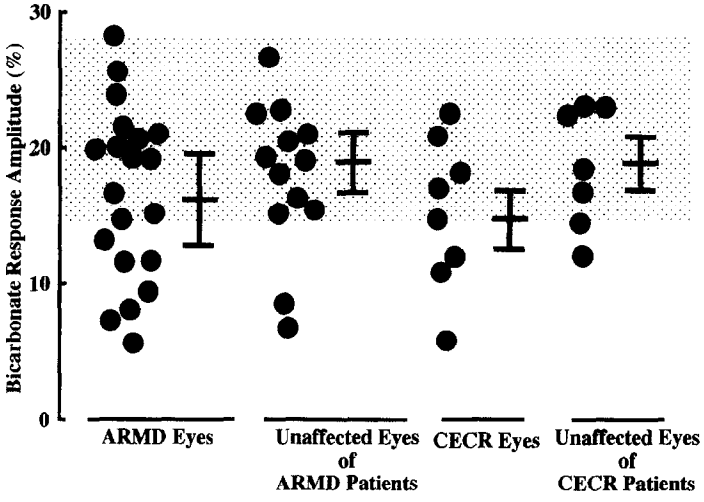

Figure 3. Scattergram of bicarbonate response amplitude in the four groups.

compared to fellow eyes of ARMD patients, and in unaffected eyes of CECR patients compared to fellow eyes of ARMD patients (Table 1). The Diamox response was not subnormal in any ARMD eyes, or in any fellow eyes of ARMD patients but it was subnormal in six of the CECR eyes and in three of the unaffected eyes of CECR patients (Figure 5).

Discussion

ARMD and CECR are often indistinguishable in fundus appearance and have a similar pathological base: disruption of the RPE and the Bruch's membrane, intrusion of neovascular tissue, and the final scarring.[1-4] These changes are supposedly localized in the macular area and, therefore, it is logical that most of the EOG parameters for RPE integrity would remain within the normal range in patients with ARMD or CECR because those EOG parameters generally represent responsiveness of the total RPE, not just the RPE in the macular area.

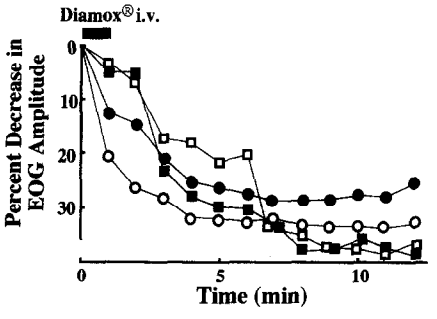

Figure 4. Typical patterns of Diamox response in ARMD and CECR subjects. ■, an ARMD eye: □, the contralateral fellow eye; ●, a CECR eye: ○, the contralateral unaffected eye. In this particular CECR subject, the Diamox response in the fellow eye was normal.

The L/D ratio represents light- and darkness-induced events in the RPE, and is determined by intrinsic factors such as the amount of some diffusable mediator released by the neural retina in response to light (or darkness), anatomical contact of the neural retina to the RPE, and physiological responsiveness of the RPE to the mediator. The present results, with the L/D ratio remaining in the normal range in almost all ARMD and CECR eyes, regardless of the presence or absence of disease (Figure 1), indicates that, in these eyes, no widespread disorder exists in the neural retina, the neural–retina–RPE interface, or the RPE ionic mechanism responsible for light peak/dark trough generation.

The hyperosmolarity response amplitude was within normal range in most of the eyes examined and no statistically-significant difference in the hyperosmolarity response amplitude was found in any two groups (Figure 2, Table 1). Because a normal hyperosmolarity response requires at least the formation of an osmotic gradient across the RPE where the choroidal side is hyperosmotic to the subretinal side,[20] these results indicate that the hyperosmotic agent is properly delivered and distributed in eyes affected with either ARMD or CECR, apparently verifying that there is no widespread breakdown of the barrier function of the retinal blood vessels and the RPE in either condition. Similarly, the mean of the bicarbonate response amplitude was not subnormal in any of the four eye groups, and did not differ significantly between any two groups. This again indicates that there is no major breakdown in the integrity of the retinal blood vessels and the RPE, or in the mechanism of the RPE responsible for the

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Table 1. Mean and Standard Deviation of the 4 EOG Responses in ARMD and CECR

	L/D Ratio	Hyperosmolarity Response (%)	Diamox Response (%)	Bicarbonate Response (%)
ARMD eyes (n = 20)	1.79 ± 0.25	29.4 ± 8.0	42.5 ± 4.5[a,b]	16.7 ± 6.1
Unaffected eyes of ARMD patients (n = 13)	1.94 ± 0.26	33.7 ± 7.5	41.1 ± 4.2[c,d]	17.9 ± 5.3
CECR eyes (n = 8)	1.68 ± 0.14	24.2 ± 4.8	31.2 ± 2.5[a,c]	15.2 ± 5.2
Unaffected eyes of CECR patients (n = 7)	1.89 ± 0.22	28.5 ± 4.5	33.7 ± 3.1[b,d]	18.7 ± 4.2

Except for [a], [b], [c], and [d], no significance was proved between the results of the same test in any two groups of eyes.
[a–d] $P < 0.01$.

generation of the bicarbonate response in ARMD or CECR.

In contrast, the mean amplitude of the Diamox response was below normal in both the CECR eyes and the unaffected eyes of CECR patients, whereas it remained normal in both the ARMD eyes and the fellow eyes of ARMD patients (Figure 3, Table 1). It may seem that the reduced Diamox response in the eyes of CECR patients is related to the statistically younger ages or predominance of women in this group, but Kawasaki et al[21] reported that Diamox response amplitude is independent of age and gender.

The significantly lower Diamox response in CECR patients could imply some disorder in the RPE. Although the EOG responses are generally considered to indicate the integrity of the entire RPE layer, and not of some localized area, the Diamox response is known to deteriorate in some conditions when the affected RPE is strictly limited to the macular area,[21] suggesting that this response may reflect RPE integrity specifically in the macular area. The present finding of the differential vulnerability of the Diamox response in ARMD and CECR indicates that RPE dysfunction in the macular area is profound enough in CECR to reduce the Diamox response and is so mild in ARMD that it leaves the response intact. We speculate that deterioration of the Diamox response, even in apparently normal fellow eyes of CECR subjects, implies some subclinical RPE disorder that could lead to the future development of the disease in those eyes, a hypothesis for future study.

Whatever the mechanism responsible for the differential vulnerability of the Diamox response amplitude, it clearly provides a new electrophysiological method of differentiating between ARMD and CECR, in addition to the conventional criteria based on patients' age and gender.

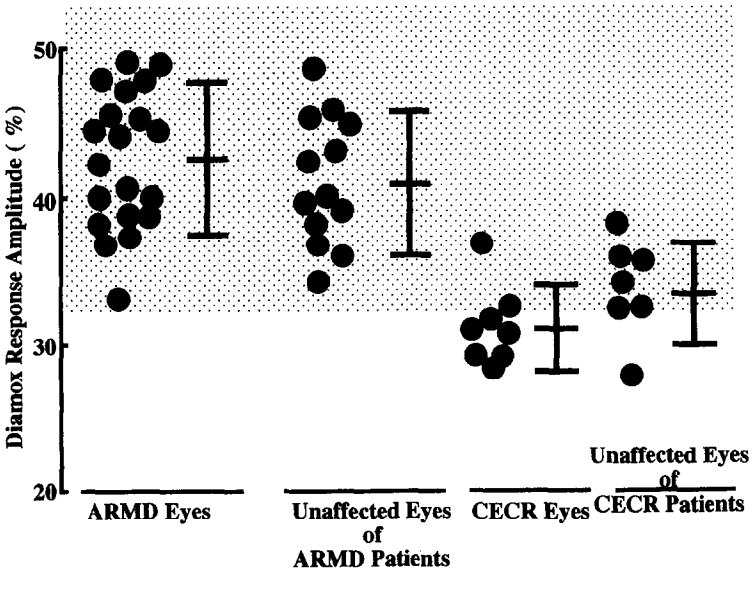

Figure 5. Scattergram of Diamox response amplitude in the four groups.

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