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Focal cone electroretinograms: Aging and macular disease

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Abstract. Focal cone electroretinograms were obtained with a 3-degree flickering stimulus from 100 normal eyes and 134 eyes with known macular disease. Responses were obtained during direct visualization of the fundus with a hand-held stimulator-ophthalmoscope. Mean foveal cone amplitude for 100 normal eyes was 0.31 μV, with 95% of all amplitudes greater than 0.18 μV. There was a significant inverse correlation between amplitude and age for responses obtained from the fovea ($r = -0.91$; $p < 0.001$) but not for responses obtained from the parafovea (midway between fovea and disk, $r = -0.53$; not significant). In eyes with known maculopathy, mean foveal cone amplitude was correlated with Snellen acuity. Even after correcting for normal decreases in amplitude with age, responses were significantly reduced in 88/94 (94%) of all eyes with 20/40 or poorer acuity, suggesting that the focal electroretinogram is a sensitive test for detecting macular disease.

Introduction

With sufficient computer averaging, focal electroretinograms (ERGs) can be recorded in response to localized stimulation of the macula [1–9]. Reduced focal ERG amplitudes have been reported in a majority of patients with central serous retinopathy [10] and in virtually all patients with juvenile macular degeneration and retinitis pigmentosa with worse than 20/40 visual acuity [11,12]. In a recent comparison of several visual function tests in eyes with maculopathy, significantly reduced focal cone ERG amplitudes were recorded from the fovea in 91% of eyes with worse than 20/40 Snellen acuity [8]. Since focal cone ERG amplitude is normal in amblyopia [13] and optic neuropathy [14], this test is useful for assessing retinal abnormalities in patients with reduced acuity. The present study evaluates the relationship between foveal cone ERG amplitude and best corrected Snellen acuity in 134 eyes with a variety of retinal diseases affecting the macula. Since existing norms for the focal ERG are based primarily on young subjects [11], it was necessary to obtain responses from normal subjects, who ranged in age from

6 to 79 years. The results directly address age-related variations in macular function and establish age-matched normal limits through age 80 years for comparisons with responses from patients.

Methods

Focal ERGs were obtained from the macula during direct visualization of the fundus with a hand-held stimulator-ophthalmoscope [8]. Responses were recorded from the anesthetized (0.5% proparacaine hydrochloride) and dilated (2.5% phenylephrine hydrochloride and 1% tropicamide) eye with a Burian-Allen bipolar contact lens electrode. A silver chloride cup electrode attached to the forehead served as a ground. The stimulus was a 3-degree white flickering (42 Hz) spot centered within a steady 10-degree white annular surround. The retinal illuminance of the annulus (5.3 log trolands) was higher than that of the stimulus (4.8 log trolands) in order to mask stray light.

Responses were differentially amplified (gain 50,000) and bandpass-amplified (gain 20) at the stimulus frequency Q = 15. Each averaged response (n = 200) was obtained on line with a general purpose computer employing an artifact reject subroutine to eliminate sweeps containing voltages > 1μV (presumably due to blinks and eye movements). Averaging was controlled by the experimenter with a foot pedal so that ERGs were acquired only when the test was centered on the retinal area of interest, which in this study was either the fovea or parafovea (midway between fovea and optic disk). Two computer-averaged responses were obtained from the fovea of each patient. The mean of these two responses was calculated if the responses were similar in amplitude and phase relationship to the stimulus. If the two responses were inconsistent, additional averaged responses were obtained. If no consistent phase relationship to the stimulus emerged, the response was considered to be nondetectable.

Patients with diseases known to affect the macula were asked to participate in the study after a specific diagnosis had been determined by an ophthalmologist specializing in retinal disorders. Attempts were made to include eyes from a broad range of diagnostic categories in order to extend the validity of the findings. Eyes with idiopathic macular holes were specifically excluded since patients with unilateral macular holes of any size may suppress the involved eye and measure 20/200 or worse Snellen acuity. Since the relationships between macular hole diameter, acuity, and focal cone ERG amplitude are complex, these patients will be the subject of a subse-

quent report. The number of eyes in each diagnostic category is shown in Table 1. Best corrected Snellen acuity was obtained prior to dilation.

Focal cone ERGs also were also obtained from 100 normal subjects. Results from one eye per subject (typically the left) were included in this study. An attempt was made to recruit approximately equal numbers of subjects from each decade of life; they ranged in age from 5 to 79. The majority were normal relatives of patients participating in the study. A few younger normal subjects were tested because of decreased acuity, which was subsequently found to be caused by refractive error. Normal subjects and patients understood the purpose of the study and they or their parents signed consent forms after the potential risks were explained. No normal subject or patient experienced any complications other than mild corneal irritation either during or after the testing.

Results

Examples of focal cone ERGs from a normal subject are shown in Fig. 1. Each trace shows four cycles of the response, with stimulus onset indicated by vertical spikes. Two repititions of each average are shown to demonstrate the importance of consistent phase relationships between stimulus and response. Responses showed no consistent phase relationship when the stimulus was occluded. The average level of asynchronous electrical activity in the absence of a stimulus was 0.06 μV, ranging from 0.02 μV to 0.09 μV on different trials and in different subjects. To further illustrate the distinction between stimulus-related activity and noise, computer-averaged responses from patients with $\leqslant 20/200$ Snellen acuity lacking any evidence of cone activity to full-field stimuli are shown in Fig. 2. Random phase relationships to the stimulus were found in patients with advanced retinitis pigmentosa, progressive cone dystrophy, and rod monochromacy.

Table 1. Study population.

Diagnosis	Number
Age-related macular degeneration	49
Juvenile macular degeneration	26
Retinitis pigmentosa	17
Chorioretinal degeneration	10
Progressive cone degeneration	9
Diabetic retinopathy	8
Other	15
Total	134

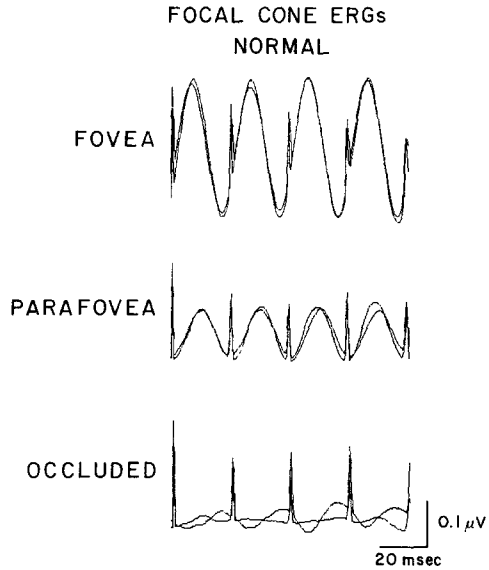

Fig. 1. Representative focal ERGs from a normal subject. Each trace shows four cycles of the response, with stimulus onset indicated by vertical spikes. Two repetitions of each average are shown to demonstrate the importance of consistent phase relationships between stimulus and response. Representative responses from the normal subject were obtained from the fovea and parafovea (midway between fovea and disk). Data in the occluded condition were obtained with the stimulus falling on the eyelid.

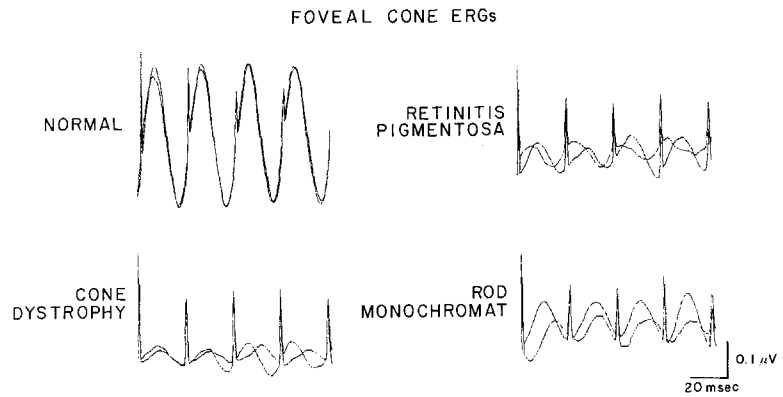

Fig. 2. Representative focal ERGs from the fovea of a normal subject and from three patients with hereditary retinal disorders. Each patient had $\leqslant$ 20/200 Snellen acuity and showed no evidence of functioning cones in the full-field ERG. Responses from these patients showed no consistent phase relationship to the stimulus.

The distribution of amplitudes from the foveas of 100 normal eyes is shown in Fig. 3. Mean foveal amplitude (± 1 standard deviation) was $0.31 \pm 0.08\,\mu V$. The distribution of amplitudes did not differ significantly from a normal distribution ($D = 0.065$, $p > 0.5$; Kolmogorov-Smirnov goodness of fit test) with 95% of all amplitudes greater than $0.18\,\mu V$. The mean phase angle between stimulus and response was -44.4 degrees, with 95% of all phase relationships less than -80.2 degrees. Foveal amplitude was approximately twice the parafoveal amplitude. Across all normal subjects, the mean ratio (± 1 standard error) of foveal to parafoveal amplitude was 2.33 ± 0.031. Responses from the parafovea were significantly slower than those from the fovea ($t = 16$, $p < 0.001$), with a mean phase angle of -69.5 degrees.

The relationship between age and focal cone ERG amplitude for 100 normal eyes is shown in Fig. 4. There was a significant decrease in foveal ERG amplitude with age ($r = -0.91$, $p < 0.001$). Focal ERG amplitude did not vary significantly with age in the parafovea ($r = -0.53$, n.s.). The regression lines relating each measure to age had significantly different slopes ($F = 7.66$, $p < 0.05$), indicating that the ratio of foveal amplitude to parafoveal amplitude decreased with age.

The relationship between foveal cone ERG amplitude and Snellen visual acuity is shown in Fig. 5 for 134 eyes with disease affecting the macula. Mean amplitude was significantly correlated with Snellen acuity over the range from 20/20 to 20/100 ($r = 0.98$, $p < 0.001$). Mean foveal cone ERG amplitudes for eyes with 20/100 or worse acuity rarely showed a consistent phase relationship to the stimulus and did not differ significantly from the

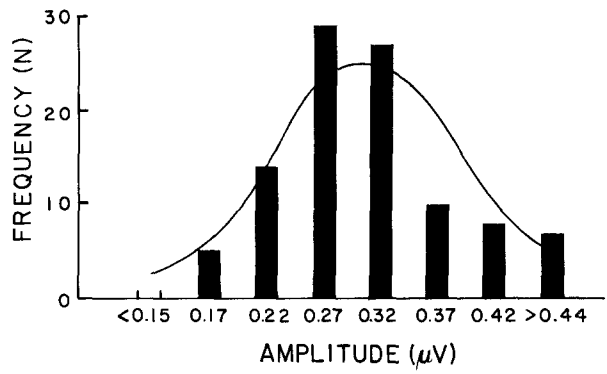

Fig. 3. Distribution of amplitudes from foveas of 100 normal eyes. Solid curve is the best-fit normal distribution with a mean of $0.31\,\mu V$ and a standard deviation of $0.08\,\mu V$.

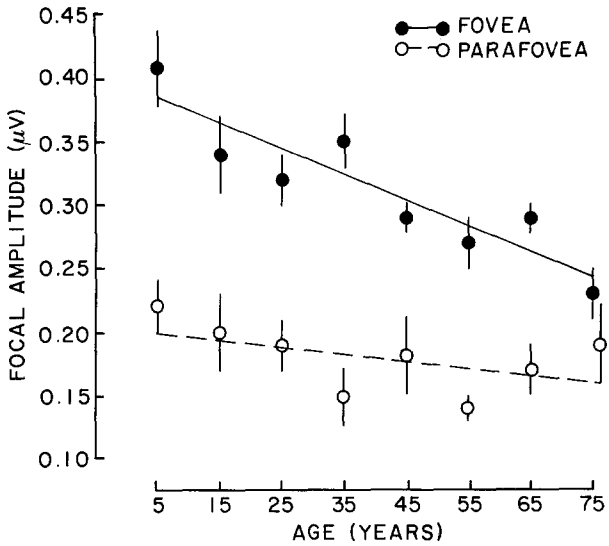

Fig. 4. Focal cone ERG amplitude as a function of age in normal subjects. Each age group contains responses from at least 10 eyes. Vertical bars indicate ± 1 standard error of the mean. Responses from the parafovea were obtained from a location midway between the fovea and optic disk.

mean activity level in the absence of the stimulus. Mean foveal amplitude for each acuity level was significantly lower than normal (t-tests, $p < 0.01$ for all comparisons). Significant correlations were also found between mean foveal amplitude and Snellen acuity for individual diagnostic categories such as age-related macular degeneration ($r = 0.73$, $p < 0.05$) and juvenile macular degeneration ($r = 0.84$, $p < 0.025$).

Foveal cone ERG amplitudes are plotted in Figure 6 as a function of age for all 134 eyes with disease involving the macula. The shaded area represents the range of foveal amplitudes encompassing 90% of the normal population. When compared with age-matched amplitudes for normal eyes, 88/94 (94%) of all eyes with disease involving the macula and 20/40 or worse acuity (solid symbols) lay significantly ($p < 0.05$) below normal. Eyes retaining better than 20/40 acuity (open symbols) were more likely to fall within the normal range.

Discussion

The results of this study suggest that focal cone ERGs from the fovea of normal eyes decrease in amplitude with age. There are several reasons why

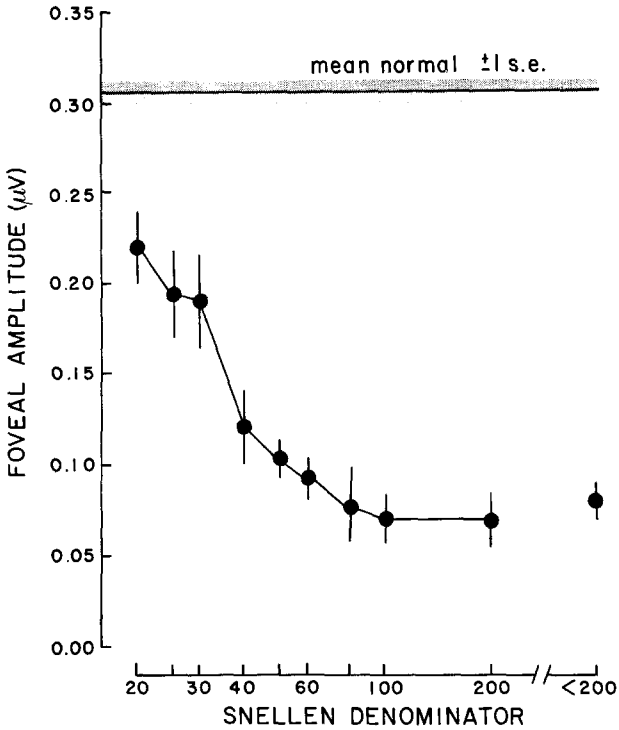

Fig. 5. The relationship between foveal cone ERG amplitude and Snellen visual acuity in 134 eyes with retinal disease involving the macula. The shaded bar indicates ± 1 standard error of the mean for foveal amplitudes from normal eyes. Solid circles represent the mean amplitude for all patients at each acuity level, with vertical bars indicating ± 1 standard error.

this decrease is probably not due to pre-retinal factors that could decrease retinal illuminance with age. First, the stimulus is presented in Maxwellian view (0.8 mm diameter aerial aperature), minimizing the effects of lenticular variations with age. Second, normal eyes included in this study did not have clinically evident opacities. Third, the stimulus was achromatic, minimizing the effect of variations in macular pigment with age. Fourth, the loss of amplitude with age was more evident in the fovea (central 3 degrees) than in the parafovea (midway between the fovea and optic disk). This selective loss in the fovea versus the parafovea is consistent with histological studies that have shown a decrease in the density of foveal cones with age [15]. Significant decreases in amplitude with age have been previously reported in rod and cone-mediated full-field ERGs [16,17,18] and in pattern reversal ERGs [19].

Previous studies have found that focal ERGs are abnormal in age-related macular degeneration when acuity is worse than 20/60 [12], and in heredit-

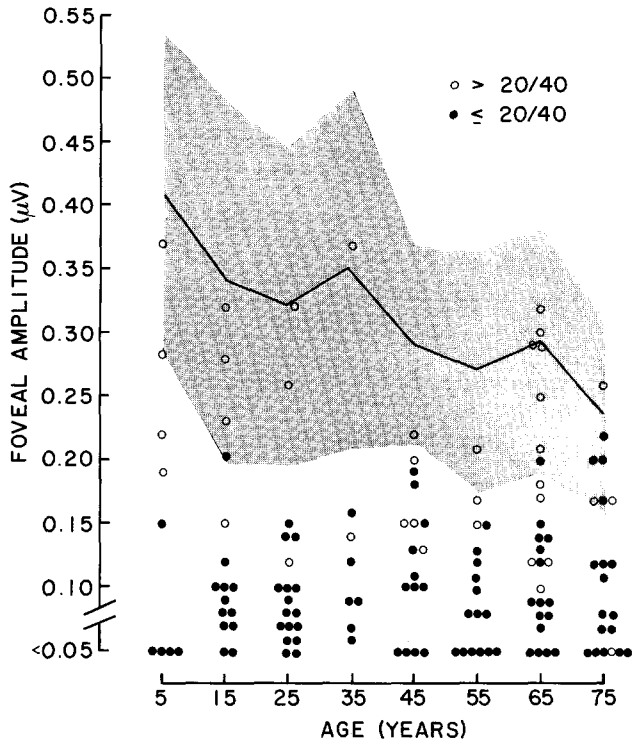

Fig. 6. Foveal cone ERG amplitudes as a function of age from 134 eyes with disease involving the macula. The solid line represents mean normal amplitude as a function of age, with the shaded area representing the range of foveal amplitudes including 90% of the normal population.

ary retinal degenerations such as juvenile macular degeneration [11] and retinitis pigmentosa [11,12] when acuity is 20/40 or worse. The results of the present study are consistent with these findings and establish a significant relationship between foveal amplitude and Snellen visual acuity across a large samples of eyes. Although this relationship was established in eyes with a variety of different diseases, caution should be exercised in generalizing too widely. In particular, eyes with discrete pathology such as idiopathic macular holes were excluded from this study. Full-thickness holes typically reduce acuity to $\leqslant 20/200$ but, if small enough, may not significantly reduce foveal amplitude (Birch et al., in preparation).

Foveal ERGs were significantly reduced in many eyes with macular disease retaining near-normal Snellen acuity. One possible explanation for this finding is that a relatively small number of healthy cones in the foveola may be sufficient to support good acuity, while a normal foveal ERG requires healthy cones throughout most of the central 3 degrees. While

reducing the overall correlation between acuity and foveal amplitude, these "false positives" may have prognostic implications, since several of these patients have subsequently shown decreased Snellen acuity. Despite these exceptions, the overall strong correlation between acuity and foveal amplitude establishes the value of the foveal cone ERG in evaluating macular function. The greatest utility of this technique may be in eyes with media opacities, where a clear view of the macula cannot be obtained. Based on the results of this study, a normal foveal ERG in an eye with 20/40 or worse acuity makes it highly unlikely that the acuity loss is due to one of the macular diseases included in this report.

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