Principles and Practice of Clinical Electrophysiology of Vision

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43

Focal Electroretinography

David G. Birch

Cones in the macula (central 10 degrees) account for only about 7% of the total cone population.[24] As a result, cone responses from the macula contribute less than 10% to the full-field cone electroretinogram (ERG), and diseases limited to the macula typically are not detected with standard ERG. Therefore, specialized techniques have been developed for recording local responses to focal stimuli within the macula. Each has had to overcome the problems of small amplitudes and responses to stray light. Early studies isolated photopic responses with counter-phase stimulation,[15, 25] which minimizes stray light by maintaining a constant space-average luminance. However, it has become apparent that responses to patterned stimuli reflect both inner and outer retinal activity,[2, 10, 17] as discussed elsewhere.

Present techniques for recording focal ERGs utilize a test stimulus surrounded by a steady background.[8] Biersdorf and Diller,[5] for example, used a Grass photostimulator behind a 4-degree aperture in a hemispherical surround. The intensity of the surround (300 foot lamberts) was above saturation for the rods and minimized stimulation of nonfocal retina by stray light from the stimulus. As a measure of foveal integrity, they calculated the ratio of the focal ERG amplitude at the fovea to that at the optic disc; the amplitude cutoff ratio for abnormal foveal ERGs was 1.5. Stray light contributes only about 1% of the ERG when the intensity of the focal stimulus is low relative to the intensity of the surround.[16] Other investigators also stressed the importance of using a focal stimulus that is dimmer than the background.[1, 23] Ganzfeld domes can also be modified by mounting an array of light-emitting diodes (LEDs) behind a diffuser.[32] One advantage to using LEDs is that they can be electronically controlled to provide precise luminance and temporal modulation.[33] A disadvantage of dome-based focal systems is that the technique is limited to use on cooperative patients who are able to fixate where directed. Young children, suspected malingerers, and patients with eccentric fixation may produce unreliable results. Pupil size also influences amplitude by affecting retinal illuminance.

Maxwellian view focal systems allowing direct visualization of the stimulus on the retina have evolved in large part as a result of the aforementioned concerns. Fundus cameras have been modified by providing infrared imaging to monitor the location of the stimulus relative to the macula.[13, 14, 21] The stimulus, background, and fixation target are introduced through the optics of the fundus camera to provide adjustable stimulus size, frequency, and intensity.

A hand-held stimulator-ophthalmoscope for obtaining focal ERGs with direct visualization of the fundus was first described by Sandberg and Ariel.[27] The device produces a white flickering (42 Hz) stimulus of 3 or 4 degrees that is centered within a steady 10-degree white annular surround. The intensity of the annulus is higher than that of the stimulus in order to mask stray light.

Because of the small (typically <5 μV) amplitude of the focal ERG, all present techniques require computer averaging with an artifact reject buffer to eliminate sweeps containing blinks and eye movements. Most investigators have used flickering test stimuli to decrease the possibility of rod contribution and increase the speed of data acquisition. An additional advantage to fast rates of flicker is that a narrowly tuned band-pass amplifier can be used to enhance the signal-noise ratio. While a variety of electrode types have been used to record the focal ERG, the Burian-Allen bipolar contact lens electrode tends to produce the largest and most repeatable signals and can be used without significantly distorting the image.

NORMAL VALUES

Normal values for the focal ERG vary with recording parameters and stimulus configuration. Table 43–1 shows normal values for stimuli centered on the foveola as a function of stimulus diameter, repetition rate, and retinal illuminance. Clearly, there is no established "standard" for the focal ERG, and each laboratory should establish norms for the particular system in use.

In determining whether a focal response lies within the normal range, the age of the patient should also be considered. As shown in Figure 43–1, there is a significant decrease in foveal ERG amplitude with age ($r = -0.91$; $P < .001$).[6] Focal ERG amplitude does not vary significantly with age in the parafovea ($r = -0.53$, NS). Therefore, the regression lines relating each measure to age have significantly different slopes ($F = 7.66$; $P < .05$). This change in ratio with age should be considered when using the ratio of foveal amplitude to parafoveal amplitude as an index of normalcy.

CLINICAL USES

All available evidence suggests that the corneal response to focal luminance modulation originates within the distal retina. Low stimulus rates produce a transient ERG with a similar waveform to the full-field ERG, including a- and b-waves and oscillatory potentials.[13, 23] High repetition rates produce a sinusoidal response localized within the outer retina.[3]

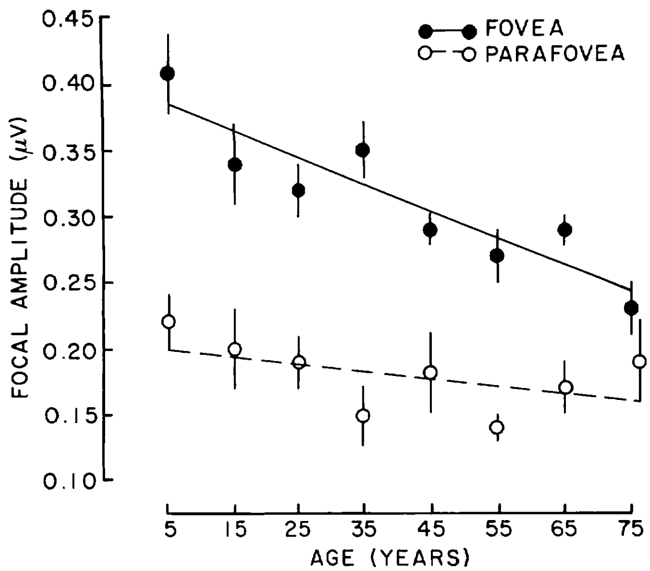

FIG 43–1.
Focal cone ERG amplitude as a function of age in normal subjects. Each age group contains responses from at least ten eyes. *Vertical bars* indicate +1 SEM. Responses from the parafovea were obtained from a location midway between the fovea and optic disc. (From Birch DG, Fish GE: *Doc Ophthalmol* 1988; 69:211. Used by permission.)

Clinical studies have shown that the focal ERG is normal in patients with optic nerve disease[28] and amblyopia.[19] Because the focal ERG is unaffected by diseases of the proximal retina and optic nerve, it is useful for discriminating eyes with macular disease from eyes with acuity loss due to other causes. Figure 43–2, for example, shows representative focal ERGs from patients with reduced acuity due to maculopathy (left column) or causes other than maculopathy (right column). Each sweep of 100-ms duration contains four responses to a 42-Hz white stimulus (3 degrees). Two repetitions of each average are shown to demonstrate repeatability, with

TABLE 43–1.
Normal Values

Stimulus Diameter (deg)	Repetition Rate (Hz)	Retinal Illuminance (log td)	Amplitude (μV)	References
3.75	5	3.2	0.66	29
4	42	4.8	0.18–0.68	30,31
10	40	3.4	5.6	26
10	30	3.4	5.4	26
10	10	3.4	7.8	26
5	5	3.2	1.27	20
10	5	3.2	2.88	20
15	5	3.2	4.96	20
3	42	4.8	.31	6

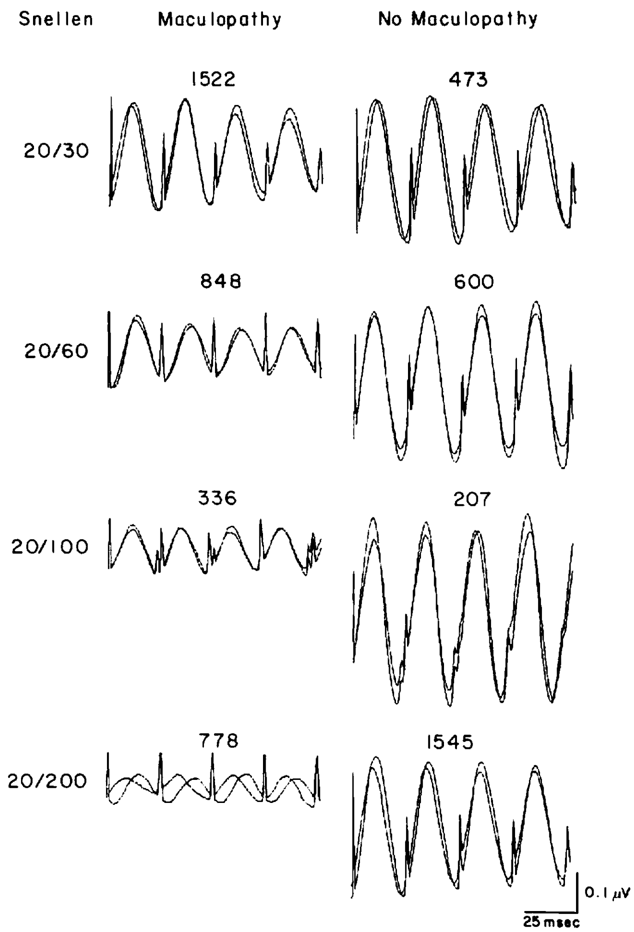

FIG 43–2.
Focal ERGs from representative eyes of patients with reduced acuity due to maculopathy *(left column)* or causes other than maculopathy *(right column)*. Two repetitions of each foveal response are shown to demonstrate repeatability. Vertical spikes are superimposed artifacts to indicate stimulus onset. Left column: no. 1522, cystoid macular edema; no. 848, hereditary macular degeneration; no. 336, age-related macular degeneration; no. 778, diabetic retinopathy. Right column: no. 473, strabismic amblyopia; no. 600, functional acuity loss; no. 207, optic neuropathy; no. 1545, nuclear cataract. (From Fish GE, Birch DG: *Ophthalmology* 1989; 96:109. Used by permission.)

vertical spikes representing stimulus onset. In general, the amplitude from the fovea decreases with decreasing Snellen acuity in eyes with maculopathy but is unrelated to acuity in eyes without maculopathy. In a recent study of 142 eyes with known macular disease, a significant inverse relationship ($r = -0.85$; $P < .001$) was found between log focal ERG amplitude and log Snellen acuity (log minimal angle of resolution [MAR]).[11] To evaluate the diagnostic value of the focal ERG, responses in eyes with maculopathy were compared with responses in eyes with reduced acuity due to causes other than maculopathy (including amblyopia, cataract, and optic neuropathy). When both amplitude and implicit time of the focal ERG were used as criteria, the overall accuracy for discriminating maculopathy from other causes of visual loss was 87%. The focal ERG was highly specific since 96% of eyes without maculopathy had normal focal ERGs. Sensitivity was also high since 85% of eyes with maculopathy had reduced and/or delayed focal ERGs.

Despite the strong overall relationship between foveal cone ERG amplitude and Snellen acuity, many exceptions have been reported. Patients with juvenile macular degeneration retaining 20/20 acuity may have an abnormal foveal amplitude and/or implicit time.[4, 11, 30] One likely explanation for these "false positives" is that a relatively small number of healthy cones in the foveola may be sufficient to support good acuity, whereas a normal foveal cone ERG response requires healthy cones throughout the test area. While reducing the overall correlation between acuity and foveal amplitude, these "false positives" have prognostic implications since these eyes typically lose vision over time.

Patients with full-thickness macular holes measuring less than 300 μm (1 degree) in diameter typically have foveal cone ERG amplitudes within the normal range.[7] These "false negatives" occur when the number of missing cones is small relative to the stimulus diameter. The focal ERG does not appear to be sensitive in eyes with aphakic cystoid macular edema, where 65% of the patients tested had normal amplitudes.[26] However, these measurements were made with a 10-degree stimulus, and sensitivity may increase with a smaller stimulus diameter.

Cataract

Focal cone ERGs obtained in maxwellian view can also be used to assess macular function in eyes with opacities. The stimulator-ophthalmoscope, for example, produces a beam of less than 1 mm in the plane of the pupil. In an eye with cataract, the examiner can easily move around the pupil while keeping the test on the macula until a relatively clear view is obtained. Clear optics are not essential in this test since the stimulus is relatively large (i.e., 3 degrees) and minimally affected by light scatter or blur. In order to assess the ability of the focal cone ERG to penetrate opacities, we analyzed the amplitudes in 50 eyes that achieved 20/25 or better Snellen acuity following cataract surgery (unpublished observations). Normal foveal amplitudes were obtained in eyes with cataracts that reduced acuity as low as 20/60. The focal gave a significantly below normal reading occasionally in eyes with 20/100 acuity and in all eyes with 20/200 acuity. These results in eyes with healthy maculas where foveal amplitudes are expected to be normal suggest that the test is useful in eyes with 20/100 or better vision. An abnormal foveal cone ERG amplitude in such an eye is not likely to be caused by the cataract, but rather should alert the physician and patient to the possibility of coexisting macular disease.

Macular Holes

In previous studies of patients with idiopathic full-thickness macular holes, the incidence of bilateral holes has spanned a larger range, with estimates as low as 6%[18] and as high as 22%.[9] A large part of this variation between studies may be due to sampling bias since many patients are referred only after the second eye develops symptoms. When the fellow eye is normal on the initial visit, studies suggest that from 4% to 12% of patients develop holes over follow-up periods of 3 to 5 years.[9, 18, 22] When the fellow eye shows macular thinning or cystic abnormalities on the initial visit, the reported percentage of eyes developing a hole rises to from 24% to 50% over 3 to 5 years' follow-up.[9, 18, 22]

Attention has been recently directed to the role of abnormal vitreoretinal relationships in hole formation and the possibility of surgical intervention to prevent hole formation.[12, 34] It has therefore become increasingly important to identify patients at risk in the fellow eye. In a recent study,[7] 35 patients with unilateral, idiopathic, full-thickness holes were followed for up to 54 months. Twenty-six patients had normal foveal cone ERGs in the fellow eye at the baseline visit and for the duration of the study. None of these eyes developed a macular hole. Seven eyes had a significantly reduced foveal cone ERG amplitude in the fellow eye despite good visual acuity and a normal-appearing macula on the initial visit. Four of these eyes subsequently developed full-thickness macular holes during follow-up. Foveal cone ERG amplitude on the initial visit was significantly related to subsequent macular hole formation. These results suggest that the focal ERG can be used in conjunction with careful ophthalmoscopic examination to help identify eyes at increased risk for macular hole formation.

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