MYOPIA AND RELATED DISEASES

Editor
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Persons with moderate to high myopia may develop visual abnormalities as a result of a true clinical retinopathy. These abnormalities can be revealed by psychophysical and electrophysiologic tests. Psychophysical tests, such as visual acuity, visual field, contrast sensitivity, color vision, and recovery of cone function after dazzling, are altered in myopic patients. However, these methods, related to a subjective cortical response, do not reveal which structures of the visual system selectively contribute to their impairment. Electrophysiologic methods allow the dissection and evaluation of the different structures composing the visual pathways. The entire visual pathway function can be objectively assessed by recording cortical potentials evoked by patterned stimuli (visual evoked potentials [VEP]). The different retinal layers can be evaluated by recording electroretinographic (ERG) signals evoked by flash or patterned stimuli (flash or pattern ERG). Focal ERG and multifocal ERG test the macular region. By comparing the VEP peak implicit time and the pattern ERG (PERG) peak implicit time it is possible to construct an index of neural conduction in the retinal visual pathways (retinocortical time).

This chapter reports the changes in electrophysiologic responses of the different structures composing the visual system observed in myopic patients with no retinopathy or early or advanced clinical retinopathy. Diagnostic techniques reviewed include ERG (scotopic and photopic according to International Society for Clinical Electrophysiology of Vision [ISCEV] standards, rod and cone photoreceptors, rod and cone b-wave intensity-response function, focal and multifocal ERG, PERG) and VEP. General methods of the functional tests, as reported in the various studies, are outlined briefly.

Methodologies

Flash ERG

Scotopic and photopic ERG responses according to ISCEV standard include a rod-mediated ERG to dim flashes (0.005 cd/m²/s) in dark adapted state; a mixed cone and rod ERG to a bright flash (1.5 to 3 cd/m²/s), dark adapted; a single flash cone ERG to white flashes (1.5 to 3.5 cd/m²/s) on a light adapting background (17 to 34 cd/m²); and a cone flicker ERG at 30 Hz (1.5 to 3 cd/m²/s) on the same background. Rod and cone photoreceptor analysis consists of recording families of rod- and cone-isolated a-waves to flashes of high intensity, in both dark- and light-adapted state. Isolation of rod and cone components can be obtained with a chromatic double subtraction technique, or by subtracting light- from dark-adapted a-waves recorded at the same intensities. Photoreponses are estimated by fitting a biochemically based model, describing the activation phase of phototransduction to the leading edge of the recorded a-waves in the intensity series. Parameters of photoactivation are the saturated photoreponse amplitude (in µV) and sensitivity (in log trondal-1 s-1), which is proportionally linked, through a conversion factor, to the photoreponse amplification constant. Rod and cone b-wave intensity/responses are obtained by measuring b-wave amplitude and time-to-peak at different flash intensities from close to threshold up to saturation. Rod and cone b-wave may be fitted with a hyperbolic saturation function (Naka-Rushton function), which provides a sensitivity parameter (i.e., the half saturating flash intensity, K) and the saturated response amplitude (Vmax). Oscillatory potentials are wavelets that are inscribed on the b-wave and can be separately analyzed by special digital filtering. These components, which are subdivided into four subcomponents, OP1 to OP4, each with a distinct retinal origin, are thought to reflect the activity of interplexiform cells in proximal retinal layers.

Focal ERG

Focal ERG are localized retinal responses recorded to uniform field flickering stimuli present-
ed in the macular or foveal region on an adapting background that minimizes the stray light effects. Special forms of focal ERG, which are sensitive although not specific for outer retinal layer activity in the macular region, are the PERG \( ^{5,11} \) and the multifocal ERG.\(^ {14,15} \)

Focal ERG represent a sensitive way to test layer by layer the function of the macular region. Focal ERG in response to 8 Hz modulated light or counterphased gratings display a major component at 16 Hz (second harmonic: 2F for light stimulation and 2P for pattern stimulation), while at 30 to 42 Hz modulated light a major component is at the stimulation frequency (first harmonic: 1F). Several studies suggest different sources for Focal ERG responses: 1F is mainly receptor/bipolar cell in origin, 2F arises both from inner and outer retinal layers, and 2P is generated by the innermost retinal layers.\(^ {13,26} \)

**Multifocal ERG**

This relatively recent technique, introduced by Sutter and Tran,\(^ {14} \) can generate multiple (100 or more) focal responses from discrete areas in the central and midperipheral retina. The whole stimulus consists of an array of hexagons, generated on a high-resolution television monitor. The size of each stimulus is typically scaled in an inverse proportion with the gradient of cone photoreceptor density of the normal retina, so that focal responses of approximately equal amplitudes are produced from central and peripheral retinal regions. The luminance of each stimulus is modulated according to a pseudorandom binary sequence (the m-sequence) of black and white presentations. Each stimulus has a probability of 0.5 of being white or black on a given frame change. Typically, the television frame is changed every 13.33 ms (a frame rate of 75 Hz). A cross-correlation technique is employed in order to extract, from the mass response recorded at the electrode site, the component corresponding to the m-sequence at which an individual hexagon is modulated. Therefore, each response is tied to stimulation in a particular hexagon.\(^ {14,15} \) Usually, the first order kernels of the cross-correlation between stimulation sequence and the continuously recorded signal are displayed and analyzed in time domain, to quantify peak-to-peak amplitude and implicit time of the major response components: a negative-positive-negative complex (known as N1-P1-N2) occurring in a time window of 15 to 50 ms after the stimulus onset.

**Pattern ERG**

PERG reflects the bioelectrical response of the innermost retinal layers to patterned stimuli.\(^ {8,11,27} \) If the visual stimulus is reversed in contrast at 1 or 2 Hz, PERG is characterized by a transient response, while with stimuli reversed at 8 Hz, a steady state PERG response is obtained. The transient PERG is characterized by several waves with three peaks that in normal subjects appear after 35, 50, and 95 ms. These peaks have negative (N35), positive (P50), and negative (N95) polarity, respectively. The steady state PERG response displays a major component at 16 Hz (second harmonic or 2P) and the amplitude and the phase of 2P are considered in the analysis of this response.\(^ {28} \)

**Visual Evoked Potentials**

VEP are defined as variations of bioelectrical potentials of the occipital cortex evoked by visual stimuli.\(^ {29} \) They are expression of complex neurosensorial events linked to the transduction and transmission of neural impulses along visual pathways, from the retinal photoreceptors to the occipital cortex. If the visual stimuli are reversed in contrast at 1 or 2 Hz, VEP is characterized by a transient response, while with stimuli reversed at 8 Hz, a steady state VEP response is obtained. The transient VEP is characterized by several waves with three peaks that in normal subjects appear after 75, 100, and 145 ms. These peaks have negative (N75), positive (P100), and negative (N145) polarity, respectively.

**Electrophysiologic Responses in Myopia**

**Flash ERG**

Since Karpe's report in 1945,\(^ {30} \) several articles have reported changes of conventional ERG in myopia. In absence of myopic retinopathy a relationship between decrease in ERG b-wave amplitude and increase of axial length was observed.\(^ {31,32} \) More recently, Westall et al\(^ {33} \) studied the changes of Standard's ISCEV ERG responses in patients with myopia ranging from -2.75 D to -14.50 D. In this study, no significant differences were observed across groups of patients with different degrees of myopia (low, moderate, or high) for b-wave sensitivity, b-wave implicit times, and the ratio of b- to a-wave amplitude; nevertheless, a correlation between decrease in ERG amplitude and increase in axial length was found, indicating that in clinical practice a calculation of normal values related to axial length, as well as an appropriate correction factor, may be required. According to the Westall et al\(^ {33} \) data, the correction factor can be derived from the slopes of linear regressions of log amplitude as a function of axial length for rod b-wave maximal amplitude
(Vmax), cone response b-wave, and summed OP dark-adapted amplitudes. These slope values ranged between -0.04 and -0.052 log µV/mm for these ERG parameters. Therefore, when considering possible ERG abnormalities reflecting retinal dysfunction in a given myopic eye, the effect of axial length, probably related to a reduced collecting area of retinal photoreceptors, should be taken into account and corrected. Examples of rod b-waves families recorded from a control emmetropic eye and a myopic eye (-8 D) are shown in Figure 1. Amplitude and implicit time versus flash intensity are also reported in the Figure. It can be seen that the myopic eye displays a slight and generalized loss of amplitude compared to the control eye, with a normal semisaturation (log K) intensity. Rod b-wave implicit times are comparable in control and myopic eyes.

**Focal ERG**

Patients with myopia ranging from -2 D to -15 D without macular involvement showed a normal macular function revealed by 2P, 2F, and 1F amplitude within normal limits. In presence of macular dystrophy (Fuchs dystrophy, subfoveal choroidal neovascularization) a dysfunction of the outer and the inner retinal layers can be detected by focal ERG recordings, which show a reduction in amplitude and a delay in phase of the 2P and 1F component. In myopic patients with a posterior staphyloma, Ishikawa et al. observed an increase in latency and a decrease in amplitude of focal macular ERG and they suggested that in this condition the ERG abnormalities can be ascribed to a reduction in the number of cones in the macular region. Examples of focal ERG in response to 41 Hz sinusoidally flickering light presented at different modulation depths to the central 18 degrees are shown in Figure 2 for a control eye and a myopic eye with maculopathy (visual acuity: 20/40). The responses from the affected eye are substantially reduced in amplitude compared to those of the control subject with a normal phase. At the lowest modulation depth affected eye responses are not significantly different from the noise level (not shown in the Figure).

**Multifocal ERG**

Kawabata and Adachi-Usami studied the ERG in response to multifocal local stimuli in patients with emmetropia/low myopia (+1 D to -3...
D), medium myopia (~3.25 D to ~6 D), and high myopia (greater than ~6 D). They evaluated the ERG in response to central stimuli (ring 1) and in response to increasingly eccentric annuli of stimulus hexagons (ring 2 to 6). Multifocal ERG topographies showed that the response density decreased in all measured retinal fields as the refractive error increased. In addition, both central (ring 1) and para-central (ring 2 to 6) ERG amplitudes decreased in relationship to the degree of myopia and the greater reduction in amplitude was observed in response to peripheral stimuli in patients with high myopia. The results obtained by multifocal ERG are consistent with those observed with standard flash ERG and therefore the bioelectrical retinal activity decreases in relationship to the increase of the axial length.

Only one study reports the multifocal ERG response in myopic patients with subfoveal choroidal neovascularization and the multifocal ERG topographies showed that the response density decreased in all measured retinal fields and a greater decrease in amplitude can be detected in the central stimulated area. In our experience, similar results have been obtained in myopic patients with subfoveal choroidal neovascularization. A topographic plot of multifocal responses obtained from a myopic eye with subfoveal choroidal neovascularization and relatively preserved visual acuity (20/30) is shown in Figure 3. Response amplitudes are significantly decreased from normal mean control values in the central and pericentral retinal regions.

**PERG and VEP**

Spada et al. evaluated the PERG and VEP responses in patients with myopia ranging from ~5 D to ~15 D and observed that in presence of refractive error and without retinal myopic involvement PERG and VEP responses in myopic patients were not significantly different from the values observed in normal subjects. This finding implies that, in myopic eyes, both PERG and VEP responses should display a diagnostic accuracy in detecting optic nerve dysfunction due to glaucoma or other optic neuropathies at least as good as in emmetropic eyes.

**Electrophysiologic Responses in Myopia Associated With Retinal Degeneration**

Many inherited retinopathies, including subtypes of retinitis pigmentosa and cone-rod dystrophies, show a significant association with myopia.

![Figure 3](image-url)
The electrophysiologic patterns of retinal dysfunction in these forms are typically related to the primary defect of rod and cone photoreceptors leading to retinal dysfunction. There are specific clinical subtypes of retinal dysfunction, however, where the ERG responses display specific and characteristic abnormalities. These subtypes include the Schubert-Bornschein type of congenital stationary night blindness (CSNB) and retinopathy of prematurity (ROP). Their ERG findings are described briefly.

The Schubert-Bornschein type of CSNB is an X-linked, nonprogressive retinal disorder characterized by night blindness, moderately decreased visual acuity, and myopia. ERG in CSNB patients are typical: in response to a bright stimulus after dark adaptation, the responses are of negative type with a normal amplitude a-wave and a b-wave that is smaller than a-wave (i.e., resulting in a severely reduced, compared to normal values, b- to a-wave amplitude ratio). Because rhodopsin optical density and kinetics are normal in CSNB patients, the defect is thought to lie in the neurotransmission from the rods to the rod bipolar cells. CSNB has been subdivided into two clinical entities: the complete type (cCSNB), with no detectable rod function, and the incomplete type (iCSNB), with small but detectable rod function. It has been shown that these subtypes of CSNB have separate genetic loci, supporting the hypothesis that they are distinct clinical entities.

Cone-mediated ERG are also characteristically affected in CSNB. The single flash cone b-wave amplitude is reduced and delayed in cCSNB. The response to long-duration flashes displays characteristic abnormalities: the on response b-wave is severely reduced, whereas the off response d-wave is preserved, suggesting a defect in the signal transmission from cone photoreceptors to the depolarizing on bipolar cells. Figure 4 shows typical Ganzfeld ERG recordings obtained from a CSNB patient with moderate myopia (−6 D, best-corrected acuity 20/30), nystagmus, and complete type CSNB. Note the typical loss of b-wave amplitude in the rod-mediated response and mixed rod-cone (maximal) response and the b-wave partial amplitude loss and delay in the single flash cone-mediated response.

More recently, multifocal ERG have been investigated in cCSNB patients and compared to myopic control patients with no retinal dysfunction. It was observed that the positive component of the first order kernel of the multifocal ERG responses had normal amplitude and delayed implicit time, compared to control values. By contrast, the second order kernel, the temporal nonlinear component of the multifocal ERG, was severely reduced in amplitude with respect to control values. These changes in cCSNB eyes were independent of retinal topography. Because the second order kernel is thought to contain a substantial contribution from the proximal retina, while the positive component of the first order kernel may reflect the activity of bipolar cells, the findings of Kondo et al. suggest that cCSNB may involve a defect in bipolar cell activity which is probably amplified at the level of more proximal retinal layers.

Rod photoreceptor function and scotopic b-wave sensitivity are attenuated in infants and children with a history of ROP. These changes, which can be detected by evaluating the a-wave saturated amplitude and gain, as well as the scotopic ERG b-wave sensitivity, are associated with an abnormal course of refractive development leading to an increased incidence of ametropias in ROP. The relationship between ERG abnormalities and refractive errors in patients with a history of ROP has been investigated by Fulton and Hansen. It was found that, in both hyperopic and myopic patients, the rod a-wave saturated amplitude and gain were attenuated, and scotopic b-wave sensitivity was low, while its saturated amplitude was unaffected. Interestingly, the oscillatory potentials of the ERG showed specific alterations depending on the refractive status. In patients with courses toward myopia, the amplitude of OP4, an off signal, was relatively more attenuated than that of OP3, an on signal. By contrast, OP4 was relatively larger in patients with courses toward hyperopia. These OP findings led Fulton and Hansen to conclude that an imbalance of on and off activity in the retina is associated with development of ametropias in ROP.

Conclusion

Electrophysiologic assessment of visual function in myopic eyes could be hampered by some difficulties related to the effect of increased axial length, and therefore of decreased photoreceptor collecting area, on the absolute amplitude values of the various responses. This effect should be taken into consideration when applying ERG testing (either conventional Ganzfeld ERG or specialized focal and multifocal ERG protocols) in myopic eyes for diagnostic purposes. On the other hand, the available data reported in the literature indicate that ERG signals may be reliable and sensitive in detecting early dysfunction of photoreceptors (especially in the macular region) associated with myopia.

References


