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Electroretinography

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1. Introduction

Electroretinography is a mainstay of clinical ophthalmic diagnostic testing. The electroretinogram, or ERG, provides an objective, quantitative measure of retinal function and allows the clinician to monitor the function of rod cells, cone cells, and ganglion cells in each eye. It uses electrodes placed on the cornea or adjacent to the orbit to monitor changes in the electrical potential of the eye in response to specific stimuli. Careful manipulation of the stimulus and testing conditions allows the clinician to investigate different cell types and layers of the retina. The ability to distinguish between different cell layers and cell types means that ERGs can be used to discern between myriad inherited retinal disorders and dystrophies that may otherwise prove clinically indistinguishable.

Several different types of ERG test provide specific information about the patient's visual function. The full-field ERG, or ffERG, is the most common form of electroretinographic testing. It provides an assessment of general retinal function and can distinguish between the various cell types, revealing the function of photoreceptors, bipolar cells, ganglion cells and amacrine cells, but cannot provide specific information about individual sectors of the retina. That information is provided by the multi-focal ERG, or mfERG, which measures the response in each of a large number of small sectors, typically either 61 or 103, of the retina. It thus provides a map that allows the clinician to locate specific areas of malfunction. The pattern ERG, or PERG, measures the response to a temporally changing pattern of contrast at a constant level of luminance, providing information about ganglion cells and generalized macular function. The electro-oculogram, or EOG, measures changes in the resting potential of the eye during adaptation to dark and light states, revealing function of the retinal pigment epithelium.

2. Basic principle

2.1 Electrical impulses of neurons

Photoreceptors and downstream neurons in the retina maintain a non-neutral electrical "resting potential" by manipulating the intracellular and extracellular concentrations of positive sodium, potassium, and calcium ions and negative chloride ions, as well as larger electronegative molecules.

Human rod cells present a model system of phototransduction. The chromophore, or light-sensing pigment, in rods is 11-*cis*-retinal, which is bound to an apoprotein called opsin,

forming rhodopsin. When a photon strikes 11-*cis*-retinal, the added energy causes it to isomerize into all-*trans*-retinal (Burns and Baylor, 2001; Stryer, 1991; Tsang et al., 1996; Yarfitz and Hurley, 1994). This conformational change causes rhodopsin to activate transducin, a heterotrimeric G protein (Arshavsky et al., 2002; Fung et al., 1981; Tsang et al., 1996). Activated transducin binds to the inhibitory subunits of phosphodiesterase 6 (PDE6), thereby de-inhibiting it. The newly active PDE6 hydrolyzes cyclic Guanosine monophosphate (cGMP), reducing intracellular cGMP levels and closing cGMP-gated cationic channels (CNG) in the rod cellular membrane (Lagnado and Baylor, 1992; Stryer, 1991; Tsang and Gouras, 1996; Yarfitz and Hurley, 1994). This reduces the influx of Na^+ and Ca^{2+} into the cell, thereby hyperpolarizing it.

The hyperpolarization of the cell causes it to cease transmitting glutamate across synapses to bipolar cells, inducing changes in their polarization. Bipolar cells transmit this signal either directly to ganglion cells, each of which has an axon proceeding out of the orbit along the optic nerve, or to amacrine cells, which then activate ganglion cells or alter the output of other bipolar cells. Photoreceptors, bipolar cells, and amacrine cells operate via graded potentials, but ganglion cells generate action potentials in response to incoming signals from bipolar and amacrine cells; these action potentials help to propagate the information along the optic nerve. The function of each of these cell types can be measured using precise electroretinographic techniques.

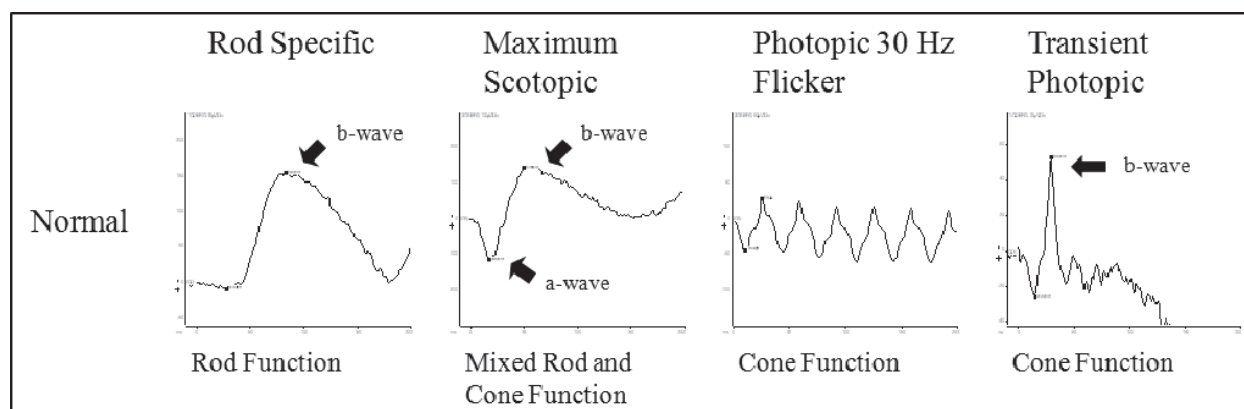


Fig. 1. Normal ERG Tracings. The a-wave and b-wave are noted where applicable.

2.2 Wave components explanation

The typical ERG waveform (see figure 1, Maximum Scotopic) is the sum result of activity in the photoreceptors and bipolar cells, with some contribution from Müller cells. The initial negative deflection, known as the a-wave, is the result of early signals from the rod and cone photoreceptors. The subsequent rise towards the positive peak, known as the b-wave, is created primarily by slower signals from the rod and cone bipolar cells. The ascending slope from the a-wave to the peak of the b-wave typically shows several small oscillations; these are called the oscillatory potentials, or OPs, and reveal the function of the amacrine cells. Other components that become apparent only under certain conditions are beyond the scope of this chapter.

2.3 Sources of variability

Because ERG measurements can vary greatly, it is important to minimize sources of variability whenever possible. Different variables of the test itself, including stimulus

duration and intensity, electrode resistance and type, and the length of dark adaptation can all induce substantial changes in the recorded potential. The International Society for Clinical Electrophysiology of Vision, or ISCEV, has developed publically available, specific standards to promote consistent ERG results and to preserve comparability between different testing centers. However, a number of factors unrelated to the hardware can also affect the recorded potential. ERGs measure the response to light, so the pupil should be maximally dilated every time an electroretinogram is performed; changes in pupil dilation can reduce the potential. Systemic blood pressure and local blood flow can affect ERG amplitude, so drugs that alter either of these should be noted. Patients also experience a diurnal change in signal amplitude as a result of circadian physiological changes including blood pressure and rod outer-segment disc shedding, so testing should be performed at approximately the same time. Certain anesthetics can affect the b-wave amplitude, so they should be noted as well. Ocular movement can generate interference in ffERG testing and strongly affects the results of spatially specific tests such as the mfERG, so the patient's fixation should be closely monitored by the clinician.

3. Hardware

The two most important pieces of hardware for obtaining an ERG are the light stimulus and the electrodes. The standard light stimulus for full-field ERGs is the Ganzfeld stimulator, a spherical device with hole to fit the patient's head that ensures the even distribution of the light stimulus.

The standard ERG setup includes several electrodes. Typically a reference electrode is placed on the skin in the middle of the forehead. Grounding electrodes for each eye are placed on the earlobes. Two different types of recording electrodes are commonly used, each with its own advantages and disadvantages. Each requires that the patient be given a topical anesthetic to prevent difficulty of electrode insertion and discomfort during the test. The strongest response signal is provided by Burian-Allen electrodes, which consist of a contact lens with a conducting surface around the edge. These electrodes reduce the negative effects of eye movements and blinking, but because the lens tends to blur the patient's vision, they are not inherently well-suited for pattern ERGs or multifocal ERGs, both of which require sensitivity to geographic distribution of the stimulus. A cheaper, more comfortable alternative to the Burian-Allen electrode is the Dawson-Trick-Litzkow, or DTL, electrode. The DTL electrode consists of a fine, single-thread silver wire that spans the eye, resting on the surface of the cornea. DTL electrodes are more comfortable for patients and therefore more suited for long tests, but they promote greater eye movement and they produce a 10-20% weaker signal than contact lens electrodes. A similar alternative is the Hawlina-Konec electrode, also called HK or metal loop electrode, which consists of a metal loop that is shaped to fit into the conjunctival sac. Much of the metal is coated in Teflon to facilitate comfort, but patches remain un-insulated to ensure recording sensitivity. These electrodes are less sensitive to movement artifacts than DTL electrodes but they produce a weaker response amplitude. Another alternative is the cotton wick electrode, first introduced by Sieving and colleagues in 1978 (Sieving et al., 1978). These electrodes consist of a cotton wick, rather than metal wire, which rests on the cornea. The use of cotton eliminates recording artifacts from the photovoltaic effect, in which light striking a metal generates a voltage potential. Because of difficulty with use, cotton wick electrodes are not widely used in clinical practice, but recent research has validated their potential for ERG testing in

animal research (Chekroud et al., 2011). Because they do not interfere with central vision, DTL, metal loop, and cotton wick electrodes are ideal for full-field and pattern ERG recordings.

4. Types of ERG

4.1 Full-field

4.1.1 Purpose

The full-field ERG is the most commonly performed, and best-understood, electroretinographic test. It consists of a full-field light stimulus, typically generated in a Ganzfeld stimulator. It can demonstrate differences between the right and left eyes, differentiate between rod, cone, and bipolar cell disorders, and show functional deficits resulting from systemic conditions or advanced degenerations. However, it is not sensitive to localized dysfunctions such as those caused by lesions or small scotomas.

4.1.2 Protocol

The testing protocol as stipulated by the ISCEV standards includes 5 different tests to be performed. After 20 minutes of dark adaptation, the electrodes are applied under dim red light in order to prevent rod photoreceptor activation. If dark adaptation occurs in a dark room, rather than through the use of eye patches or a mask, the electrodes may be applied before adaptation begins. The full-field ERG can be performed using any of the common types of electrodes. The standards set forth by the ISCEV should be followed when performing an ERG.

After dark adaptation and electrode application, the five standard tests are performed in a specific order. The first three tests are performed directly following dark adaptation and consist of light flashes against a dark background. This enables them to detect the rod response. The last two tests are performed against a light background, which cancels out the rod response, allowing the cone response to be isolated. First is the dark-adapted, or scotopic, dim ERG to measure rod responses. The stimulus is dim ($0.01 \text{ cd} \cdot \text{s} \cdot \text{m}^{-2}$) in order to prevent cone stimulus, thereby allowing the rod response to be isolated and quantified. Second is the dark-adapted (scotopic) bright ERG to measure combined rod and cone function. This and the following tests use a bright stimulus ($3.0 \text{ cd} \cdot \text{s} \cdot \text{m}^{-2}$) in order to stimulate both rods and cones. Following the second test, the patient must be light-adapted for ten minutes. Third is the scotopic bright oscillatory potential. Fourth is the light-adapted, or photopic, bright ERG to measure cone response. Fifth is the photopic bright flicker ERG at 30 Hz. During each test, fixation must be monitored to ensure proper measurement, and after each test, artifacts from disruptions such as blinking should be removed from the data before averaging the results.

4.2 Multi-focal

4.2.1 Purpose

The multifocal ERG provides some spatial sensitivity, allowing the clinician to simultaneously measure the retinal response from each of a large number of sections on the retina. The mfERG is an important clinical tool both because it can detect localized abnormalities and because it provides a means to assess central and peripheral function separately.

The most common patterns test either 61 or 103 different hexagonal elements, with central elements that are much smaller than peripheral elements because the receptive fields are larger in the periphery. The tested area typically spans 20-30 degrees to each side of the fovea. During the test, approximately half of the elements are illuminated at any given time, but each follows a distinct, pseudorandom "m-sequence" (Sutter, 1991) pattern of bright and dark states. Because the electrodes are placed on the cornea and offer no spatial resolution by themselves, the response generated is not truly a series of individual response elements but rather the result of mathematical calculation. The signal from the electrodes is amplified and then analyzed by complex software that determines the response to each spatial element by analyzing the response at the time points when the element was illuminated.

The results of the mfERG test can be displayed in several ways. The standard trace array is an array of the waveforms from each element, organized spatially as are the elements themselves. This allows general trends in the amplitudes of the waveforms to be observed and compared. Another method of presenting the data is a 3-dimensional plot, referred to as a topographic density plot, in which the relative wave amplitudes are quantified and presented as a color-coded map of hexagons in which the height represents the wave amplitude.

A number of artifacts can make mfERG interpretation difficult and should be avoided if possible. Electrical noise from ambient surfaces or the electrical power source (typically 50 or 60 Hz) is easily discernible as regular oscillations rather than typical wave forms on the trace array, but on the topographic map they can be misinterpreted as physiologic responses. Small errors of ocular movement or poor fixation can cause the elements to average with their neighbors, reducing the available resolution. Large movement errors produce abnormal signals and should be removed prior to data analysis. The hexagonal elements are not uniformly sized; they are smaller in the central region to provide greater resolution and sensitivity. One result of this configuration is that relatively low levels of noise can cause larger disturbances centrally than peripherally because they are averaged out over a larger area in the periphery. Thus small noise levels often create artificially high central peaks on the topographic map. Electrodes that interfere with central vision should not be used; others, such as DTL electrodes, are preferable. Contact lens electrodes can be effectively used for mfERG testing provided that they are calibrated to the patient's refraction. The standards set forth by the ISCEV should be followed when performing an mfERG.

Summation of all the responses to the mfERG generates a waveform similar to that of the ffERG maximum response, and the signals share the same sources, but the two traces represent very different measurements. The full-field ERG shows the direct response to changes in luminance, whereas the multifocal ERG is a mathematically derived representation of the response to changes in contrast. As such, while the summation of the mfERG shows features similar to the a-wave and b-wave, they are labeled differently to reflect the difference. The initial negative deflection resembling the a-wave is referred to as N1 (for the first negative deflection), the large secondary, positive deflection is referred to as P1 (for the first positive deflection), and a subsequent negative deflection is referred to as N2 (the second negative deflection).

4.3 Pattern

4.3.1 Purpose

The pattern ERG provides a useful measure of macular function and generalized bipolar cell function. The pattern ERG aids the clinician in interpreting the results of the visual evoked

potential test (VEP; not covered in this chapter), as the PERG can distinguish between the contributions of impaired macular function and impaired optic nerve function to a reduced VEP waveform.

4.3.2 Stimulus

The stimulus for the PERG is subject to certain constraints. The test measures response to contrast changes, not luminance changes, so the overall luminance of the stimulator must remain constant. Furthermore, any spatial irregularities would contribute to local luminance changes, so it must be spatially regular, fully symmetrical, and centered on the fovea. The most common spatial pattern is a checkerboard stimulus composed of white and black squares (see figure 2). However, there are two options for the temporal pattern of stimulation. The first and simplest to calibrate is referred to as reversal stimulation and consists of alternating white and dark squares in the aforementioned checkerboard pattern; e.g. the central square would be white, then change to black, then back to white. The alternative, referred to as onset stimulation, consists of an even, grey background, which then switches to the checkerboard pattern. This temporal stimulation is difficult to calibrate, as the average luminance of the grey background must be exactly the same as the average luminance of the checkerboard pattern. Any imbalance in luminance between the two states of the stimulation pattern will lead to uneven modulation of the on- and off- pathways in the retina, creating an unusual waveform. As with the mfERG, the electrodes used should not interfere with central vision; as such, DTL or metal loop electrodes are ideal. The standards set forth by the ISCEV should be followed when performing a PERG.

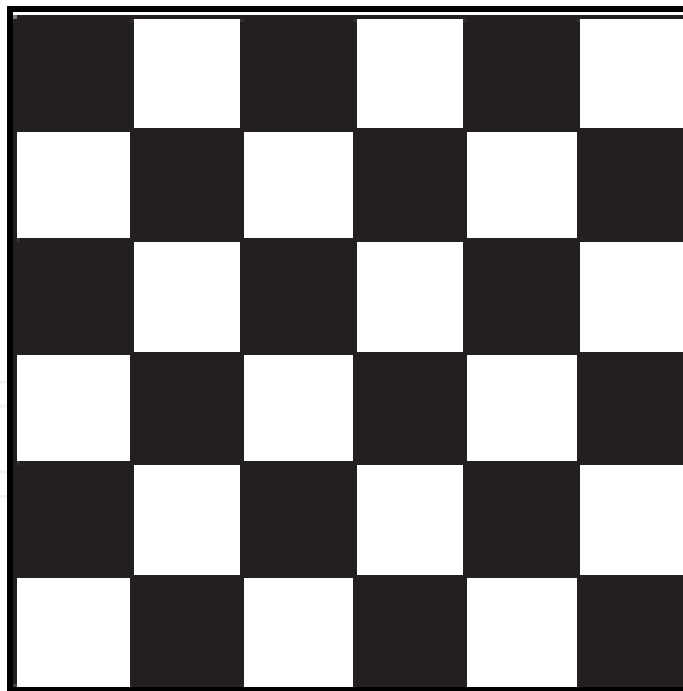


Fig. 2. Sample of an appropriate PERG stimulus. Note the symmetry around the center, sharp contrast between squares, and even luminance levels when averaged over any section of the pattern. In a reversal test, the pattern would reverse such that the top-left square would be white, and then reverse back to black; this would stimulate the retina at each reversal, or twice per cycle.

The source of the PERG waveform was determined with a series of experiments. After the first PERG recordings by Riggs and others in 1964 (Riggs et al., 1964), Sieving and Steinberg attempted to locate the electrical source by measuring electric potential with an electrode in various layers of the cat retina (Sieving and Steinberg, 1987). They determined that the source was located in the proximal layers of the retina, rather than the distal photoreceptors responsible for much of the ffERG response. Later experiments examined patients with unilateral optic nerve atrophy and knocked out animal ganglion cell activity with various means, including tetrodotoxin (which blocks action potentials), and determined that ganglion cells are the primary source of the PERG response (Bach et al., 1992; Harrison et al., 1987; Maffei and Fiorentini, 1981; Maffei et al., 1985; Menger and Wässle, 2000; Miller et al., 2002; Sherman, 1982; Viswanathan et al., 2000).

5. EOG

The electro-oculogram, or EOG, provides a measurement of the standing potential of the eye in light- and dark-adapted states. The value of the resting potential itself is of little clinical relevance, but the ratio between the light and dark values can be diagnostically important. This potential is primarily generated in the retinal pigment epithelium (RPE). Because the resting potential of the eye is the result of polarity of the eye itself, the EOG test procedure consists of the patient alternating between a fixation point to the right and a fixation point to the left, thereby alternating the polarity of the eye with respect to electrodes placed on the medial and lateral canthi. A ground electrode is placed on the forehead. The alternating horizontal ocular motion is performed periodically during an initial period of 15 minutes of light adaptation, then regularly during 15 minutes in the dark, then regularly during another 15-minute period of light-adaptation. The sequence of light and dark adaptations provides a measure of the speed with which the patient adapts to each state.

After the light is turned off, the difference in potential between the poles of the eye steadily decrease, reaching a minimum “dark trough” after roughly 8 to 12 minutes. Once the light is turned on, the potential difference increases steadily until it reaches a “light peak” after approximately 6 to 9 minutes. The ratio of the light peak to the dark trough is the primary metric obtained in the EOG. Substantial variability exists between testing centers, patients, and even multiple tests in a single patient, but a ratio of approximately 1.8 or higher is considered normal, while a light peak to dark trough ratio of 1.6 or less is considered abnormal. The standards set forth by the ISCEV should be followed when performing an EOG.

The light rise, light peak, and dark trough are the result of slow changes in the state of ion channels in the retinal pigment epithelium. As such, the EOG provides a clinical measure of RPE function. However, the clinical relevance of the EOG is limited by the length of the test.

6. Diagnosis/prognosis

Electroretinography is an important test with both diagnostic and prognostic applications. It can help to diagnose a patient with various visual symptoms including nyctalopia, photophobia, field defects, and reduced visual acuity, and it can be of use when the symptoms seem incompatible. It can also help determine the significance of fundus abnormalities and provide an early diagnosis for patients with a family history of inherited retinal disease. Furthermore, electrophysiology can help to assess the post-retinal,

intracranial visual pathway. ERG testing is especially significant because it provides an objective, quantifiable evaluation of visual function, unlike tests such as microperimetry that require reliable patient input.

7. Toxicity and vitamin deficiency

Numerous toxic compounds diminish retinal function and can be assessed and monitored with ERG testing. For example, vigabatrin, an anti-epileptic that functions by inhibiting GABA transaminase, causes irreversible retinal damage in approximately ten percent of patients. Patients taking vigabatrin are typically required to participate in regular electroretinographic recording to monitor retinal function. A decreased b-wave to a-wave ratio is an early indicator of retinal damage in patients taking vigabatrin. Such patients also tend to show a reduced 30-Hz flicker amplitude and a loss of the oscillatory potentials in the maximum response.

An early symptom of vitamin A deficiency, rare in the western world but common in third-world countries, is night blindness. Rhodopsin, the light-sensitive protein in rod cells, consists of 11-*cis*-retinal bound to the apoprotein opsin. 11-*cis*-retinal is an aldehyde of vitamin A, so reduced intake of the vitamin leads to a scarcity of the photopigment, causing night blindness. Vitamin A deficiency can be suggested by an undetectable scotopic ERG and maximum response, even with increased luminance, in conjunction with minimally reduced 30-Hz flicker and photopic responses. Visual function can be largely restored within a week of treatment.

In instances of suspected damage to the visual pathway, combined ffERG and PERG testing can elucidate the site of the damage. An ERG abnormality would indicate photoreceptor dysfunction; combined ffERG and PERG abnormalities may indicate bipolar dysfunction; VEP abnormality would suggest dysfunction late in the visual pathway.

8. Stationary rod dysfunction

Stationary rod dysfunctions including congenital stationary night blindness (CSNB) can be assessed via ffERG testing. CSNB is an inherited condition affecting rod cells, thereby preventing night vision. It typically stems from a signaling deficit between rod cells and their post-synaptic bipolar cells, but variants affecting rod phototransduction exist as well. Cases of CSNB have been observed to follow autosomal dominant, autosomal recessive, and X-linked recessive inheritance patterns. Patients with autosomal dominantly inherited CSNB often have normal visual acuity and no myopia, but autosomal recessive and X-linked forms of the disease often confer reduced visual acuity and myopia.

Cases of CSNB vary widely in their electrophysiological presentation. Some patients show only rod-specific scotopic reduction, while many others experience an electronegative b-wave on the maximum scotopic test as well (see figure 3). The transient photopic b-wave is delayed in some patients.

9. Stationary cone dysfunction

Patients with congenital achromatopsia (referred to as “monochromats” because they see shades of grey) can be classified into two separate groups. Typical (rod) monochromats show symptoms similar to those of progressive cone dystrophies, such as photophobia, decreased visual acuity, and poor color perception. Although they typically have normal fundus appearance, they often have characteristic ffERG recordings with extinguished cone

function response, reduced maximum response, and relatively normal scotopic rod response (see figure 4). Atypical (cone) achromatopsia is a rare disorder thought to originate in the post-bipolar cell transmission of color vision, as it often presents a nearly normal photopic ERG response.

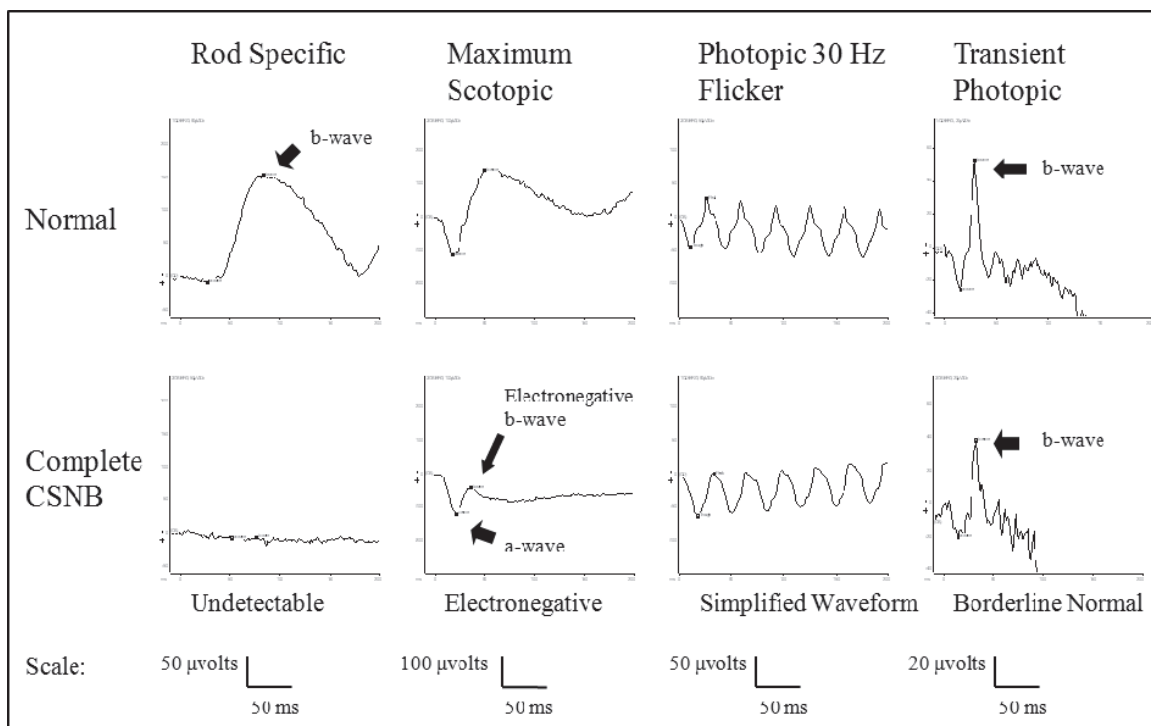


Fig. 3. ERG tracings from a normal patient and a patient with congenital stationary night blindness. Note the undetectable rod response and electronegative maximum response.

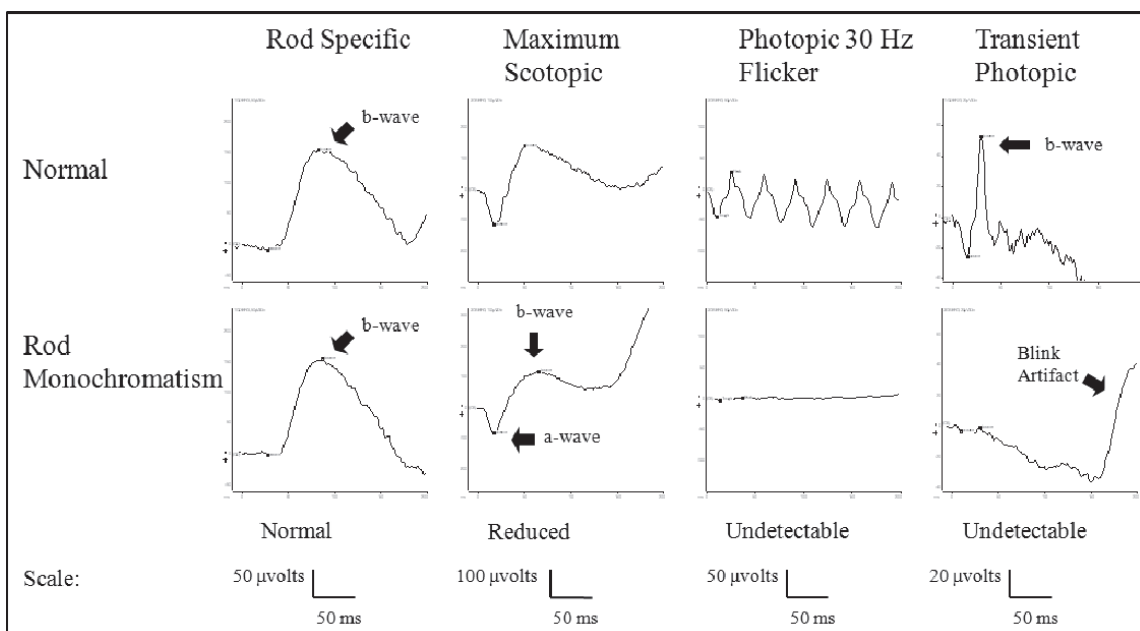


Fig. 4. ERG tracings from normal patient and from patient with rod monochromatism. Note the undetectable 30 Hz flicker and transient photopic responses.

10. Progressive retinal dysfunction

The electroretinogram is an essential diagnostic and prognostic tool for patients with progressive retinal degenerations such as retinitis pigmentosa (RP) or Leber's Congenital Amaurosis (LCA). The degree of amplitude reduction in the various tests of the ffERG can help to differentiate between rod-cone and cone-rod degenerations.

Rod-cone degenerations such as RP are characterized by progressive photoreceptor loss, with cone death secondary to rod death. As such, patients often present with reduced or extinguished night vision, followed by reduced daytime visual acuity or visual field defects. Cone death in RP often begins in the periphery and develops into a progressively constricting ring around the macula. As such, patients often develop tunnel vision, followed in time by blurred then extinguished central vision. While the progression of the ring constriction can be monitored with autofluorescent fundus imaging, the degree of visual function is typically assessed with the ffERG.

Retinitis pigmentosa is characterized by pigmentation of the peripheral retina and reduced rod function (leading to early night blindness). Patients with early-stage RP tend to show greatly reduced or even extinguished scotopic rod response and some decrease in maximum response amplitude, corresponding to the early loss of rod photoreceptors. As the disease progresses, the maximal ERG, 30-Hz flicker, and photopic responses also steadily diminish as cone cells die (see figure 5). An implicit time delay is often seen, which demonstrates generalized dysfunction.

Retinitis pigmentosa is a heterogeneous disease that has been associated with mutations in 34 different genes (see table 1). The specific gene affected in a given patient dictates the inheritance pattern. Autosomal recessive cases account for approximately 60 percent of total RP cases and have been associated with mutations in 17 different genes. Autosomal dominant inheritance defines approximately 15 to 35 percent of cases and is associated with 15 known mutations. The X-linked form of RP is associated with just three genes and accounts for approximately 5 to 18 percent of total cases.

The autosomal dominant form of RP (adRP) tends to be milder and progress more slowly than the other forms. Patients with adRP often present with reduced visual acuity in late adulthood and may progress to legal blindness by the age of 70 or 80. In early adulthood, such patients are often funduscopically indistinguishable from normal patients. However, the scotopic ERG response may be reduced years earlier than other symptoms appear.

Autosomal recessive RP (arRP) typically is more severe, progresses more quickly, and presents earlier than adRP. Patients often notice reduced visual acuity in their early 20s and may progress to legal blindness by the age of 50.

Sex-linked RP (XLRP) is the most severe form of retinitis pigmentosa. It often presents in the first two decades of life and may progress to legal blindness by the age of 25. Female carriers of XLRP that are over the age of 60 can show a characteristic tapeto-like sheen on autofluorescent images and may show a diminished scotopic response on ffERG.

The full-field ERG is an essential clinical tool for diagnosing and monitoring retinitis pigmentosa. The 30 Hz flicker amplitude can be used to estimate the length of time that a patient will retain useful vision, based on an assumed loss of approximately 10 percent each year with no treatment (Berson, 2007). This provides an approximate prognosis after a single visit. However, repeated visits over several years are important to examine the rate of visual decline and develop a more accurate prognosis. Because of its early diagnostic potential, the ffERG is also important for genetic counseling. ERG testing is often much cheaper than genetic screening, and it provides an opportunity for would-be parents with a family history

of RP to determine if they carry the mutant gene. Full-field ERG testing can also help determine early in a patient's life whether they will develop symptoms in later decades. This allows patients to plan accordingly, as unexpected vision loss severely disrupts the patient's well-being.

Disease	Gene	Protein	
adRP, arRP, CSNB	<i>RHO</i>	Rhodopsin	
adRP	<i>HPRP3</i>	Pre-mRNA splicing factor 3	
	<i>PRPF8</i>	Pre-mRNA processing factor 8	
	<i>PRPF13</i>	Pre-mRNA processing factor 13	
	<i>PRPF31</i>	Pre-mRNA processing factor 31	
	<i>RP17</i>	RP17	
	<i>CRX</i>	Cone-rod otx-like homeobox	
	<i>FSCN2</i>	Fascin	
	<i>ROM1</i>	Retinal outer segment protein 1	
	<i>NRL</i>	Neural retinal leucine zipper	
	<i>IMPDH1</i>	Inosine monophosphate dehydrogenase 1	
	<i>RP9</i>	RP9	
	arRP	<i>CNGA1</i>	Alpha subunit of rod cGMP-gated channel
		<i>CNGB1</i>	Beta subunit of rod cGMP-gated channel
<i>PDE6A</i>		Alpha subunit of PDE	
<i>PDE6B</i>		Beta subunit of PDE	
<i>USH2A</i>		Usherin	
<i>LRAT</i>		Lecithin retinol acyltransferase	
<i>RGR</i>		RPE-retinal G protein-coupled receptor	
<i>RLBP1</i>		Cellular retinaldehyde-binding protein 1	
<i>RPE65</i>		Retinal pigment epithelium-specific 65 kD protein	
<i>CRB1</i>		Crumb's homolog 1	
<i>CERKL</i>		Ceramide kinase-like protein	
<i>TULP1</i>		Tubby-like protein 1	
<i>MERTK</i>		C-mer proto-oncogene receptor tyrosine kinase	
<i>RP22</i>		RP22	
<i>RP25</i>		RP25	
<i>RP28</i>		RP28	
<i>RP29</i>		RP29	
XLRP		<i>RP6</i>	RP6
	<i>RP23</i>	RP23	
	<i>RP24</i>	RP24	
Stargardt	<i>ABCA4</i>	Rim	
VMD	<i>RDS</i>	Peripherin 2	
	<i>VMD2</i>	Bestrophin	

Table 1. Genes known to be associated with congenital retinal dysfunction.

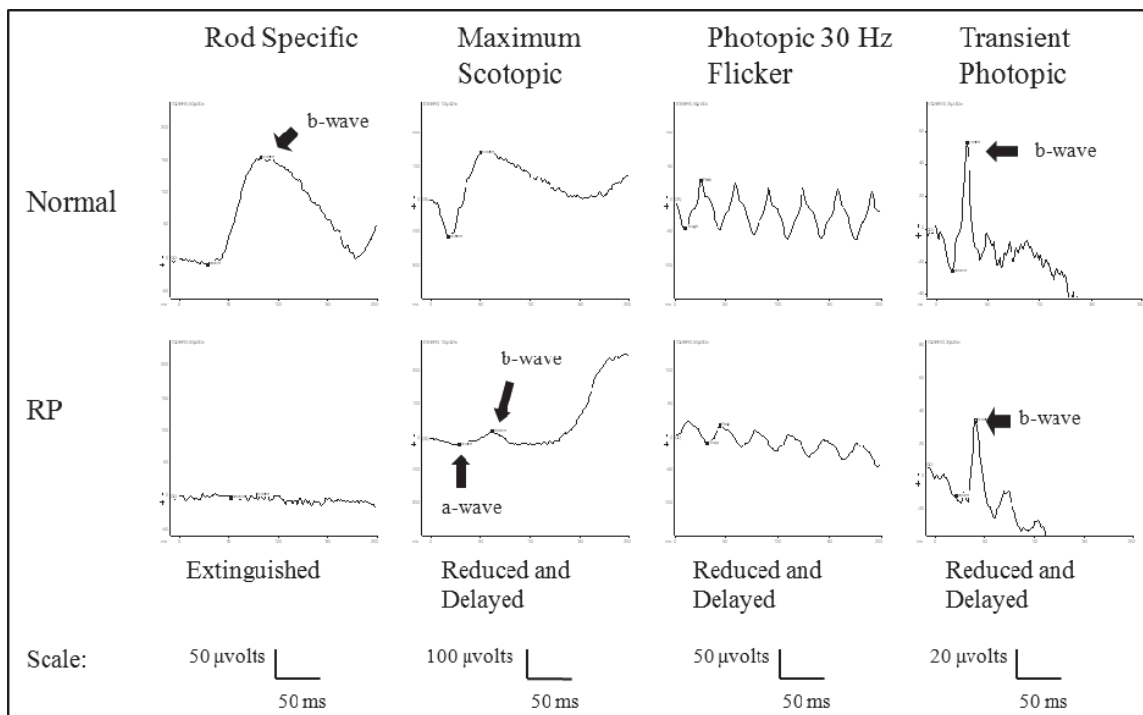


Fig. 5. ERG tracing from a normal patient and from a patient with retinitis pigmentosa. Note extinguished rod response and diminished cone response.

11. Central dystrophies

Central dystrophies such as Stargardt disease (STGD) can show a reduced or extinguished PERG even with no discernible reduction in the full-field ERG. In these diseases, full-field ERG results may still respond to very advanced disease progression and can be useful for categorizing the disease state. Pattern ERG results are far more clinically relevant, as they can be used to track the disease progression and monitor the success of potential therapies.

11.1 Stargardt

Stargardt disease is a progressive cone-rod disease known to be associated with mutations in the *ABCA4* gene. It often presents in the first two decades of life and progresses rapidly, although it often reaches a plateau before extinguishing vision. Though not a universal system, some clinicians classify the disease into three distinct groups, according to the photoreceptor responses as measured by full-field ERG (see figure 6). Group 1 Stargardt disease is classified by relatively unaffected rod and cone function on ffERG, although such patients often have severely impaired central vision and diminished or undetectable PERG recording. Group 2 Stargardt disease is marked by diminished cone function but unaffected rod function. Group 3 Stargardt disease shows diminished or extinguished rod and cone function on ffERG. While the disease is often considered to be progressive, the group classification can be misleading, as the disease often plateaus and therefore will not necessarily progress, for example, from Group 1 to Group 2.

11.2 Vitelliform macular dystrophy

Vitelliform macular dystrophy (VMD) is a progressive disorder marked by vitelliform ("egg-like") lesions in the macula that presents in children and middle-age adults. The early-

onset form of the disease, known as Best disease, is inherited in an autosomal dominant fashion and tends to be more severe than the adult-onset form. Patients with vitelliform macular dystrophy often experience progressive loss of central vision, progressing to central blindness and a visual acuity of approximately 20/100. As the vision deteriorates, the central lesion tends to atrophy and scarred and fibrotic. Two genes are associated with vitelliform macular dystrophy: *VMD2* and *RDS*. Best disease is associated with *VMD2* but both mutations are associated with adult-onset vitelliform dystrophy.

Patients with Best vitelliform macular dystrophy maintain normal peripheral vision and as such, full-field ERG results are typically normal. However, Best disease can be definitively diagnosed by a diminished light-peak to dark-trough ratio in an EOG.

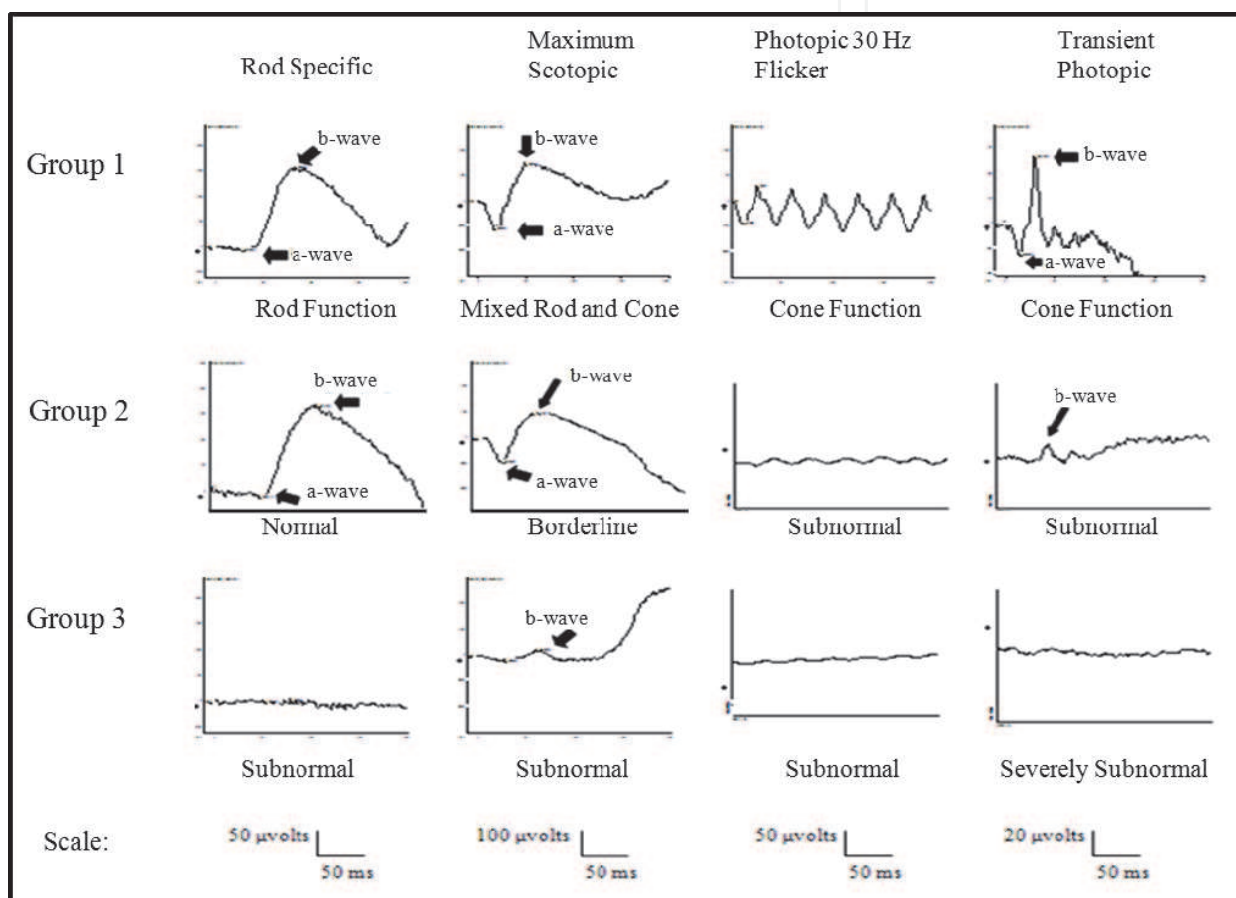


Fig. 6. Representative ERG tracings from Group 1, Group 2, and Group 3 Stargardt patients. Note normal function in Group 1; reduced cone response in Group 2; and nearly extinguished cone response and diminished rod response in Group 3.

11.3 AMD

Age-related macular degeneration (AMD) is a common progressive degeneration of the macula. Its incidence is expected to double within a decade, affecting 20 percent of all Americans between the ages of 65 and 75. AMD typically presents as blurry central vision between the ages of 60 and 70 (Friedman et al., 2004). The vision loss progresses in the central retina but does not expand outside of the macula. Because it is contained within the macula, the full-field ERG often shows normal overall function. There may be a slight drop in

cone response amplitude, but the implicit time, which typically signals generalized function, is normal. However, the pattern ERG, which measures macular function, is markedly reduced.

Patients with AMD are typically classified as having either “dry” or “wet” AMD depending on whether they show signs of neovascularization. Wet, or neovascular, AMD can be treated with several different methods. Elevated levels of vascular endothelial growth factor, or VEGF, lead to the formation of new blood vessels. As such, subretinal injection of anti-VEGF therapeutics can stop or slow the neovascular development and prevent further loss of vision. An alternative is photodynamic therapy. In photodynamic therapy, a high-energy laser is used to coagulate the retina in a number of small spots around the neovascular area. This initiates chemical changes in the retina that prevent further neovascularization. After either treatment, PERG recording on follow-up visits can measure the degree of recovery or monitor further vision loss.

12. Conclusion

Electrophysiological recording is a valuable asset for the clinician. Because ERG tests can measure the function of different cell types and cell layers, they can aid the clinician in distinguishing between symptomatically similar diseases. Furthermore, because they provide an objective measure of retinal function, they can help clinicians evaluate very young patients, very old patients, and others that may otherwise be difficult to diagnose. The quantitative results that ERG tests provide make them useful as tools for both prognosis and disease monitoring. Because of the importance of accurate data and the large number of sources of variability, it is essential that all ERG testing be performed according to the standards established and regularly reviewed by the International Society for Clinical Electrophysiology of Vision, or ISCEV.

13. Acknowledgement

We would like to thank Luz Amaro-Quireza, O.D., and Vivienne Greenstein, M.D., for their help.

14. References

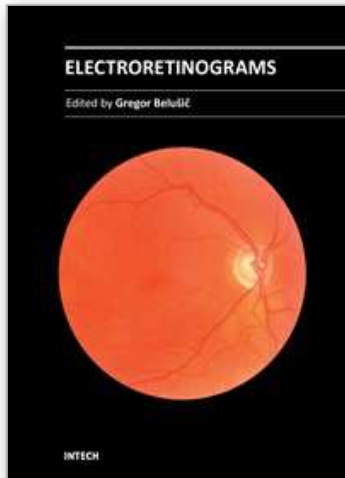
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Edited by Dr. Gregor Belusic

ISBN 978-953-307-383-5

Hard cover, 238 pages

Publisher InTech

Published online 09, August, 2011

Published in print edition August, 2011

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How to reference

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