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Chapter 5

Clinical Ocular Electrophysiology

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http://dx.doi.org/10.5772/57609

1. Introduction

Ocular electrodiagnostic tests are invaluable tools in most clinical circumstances in routine ophthalmology practice. Sometimes, these tests are the only methods exploring the functional deficits of the patient in otherwise normal structure. In contrast, ocular electrophysiological tests may explore normal function in cases with functional vision loss. In this chapter, we will focus on the clinical use of ocular electrophysiological tests after a short explanation about recording parameters. A basic clinical use of ocular electrophysiological tests will be discussed rather than detailed and theoretical explanations.

2. Full-field electroretinogram

Full-field electroretinogram (ERG) represents a mass-response of the retina to a full-field flash of light. The resultant single waveform is the total response of the retina. The details of full-field ERG recording techniques may be obtained from ISCEV (International Society for Clinical Electrophysiology of Vision) standards [1]. The functions of rod, cones and inner retinal layers may be recorded separately by changing stimulus parameters and the adaptive state of the eye to the light.

In a typical full-field ERG (Figure 1), five recordings are performed. At first, the patient is dark adapted for at least 20 minutes. A dim white or blue flash light [2.0 log unit below the standard flash intensity (Standard flash: 3.0 cds/m²)] is used to stimulate the retina. This response is shown as ‘DA 0.01 response’ in the latest ISCEV guideline for full-field ERG recording. At that flash intensity, only rod photoreceptors are stimulated and the resultant waveform belongs to rod functions. In that response, only a positive b wave originated from rod ON-bipolar cells is recorded. This means that DA 0.01 response is an indirect indicator for rod photoreceptor.
function. Secondly, DA 3.0 response is recorded. A standard flash light is used to stimulate both rod and cone photoreceptors and combined response of rod and cone photoreceptors is recorded. The first negative peak, a-wave is caused by the hyperpolarization of photoreceptors. However, in DA 3.0 response, a-wave has a bifid configuration which makes the evaluation of photoreceptor function problematic. For this reason, ISCEV recommended the use of bright flash ERG recordings (DA 10.0 ERG or DA 30.0 ERG) for photoreceptor function evaluation. In these brighter light levels, a–wave has a clear single peak. Oscillatory potentials, which reflects amacrine cell function is recorded using standard flash light intensity under dark-or light-adapted (LA; at least 10-min of light adaptation using a background luminance of 30cd/m²) conditions. LA 3.0 response is generated within cone system. LA 3.0 30 Hz flicker response is the most sensitive indicator of cone system however, it arises in the inner retina and cannot be used to localize the level of abnormality within the cone system [2].

Each retina consists of approximately 4-5 million of cone and 100-120 million of rod photoreceptors. The rods contain light-sensitive pigment rhodopsin with a spectral absorption peak at 496 nm. Each cone contains one of three types of color sensitive pigments. L, M and S-cones (L: long wavelength cones, M: middle wavelength cones, S: small wavelength cones) have peak absorption spectra at 558nm, 531nm and 419nm, respectively. L, M and S cones is also named as red cones, green cones and blue cones with respect to colors of peak-sensitized light [3].

It is apparent from the stimulation technique that small areas of retinal dysfunction cannot be explored by full-field ERG, such as cases with Stargardt macular dystrophy or age-related macular degeneration, macular edema, etc. The cone photoreceptors are the most heavily packed in the macula, however 85-90 percent of cone photoreceptors reside in extra-macular retina. For this reason, full-field ERG is not a good way to investigate functional status or follow-up of retinal diseases known to be restricted to the macular area. Full-field ERG should be used for generalized retinal dysfunction.

![Figure 1. A representative full-field ERG response from a healthy subject.](image-url)
Retinitis Pigmentosa: Retinitis pigmentosa refers to a large group of genetically heterogeneous disorders characterized by rod dysfunction in the early stages of the disease and progressive rod-cone dysfunction. In typical retinitis pigmentosa, full-field ERG is almost non-recordable in most clinical situations. Rod functions are generally deteriorated earlier and more severely than cone functions. Figure 2 shows a full-field ERG recording belonging to a 21-year-old male patient with retinitis pigmentosa.

Figure 2. Full-field ERG responses belonging to a healthy subject and a 21-year old male with retinitis pigmentosa. DA 0.01 response is non-recordable. DA 3.0 response has a very low b wave amplitude. LA 3.0 and LA 3.0 30 Hz responses are reduced.
The original report of the ERG in primary retinitis pigmentosa revealed nondetectable or very small responses but these patients usually had advanced disease with attenuation of retinal vessels and extensive pigmentary changes in the retina. However, later studies showed that in the early stages of the disease, the ERG amplitudes are generally subnormal when the patient is asymptomatic. In that stage, however, delays in the implicit times helps in the establishing of widespread progressive forms of retinitis pigmentosa [4].

Retinitis pigmentosa has mainly three types of genetic transmission, autosomal dominant, autosomal recessive and X-linked recessive forms. Almost 50% of patients are sporadic retinitis pigmentosa patients which means that the most common form is this form of the disease. The worst prognosis is seen in X-linked recessive inheritance. These patients generally have non-recordable rod and cone ERG until the end of first decade. However, autosomal dominant type has the best prognosis, and patients with autosomal dominant inheritance may have good rod and cone functions until the fourth and fifth decades [4].

In cases with non-recordable full-field ERG, the follow-up of the macular function may be performed with multifocal ERG, focal ERG or pattern ERG. This will be discussed in the next parts of this chapter.

Cone dystrophies: Cone dystrophy refers to a large group of genetically heterogeneous disorders characterized by progressive diffuse cone dysfunction. Patients have progressive visual acuity loss, decreased color vision and, aversion to bright light. In cone dystrophies, rod function is normal in the early stages of the disease, however may deteriorate in the late stages. Combined rod-cone bright flash ERG shows a mild to moderately reduced a wave and b wave with variable prolongation and oscillatory potentials are also reduced. Single cone responses and 30 Hz cone responses are reduced and prolonged (Figure 3) [5].

Congenital Stationary Night Blindness (CSNB): In contrast to retinitis pigmentosa which is characterized by progressive night vision blindness and photoreceptor loss, CSNB refers to a group of congenital hereditary retinal diseases with non-progressive night blindness and no structural photoreceptor damage. The patient even may not recognize night blindness if the symptoms are mild. Schubert-Bornschein type of CSNB is the most frequent type and is characterized by negative full-field ERG. Negative ERG is told to occur when a b-wave amplitude lower than a-wave amplitude in combined rod-cone response. That is, the peak of the b-wave is under the isoelectric line of the full-field ERG and b/a ratio is under 1 (Figure 4). CSNB represents only one of the stationary night blinding disorders. Others are fundus albipunctatus, Oguchi disease and fleck retina of Kandori. However, CSNB may be said to be the only one with normal fundus, except myopic fundus changes in some subgroups.

Negative ERG is seen in stationary night blindness but is not limited to this condition. A normal a wave and reduced b wave means that there is problem in the transmission of electrical biopotential from the photoreceptors to the inner retinal layers. The retina has a dual circulation. Photoreceptors are nourished by choroidal circulation while inner retinal layers are nourished by retinal circulation. The biopotential cannot be transferred to inner retinal layers if a problem exist in the retinal circulation. For this reason, central retinal artery obstruction,
central retinal vein obstruction may cause negative ERG. Similarly, juvenile retinoschisis is one of the causes of negative ERG.

Figure 3. Full-field ERG responses belonging to a healthy subject and a 23-year old male with cone-dystrophy. DA 0.01 and DA 3.0 responses are normal. LA 3.0 response is almost non-recordable. LA 3.0 30 Hz responses are very much reduced.
Figure 4. Full-field ERG responses belonging to a healthy subject and a 20-year old male with congenital stationary night blindness. DA 0.01 is non-recordable, DA 3.0 response has a negative configuration that is b-wave amplitude is lower than a-wave amplitude. LA 3.0 response and LA 3.0 30 Hz responses are mildly reduced.

Cone dystrophy with supernormal rod ERG. Cone dystrophy with supernormal ERG was first described by Gouras et al. in 1983 [6]. This autosomal recessively inherited syndrome is characterized by reduced visual acuity, abnormal color vision, discrete macular changes, and specific alterations of ERG responses. Full-field ERG changes are: (1) reduced and delayed cone responses, (2) a reduction and marked delay of rod b-waves at low light intensities, (3) elevated rod b-wave amplitudes at higher light intensities [7]. In the early stages of the disease, the fundus appearance may be normal, however macular pigmentary changes and macular atrophy may occur in the later stages [8]. The dystrophy was shown to be caused by KCNV2 gene mutation [9-11]. This gene encodes a subunit of a voltage-gated potassium channel expressed in both rod and cone photoreceptors [9]. It is probable that the rapid increase in b-wave amplitude over a short range of stimulus may result from a ‘gated’ mechanism, occurring only after an abnormally high threshold has been exceeded, enabling channel activation and ERG b-wave generation. Robson et al. reported that the ERG to the bright-flash showed a
broadened and delayed a-wave through with a rhomboid-like shape [8]. Figure 5 shows a cone dystrophy patient with supernormal rod ERG [12].

**Figure 5.** Full-field electroretinogram with very delayed rod response, a rhomboid a-wave and supernormal b-wave in bright-flash rod-cone response and very reduced cone responses in a patient with KCNV2 mutation (Used with permission of Journal of Retina-Vitreus, 2011).

**Diabetic retinopathy.** Full-field ERG changes are somewhat equivocal in diabetes mellitus. However, there are a number of studies reporting full-field ERG changes in diabetes mellitus. In one study, several ERG changes were reported in diabetics with or without retinopathy. From the literature, it is apparent that full-field ERG changes were found in diabetic patients with and without diabetic retinopathy [13]. Holopigian et al. found several ERG parameters to be abnormal in early diabetic retinopathy [14]. Reductions in the oscillatory potentials were reported in diabetic retinopathy, [13, 15, 16] however there was no changes in one study [17]. Bresnick et al. found that oscillatory potential amplitudes predicted the progression of mild nonproliferative diabetic retinopathy to severe proliferative diabetic retinopathy [15, 18].

**Toxic effects.** Many drugs may have toxic effects on the retina, including choroiquine/hydroxychloroquine, chlorpromazine, thioridazine, indomethacine, quinine, methanol, gentamicin, cisplatin, vigabatrin, desferroxamine, sildenafil, etc.
Chloroquine/hydroxychloroquine is used in the treatment of rheumatoid arthritis, systemic lupus eritematosus, and malarial fever. Both drugs have an affinity to melanin and tends to accumulate in the choroid, ciliary body, and retinal pigment epithelium. When the degenerative changes are limited to the macular area, normal or subnormal full-field ERG responses are obtained. In the late stages of the toxic effect, peripheral pigmentary changes become apparent. In this stage, minimal or non-recordable responses are obtained. Because full-field ERG responses are minimally affected in the early stages, this test is not recommended to detect early functional deficits. Instead, central 10/2 visual field testing and multifocal ERG is more appropriate for this purpose [19].

Photopic negative response. The photopic negative response is a negative-ongoing wave that occurs following the b-wave in response to a long flash. It is particularly easy to see in red flashes on blue backgrounds. Several studies indicated that the photopic negative response originates from the retinal ganglion cells. The photopic negative response is significantly reduced in patients with primary open-angle glaucoma, anterior ischemic optic neuropathy, and other optic neuropathies, consistent with an origin in ganglion cells or their axons [27].

3. Multifocal electroretinogram

Multifocal ERG, first developed by Sutter and Tran in 1991 [28], provides a topographic map of the retinal function. As discussed above, full-field ERG is a mass response of the retina and small areas of retinal dysfunction cannot be explored with full-field ERG. At that point, multifocal ERG has its own advantages. By using a single electrode, multifocal ERG technique allows the recording of the functions of 61, 103 or even more retinal areas in less than 7-8 minutes. The recordings belong to central 30 to 50 degrees of the retina. For this reason, it is an excellent tool in detecting macular function. Multifocal ERG is a reproducible technique although very small responses are produced in each hexagonal area [29].

Multifocal ERG responses may be presented as single waveforms for each hexagonal area, ring analysis beginning from the most central to the periphery of the stimulated area and 3-D presentation (Figure 6).

The multifocal ERG stimulus is displayed on a video monitor. The stimulus consists of a pattern of hexagonal areas which are scaled to produce equal ERG responses from the retina (Figure 7). During stimulation, the display appears to flicker because each hexagon goes through a pseudo-random sequence (the m-sequence) of black and white presentations. Each hexagon has a probability of 0.5 of being white or black on each frame change [30]. Complex mathematical analyses between each retinal response and pseudo-random m sequence provide local retinal responses belonging to each hexagonal area.
Figure 6. A normal multifocal ERG response output. Upper left: Plots diagram showing single responses from each retinal area. Upper right: Ring analyses. The upper rings show central retinal functions, the lower rings show peripheral functions. Lower right: 2-D amplitudes with color-coded diagram. Lower left: 3-D amplitudes.

Figure 7. Multifocal ERG stimulus

**Macular disease.** One of the best uses of multifocal ERG is in Stargardt disease. The central responses are reduced and delayed and the better responses are obtained in the peripheral rings.

Central areolar choroidal dystrophy, first described by Nettleship in 1884, is a macular dystrophy characterized by the development of fine, mottled, depigmented retinal pigment epithelium in the macula. After several decades the pathognomonic zone of circumscripct atrophy, affecting retina, retinal pigment epithelium and choriocapillaris, develops in the macular region of the eye [31, 32]. Although, most cases are sporadic, autosomal dominant and recessive inheritance patterns have been reported [33]. In a recent study, we have showed that mfERG responses were reduced corresponding to the areas of ophthalmoscopically visible
lesion and there were significant correlations between foveal retinal sensitivity in the Humphrey visual field and mfERG P1/N1 amplitudes (Figure 8) [34].

![Figure 8. Color fundus photographs, pattern deviation of Humphrey visual fields and multifocal ERG results of four patients with central areolar choroidal dystrophy. Central responses are markedly reduced and delayed in multifocal ERG. (Used with permission of Wichtig Editore. From 'Multifocal electroretinogram and central visual field testing in central areolar choroidal dystrophy', Gundogan et al, European Journal of Ophthalmology, Volume 20, Number 5, 2010).](image)

Multifocal ERG was used to evaluate macular function and the response of macular edema to different types of treatment in different types of macular edema. In one of them we showed that multifocal ERG is not a good way to monitor the macular function in chronic macular edema [35].

**Diabetic retinopathy.** One of the important features of early diabetic retinopathy is its focal nature. Full-field ERG is a mass response of all retinal areas. For this reason, full-field ERG recordings cannot detect smaller areas of focal retinopathy in early diabetic retinopathy. Because multifocal ERG records the function of very small retinal areas, it may be used to detect very early local retinal dysfunctions in diabetic retinopathy. Holm et al. showed that hard exudates prolongs the implicit times of the multifocal ERG independent from the macular thickness [36]. In accordance with this finding, Dhamdhere et al. found that local neuroretinal function is not associated with full retinal thickness measured locally in patients with diabetes and no retinopathy, even in abnormal locations. The authors concluded that full retinal thickness measured locally by OCT is not a surrogate for multifocal ERGs in early diabetic retinopathy [37].

**Follow-up of retinitis pigmentosa.** Multifocal electroretinography is a powerful tool in the follow-up of residual central cone functions in retinitis pigmentosa. In these cases, full-field ERG is generally not reproducible and cone functions are non-recordable. In one study, [38]
yearly progression according to the multifocal ERG values was found to be approximately 6% to 10% in the outer three rings. Ring 5 amplitudes of the multifocal electrotoretinogram correlated well with the scotopic full-field mixed rod-cone ERG response amplitude.

Glaucoma. Glaucoma primarily affects the inner retina, specifically the retinal ganglion cells, most likely with unremarkable signs or symptoms in the early stages. The damage to retinal ganglion cells results in visual field loss. However, approximately 30-35% of ganglion cells should be lost for an evidence of visual field loss. In recent years, retinal nerve fiber layer analysis by optical coherence tomography has become the most common technique for glaucoma detection [39]. Several studies have used multifocal ERG in detecting signs of glaucoma in terms of amplitude [40] and implicit times [41]. The amplitude of the multifocal ERG is also reduced in patients with ocular hypertension [42].

One of the most important studies on the use of multifocal ERG for glaucoma detection was performed by Sutter and Bearse [43]. The authors used a mathematical algorithm to extract a component with a latency, which increased in proportion to the estimated length of the ganglion cell axons from the site of stimulation to the optic nerve head. The authors found that glaucomatous damage may reduce the magnitude of this component (optic nerve head component) [39, 43].

4. Focal electroretinogram

Focal ERG is used to record local ERG response. In contrast to multifocal ERG stimulus, a direct focal light is used over the retinal area being tested, mostly the macular or foveal region. The response to such a stimulus is about a few microvolts, for this reason, signal-to-noise ratio is low in focal ERG. To overcome this issue, hundreds of stimulus should be used to have a reliable average response. Second problem in focal ERG is the scattered light. The original ring-shaped light is scattered in the eye and may easily stimulate the area outside the intended retinal area. For this reason, the stimulating light is encircled by an annulus ring of steady background light that is typically brighter than the test stimulus. However, this is not an unproblematic solution, because it use of a brighter background light prevents the recording of rod functions [44]. Focal ERG is generally not used in routine clinical practice in most electrophysiological units because of these difficulties and the emergence of multifocal ERG in 1992.

5. Pattern electroretinogram

Pattern ERG is a retinal response to a checkerboard pattern stimulus with alternating black and white squares. In low temporal frequencies (<6 reversals per second), a positive component, P50 (positive peak around 50th milliseconds), and a negative component, N95 (negative component around 95th milliseconds), are observed. Sometimes, a negative component
around 35 milliseconds may be recorded (N35). This response to low-frequency stimulus is called ‘transient PERG’. (Figure 9)

![Figure 9. A typical pattern ERG recording.](image)

In high temporal frequencies (>7 reversals per second), P50 and N95 peaks are merged into a sinusoidal waveform, dominated by the N95 component. This response is called ‘steady-state pattern ERG’. In steady-state pattern ERG, it is impossible to distinguish the original P50 and N95 peaks [45].

Initially it was thought that PERG is almost totally originated from ganglion cell functions. However, later studies showed that P50 peak has an earlier component originated from cells distal to the ganglion cells and reflecting mostly the macular function [46-49]. In two reports [50, 51], it has been detected that some pattern ERG response still may be recorded after post-traumatic and surgical optic nerve section despite no light perception. In one of them, P50 amplitude reduction with P50 latency shortening was observed. These findings too imply that pattern ERG is not completely originated from ganglion cells. In addition, shortening of the P50 latency caused the theory that a later part of the P50 response is related with ganglion cell function and P50 latency shortens if ganglion cell function extinguishes.

It is apparent from the Figure 9 that P50 amplitude reduction is accompanied by a secondary N95 reduction, as N95 amplitude is measured from P50 peak to N95 trough. However, this is not the same for N95 amplitude reduction. N95 amplitude reduction may be selective. For this reason, the ratio of N95 amplitude to P50 amplitude has an importance in detecting whether the visual loss is related to macular disease or ganglion cell disease. If N95/P50 ratio is normal, then it may be thought that the visual loss may be attributed to macular disease. If the ratio is lower than normal (which is called as ‘selective N95 reduction’), visual loss may be attributed to ganglion cell disease. N95/P50 ratio is about 1.5 in the author’s electrophysiology laboratory.

5.1. Chronic effect of optic nerve disease to pattern ERG.

The first reports about N95 in optic nerve demyelination were presented by Holder. Holder reported that pattern ERG abnormalities could be limited to N95 component. The author also reported that there was a 40% pattern ERG abnormality among 200 patients with optic nerve demyelination, however 85% of the abnormalities were detected in N95 [52, 53].
Figure 10 and figure 11 show P50 and N95 results of 382 patients with optic nerve demyelination. As shown in Figure 10, most of the patients have normal P50 amplitudes despite prolonged P100 latency in pattern VEP. However Figure 11 shows that N95/P50 ratio decreases as P100 latency increases [52].

Figure 10. Pattern ERG P50 amplitudes in patients with optic nerve demyelination. (Used with permission of Pergamon. From ‘Pattern Electroretinography (PERG) and an Integrated Approach to Visual Pathway Diagnosis’, Holder GE, Progress in Retinal and Eye Research, Volume 20, Number 4, 2001).

Figure 11. Pattern ERG N95/P50 ratio in patients with optic nerve demyelination. (Used with permission of Pergamon. From ‘Pattern Electroretinography (PERG) and an Integrated Approach to Visual Pathway Diagnosis’, Holder GE, Progress in Retinal and Eye Research, Volume 20, Number 4, 2001).

Acute effects of optic nerve disease on pattern ERG. Pattern ERG changes in the acute phase of the optic nerve inflammation is not simply as mentioned above. In the acute phase of the
inflammation, P100 amplitude in pattern VEP is reduced with less latency changes while P50 in pattern ERG is also reduced. A few weeks later, as the inflammation subsides P50 amplitude in pattern ERG and P100 amplitude in pattern VEP recover, however, ganglion cell dysfunction or demyelination begin to appear. N95 is reduced (selectively as mentioned above) while P100 is delayed. N95/P50 ratio is lowered in the chronic phase of the inflammation. MRI findings in the acute and chronic phase of the inflammation was shown to be consistent with this theory [52, 54].

**Glaucoma and pattern ERG.** Hood et al. [55] studied pattern ERG in glaucoma patients with confirmed visual field deficits. The authors included 21 eyes of 15 patients with glaucoma. Pattern ERG was within normal limits for 4 of the worse eyes of 15 glaucoma patients. Overall, 6 of the 21 eyes that met the criteria for glaucomatous damage had normal pattern ERGs on both N95 amplitude and N95/P50 ratio. Second, the N95 amplitude was nonlinearly related to visual field sensitivity. Small field losses were associated with disproportionately large losses in pattern ERG amplitude. Third, the PERG from both eyes of a patient were very similar, even when the visual fields suggested very different levels of damage.

Ventura et al.[56] investigated the steady-state pattern ERG responses with PERGLA paradigm in 200 glaucoma suspects with increased optic disc cupping and normal visual field and in 42 patients with early manifest glaucoma. The PERG was abnormal in amplitude, phase, or interocular asymmetry in amplitude and phase in 52% of glaucoma suspect patients and 69% of EMG patients. The pattern ERG amplitude was correlated weakly with both mean deviation and vertical C/D (p=0.05). The correlation between pattern ERG amplitude and MD and C/D was stronger for inter-ocular differences rather than absolute measures. Inter-ocular pattern ERG amplitude asymmetry was positively correlated with the severity of the disease. Compared to white glaucoma suspects, a lower pattern ERG amplitude was found in black glaucoma suspects and early manifest glaucoma patients, but not in black glaucoma controls.

6. Electro-oculogram

Unlike full-field ERG, electro-oculogram (EOG) is not a stimulated response. EOG records the continuous resting potential across the retinal pigment epithelium which is named as ‘transepithelial potential’. This potential is only about a few millivolts. Transepithelial potential is mainly generated by retinal pigment epithelium. However, as well as the integrity of the retinal pigment epithelium, photoreceptor and interphotoreceptor matrix integrity and function should be intact. For this reason, EOG is decreased in photoreceptor diseases, retinal detachment and other generalized outer retinal damages in addition to primary retinal pigment diseases such as Best disease.

The resting potential across the retinal pigment epithelium is not a steady potential. In the dark-adaptation, transepithelial potential is decreased to a minimum value (dark trough) after about 12 minutes. In the light-adaptation, the transepithelial potential increases to a peak value (light-peak) after about 7-12 minutes [57]. The ratio of light-peak to dark-trough is called Arden ratio or ‘EOG ratio’. This value should be 1.8 or greater in normal subjects and considered
abnormal under 1.6. In the author’s institution, Arden ratio is 2.35±0.44 (mean±SD) [58]. Figure 12 shows EOG recordings of a patient with Best disease. There is almost no light peak with light stimulation in EOG. Arden ratios are 1.18 in the right eye and 1.17 in the left eye.

Figure 12. Fundus photo of a patient with Best disease and EOG recordings. Arden ratio is 1.18 in OD and 1.17 in OS. This implies very small change in transepithelial potential with light stimulation.

7. Visual evoked potential

Visual evoked potential (VEP) represents the cortical response to a checkerboard-pattern stimulus (pattern VEP) or a flash stimulus (flash VEP). Pattern VEP components that are commonly measured are N75, P100 and N135 peaks (Figure 13).

Figure 13. Representative pattern VEP waveforms to five consecutive check sizes.
The amplitudes of the peaks are measured from the peak of the one component to the trough of the preceding component. P and N refer to positive and negative voltages recorded at the occipital electrode with respect to the voltage at the reference electrode.

Flash VEP components are defined as N1, P1, N2, P2, etc (Figure 14).

Figure 14. Flash VEP responses in a patient with intravitreal hemorrhage in the left eye. Left-eye flash VEP responses are very much reduced.

VEP response primarily reflects the central retinal function although the stimulated retinal area in pattern VEP and flash VEP is about 50 degrees and full retinal areas, respectively. There are three main reasons for this contribution of the central retina [59]. (1) The central visual field is represented at the outer surface of the visual cortex while peripheral retina is represented at the deep surfaces of the calcarine sulcus. Active electrode in VEP recordings is placed approximately 2 cm above the protuberentia occipitalis externa which is the nearest point to the surface of the visual cortex. (2) Cortical magnification phenomenon. In the central retina each photoreceptor transmits its signal almost to one ganglion cell, while many photoreceptors converges on a single ganglion cell in the peripheral retina. Thus, more than 50% of the cells in the visual cortex represent approximately central 10 degrees of the retina. (3) In PVEP testing, small checkerboard stimuli may be used. These small sized stimuli may only be resolved by the central retina which has the highest concentration of photoreceptors.

Because of the reflection of the central retinal function, pattern VEP is used to estimate visual acuity in many clinical situations besides optic nerve function [60]. An impaired VEP is anatomically non-specific. However, a through ocular examination including the retina, optic nerve and brain frequently explores the localization of the problem [61]. Pattern VEP is more valuable than flash VEP in the clinical evaluations of the visual pathway. However, flash VEP is valuable in the situations of fixation problem, mature cataract, intravitreal hemorrhage, ocular trauma or any other circumstance that prevents patient cooperation. In these situations, flash VEP gives important knowledge about visual status.

Pattern VEP recording requires fixation to a point in the screen. Impaired VEP responses may be produced by deliberate poor fixation, defocusing to the fixation point, or conscious suppression.[61-64] This is an important issue in the evaluation of patients with functional
visual loss. Voluntary flash VEP suppression is more difficult, because it does not require fixation.

**Optic nerve disease.** VEP is commonly used to detect visual pathway deficits in patients with no apparent objective signs of ocular dysfunction. In a study on MS patients with no clinical history of optic nerve involvement, we showed that 21 of 39 patients had delayed P100 latency [65]. Figure 15 shows PVEP recording of an MS patient included in that study. Snellen visual acuity was 1.0 in both eyes although P100 latency was clearly prolonged in the left eye.

Figure 15. Pattern VEP traces belonging to a normal and a multiple sclerosis patient. P100 latency to 2 degree check size is about 150 ms in the left eye while it is about 100 ms in the right eye.

**Functional Visual Loss.** The term ‘functional visual loss’ is used when the visual loss cannot be explained with organic lesions in the visual pathway. ‘Vision’ is a cortical function and the bio-potential change in the visual cortex after a visual stimulus is evaluated with visual evoked potentials. In a study, we showed that pattern VEP recordings to five check sizes (2 degree, 1 degree, 30 minute, 15 minute and 7 minute) may be used objectively to estimate visual acuities of the patients with suspected functional visual loss [66].

Figure 16 shows PVEP recordings to 5-consecutive check sizes of an African woman with no light perception in the left eye for 2 years. Biomicroscopic and fundoscopic examinations were unremarkable. No relative afferent pupillary defect was detected. Pattern VEP responses in both eyes were totally in the normal limits in terms of P100 amplitude and latency values. In this patient, we were able to show that the patient was capable of reading at least 0.3 in Snellen chart from 6 meters with the use of polaroid glasses.
Figure 16. PVEP response to five consecutive check sizes in a malingering who claimed no light perception in the left eye.

8. Conclusion

Full-field ERG is invaluable in generalized retinal diseases. Pattern ERG is complimentary test for full-field ERG, because it may localize the problem to macula or ganglion cells. Multifocal ERG is used to evaluate central retinal function. EOG is the recording of transepithelial potential. VEP is a cortical potential that is the end of visual pathway, for this reason it gives important knowledge about the ‘vision’ itself. The ophthalmologist can localize the visual problem with a thorough understanding of the origins of these tests.

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