Course Description: This course describes the applications of electroretinography (ERG) and visually-evoked potential (VEP) in primary eye care. Included are data acquisition from ERG and VEP, diagnosis, and differential diagnoses from these tests.

Objectives: At the completion of this course, practitioners will be able to describe:
1. How ERG and VEP electrodiagnostic testing works
2. The physiology of these small milli- and micro-volages across the retina and visual pathways
3. Indications for electrodiagnostics, and
4. Differential diagnoses and disease progression monitoring from ERG and VEP
Electroretinogram (ERG)

Many clinicians think about an ERG as being only for research, but recently ERG instruments have become much smaller, quicker, and easier to use. Figure 1 shows two of the clinically available systems. The testing no longer requires a huge contact lens device be placed on the eye. Instead, a small probe can be placed between the lower lid and conjunctiva. Additionally, the results can be helpful in diagnosing common conditions, including glaucoma, subtle macular degeneration, and diabetic retinopathy.

An ERG evaluates the function of the retina. It measures the electrical response when light hits the retina. This electrical potential is transferred to the cornea and measured by an electrode placed near the surface of the cornea. The information can then be stored and analyzed.

Different types of ERGs may be useful depending on the circumstances. A full-field ERG uses diffuse flashes of light to measure the overall electrical activity of the retina. This is most useful in diffuse retinal disorders. Even large defects can be missed with a full-field ERG since data from the entire retina is combined. Activity from the healthy portions of retina may outweigh information from the damaged retinal areas.¹
Once light from the ERG stimulus hits the retina, a waveform is recorded. The majority of the response comes from the outer retina. There is an initial negative movement, called the a-wave (Figure 2). The a-wave is mainly produced by the photoreceptors. This is followed by a positive spike known as the b-wave. The b-wave is made up of electrical pulses from the bipolar and Muller cells. Ganglion cells do not contribute much to the full-field ERG response.

Measurements are made (Figure 2), including the amplitude of the a-wave (from the initial starting point to the lowest point of the a-wave), the b-wave amplitude (from the lowest point of the a-wave to the highest point of the b-wave), and the implicit times (time from the flash to the lowest point of the a-wave or from the flash the height of the b-wave).

Figure 2: The waveform created by the full-field ERG. The a-wave is indicated by the black “a”, and the b-wave is indicated by the black “b”. The amplitude of the a-wave is shown by the red (a). The amplitude of the b-wave is indicated by the orange (a). The implicit times are shown with the blue (t).
Another type of ERG, the pattern ERG, uses a checkerboard pattern rather than a full-field flash stimulus. The pattern ERG mainly measures the retinal ganglion cells responses, which ultimately arise from photoreceptor cells. Because it measures responses from smaller areas of the retina, it is useful in determining macular dysfunction. Its ability to measure ganglion cell responses makes this type of testing useful in those with glaucoma and optic nerve disease. The pattern ERG waveform looks similar to that seen with the full-field ERG (Figure 3). The first trough is called N35. This is followed by the P50 peak and the N95 trough. N95 is thought to represent ganglion cell activity, whereas the P50 peak is more indicative of outer retinal function.

![Figure 3: A pattern ERG response.](image)

A focal ERG uses a flickering light to assess the foveal region. The standard stimulus is a 3 to 5° spot flickering at 30 to 45 Hz, but different spot sizes and flicker frequencies can be used. It is able measure cone photoreceptor and bipolar cell function. However, the readings are limited to a single area of the retina.

A multifocal ERG uses flickering hexagons of varying sizes to obtain responses from multiple, small areas of the retina. Either 61 or 103 focal responses over a 50° diameter around the fovea are recorded simultaneously. Obtaining individual readings over a large retinal area allows one
to compare responses inside and outside of a lesion. The multifocal ERG mainly measures cone, rather than rod, responses. The flicker rate and the room illumination that are used while performing the test help to isolate the cone responses.

The waveform obtained from a multifocal ERG appears similar to that obtained from a traditional full-field ERG. However, they are obtained and analyzed differently. One should not refer to the peaks and troughs seen in a multifocal ERG as a-waves and b-waves. Rather, the first depression is called N1 (Figure 4). This is primarily driven by cone photoreceptors. P1, mainly bipolar cell responses, is the first large peak. N2 is the second trough. Evaluation of the amplitude (between the first trough and the highest peak) and implicit time (onset to the first peak) can aid in determining if the patient has a disorder involving the outer retina.

![Waveform from a multifocal ERG response.](image)

**Figure 4:** The waveform from a multifocal ERG response.
Indications

One of the most valuable uses of a multifocal ERG is to help differentiate between various conditions. The multifocal ERG can help to distinguish diseases that affect the outer retinal layers from neurologic dysfunction affecting the ganglion cells or optic nerve. In many of these conditions, the retina and optic nerve appear normal. However, an abnormal multifocal ERG will be present with outer retinal disease. Conditions affecting ganglion cells or optic nerve, including glaucoma, will generally have a normal multifocal ERG.

Some of the most difficult cases are when patients have both a neurologic and retinal condition. The multifocal ERG can aid in determining the extent each condition is affecting the visual function.

A multifocal ERG can also aid in following the progression of retinal disease. This provides an objective way of following the patient’s condition. It is especially helpful if you are unable to obtain reliable visual field results. The multifocal ERG is one of the tests recommended for detecting early hydroxychloroquine toxicity, but it can be used for detecting toxicity of other medications, such as tamoxifen or ethambutol. Multifocal ERG can be useful in following patients after macular degeneration treatment. Additionally, studies have found multifocal ERG abnormalities prior to retinal vasculopathy in diabetic patients. Hopefully, with more studies, this will lead to earlier preventative treatment for patients with diabetic retinopathy.
Combined with the multifocal VEP, the multifocal ERG can be very valuable in evaluating functional vision loss. If the multifocal ERG is normal, a multifocal VEP should be performed to rule out optic nerve disease. If both are normal, functional vision loss is likely.

Because glaucoma mainly affects the inner retina, a multifocal ERG is usually not helpful. A pattern ERG will be more useful in detecting glaucomatous changes. A pattern ERG may also be useful in other optic nerve disorders, including compressive, inflammatory, ischemic, and hereditary conditions.

**Procedure**

The full-field ERG procedure involves dark or light adaptation and selecting certain stimuli to isolate either the rod or cone photoreceptors. A deep blue light after dark adaptation will isolate the rod response, while photopic conditions, a red stimulus, or a flicker of 30 Hz will isolate cone responses.

The procedure for performing a pattern or multifocal ERG is less time consuming. Some multifocal ERG equipment still requires a contact lens electrode be placed on the eye. However, it can be done with a foil or thread electrode that is placed between the lower lid and conjunctiva. Although I would recommend the use of topical anesthetics prior to placing the electrode, I was able to do the entire test sequence without anesthetic. At first it felt similar to a Schirmer strip (used for dry eye testing), but after a couple minutes I was able to ignore the sensation. After cleaning and applying a conductive paste, another electrode is placed on the earlobe (Figure 5).
The multifocal and pattern ERG are performed with the lights on. The patient focuses on the center of the screen. During the multifocal ERG procedure, they will see 103 hexagons that increase in size toward the periphery of the screen. The hexagons will appear to flicker or alternate between black and white (Figure 5). Patients will see a checkerboard pattern if performing a pattern ERG.

The computer continually takes reading for about 8 to 10 minutes. During the test, assure that the patient maintains fixation. If the patient is unable to see the fixation target, instruct them to fixate in the center of the screen. Poor fixation can result in diminished responses in the central 5 to 10 degrees. Looking at the area of the blind spot relative to the most sensitive area (highest peak) on the multifocal ERG can aid in determining if the patient was eccentrically fixating.

Because you want optimal image quality, have the patient wear their best correction for the 33 cm working distance. Bifocals or progressive lenses will not allow for good image quality over
the entire screen. Therefore, a trial frame should be used. Cataracts and other media opacities can cause reduced amplitude and increase the implicit time of both pattern and multifocal ERG results. This must be taken into account when evaluating the results.
Interpretation

The responses from a multifocal ERG are displayed on a 3-dimensional plot (See Figure 6). The highest peak (white color in Figure 6) represents the most sensitive area of the retina. In a healthy eye, this is the macula. The lowest sensitivity will be found at the optic nerve. This is typically a blue color.

**Figure 6: A 3D plot from a multifocal ERG.**

Because the 3D plot can be misleading, always look at the trace array (Figure 7). The multifocal waveform is shaped greatly by activity of the bipolar cells. Therefore, any damage at or before the bipolar cells will result in a diminished waveform amplitude. Ganglion cell damage will not affect the amplitude of the multifocal ERG wave. In looking at the waveform, it can be very helpful to compare responses between the two eyes.
The multifocal ERG can be compared to Humphrey 24-2 Visual Field results, as the area of retina being tested is similar. Assure that the visual field loss corresponds to the area of decreased amplitude on the multifocal ERG. In those with glaucoma, the multifocal ERG should appear normal in the area associated with the glaucomatous visual field loss.¹

Those with a normal amount of, but abnormally functioning, cones will have a delayed implicit time. A reduced number of functioning cones will result in decreased amplitude. Some retinal conditions have specific characteristic features that will be seen on multifocal ERG (Table 1).

**Table 1: Characteristic patterns seen with multifocal ERG.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Multifocal ERG characteristics</th>
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<tbody>
<tr>
<td>Acute idiopathic blind spot enlargement</td>
<td>Reduced amplitude or delayed implicit time⁷</td>
</tr>
<tr>
<td>Age-related macular degeneration</td>
<td>Reduced P1 amplitude and increased N1 latency³,⁸</td>
</tr>
<tr>
<td>Cone dystrophy</td>
<td>Decreased amplitude and delayed implicit time¹</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>Delayed implicit time⁹,¹¹</td>
</tr>
<tr>
<td>Melanoma-associated</td>
<td>Decreased amplitude in areas of VF loss¹</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Description</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Multiple evanescent white dot syndrome</td>
<td>Reduced amplitude in area around the blind spot(^{12})</td>
</tr>
<tr>
<td>Paraneoplastic retinopathy</td>
<td>Reduced amplitude in the central area(^{13})</td>
</tr>
<tr>
<td>Resolved central serous retinopathy</td>
<td>Depression of the mgERG(^{1})</td>
</tr>
<tr>
<td>Retinal artery occlusion</td>
<td>Reduced amplitude in area of the loss(^{1})</td>
</tr>
<tr>
<td>Retinal vein occlusion</td>
<td></td>
</tr>
<tr>
<td>Retinitis Pigmentosa</td>
<td>Delayed implicit time(^{1,10})</td>
</tr>
<tr>
<td>Stargardt’s disease</td>
<td>Reduced amplitude with normal implicit time(^{1})</td>
</tr>
<tr>
<td>Toxic retinopathy (hydroxychloroquine)</td>
<td>Reduced P1 and N1 amplitude and delayed implicit time(^{12,14,15})</td>
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Pattern ERG can be helpful in differentiating optic neuropathies. Optic nerve disease is more likely to alter the N95 trough, whereas retinal diseases are more likely to affect the P50 peak\(^{16-18}\).

In addition, there is a decreased N95 amplitude in those with multiple sclerosis, even without a history of optic neuritis\(^{19}\). Table 2 reviews the characteristics of pattern ERG with different optic neuropathies.

The pattern ERG may be useful in predicting the prognosis for visual function after surgery in those with compressive chiasmal lesions. Those with a normal N95 and P50 measurement are more likely to recover visual field loss following surgery\(^{16}\).

The pattern ERG is useful in diagnosing and following glaucoma. There is reduced amplitude that occurs prior to change on the visual field\(^{5}\) or optical coherence tomography (OCT)\(^{20}\). The implicit time is generally not affected in glaucoma\(^{5}\). This may allow for earlier intervention, decreasing the incidence of permanent loss of the nerve fiber layer.
There are a number of factors that make the analysis of ERGs difficult. Poor fixation or reduced retinal image quality can affect the results. Also, keep in mind that the amplitude reduces with age. Therefore, you must use age-matched controls when interpreting the results.

**Table 2: Characteristic seen with the pattern ERG.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pattern ERG characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression of the optic nerve or chiasm</td>
<td>Reduced P50 and N95 amplitudes or reduced N95 amplitude with sparing of the P50 amplitude</td>
</tr>
<tr>
<td>Demyelinating optic neuritis</td>
<td>Reduced N95 amplitude with sparing of the P50 component or reduction of both the N95 and P50 amplitude with recovery of the P50 amplitude upon remission</td>
</tr>
<tr>
<td>Dominant optic atrophy</td>
<td>Reduced N50 and N95 amplitude and delayed P50 implicit time</td>
</tr>
<tr>
<td>Leber hereditary optic neuropathy</td>
<td>Reduced N95 amplitude with preservation of the P50 component</td>
</tr>
<tr>
<td>Nonarteritic anterior ischemic optic neuropathy</td>
<td>Reduced N95 amplitude. The P50 amplitude and latency vary.</td>
</tr>
<tr>
<td>Toxic or nutritional optic neuropathy</td>
<td>Reduced N95 amplitude</td>
</tr>
</tbody>
</table>

**Visual Evoked Potential (VEP)**

The VEP records signals originate at the retina and end at the visual cortex, where the electrical potential is generated. It is very reliable in picking up optic nerve problems. Post-chiasmal reading may be less reliable.

Similar to the full-field ERG, the flash VEP illuminates the complete field and sums readings from the entire anterior visual pathway. Therefore, small defects are easily missed. The multifocal VEP takes simultaneous readings from smaller areas throughout the central visual
field. It uses a dartboard pattern made up of 60 regions. This pattern covers about the same area on the retina as a 24-2 Humphrey Visual Field.\textsuperscript{21} The multifocal VEP is better able to detect local defects as compared to a flash VEP and can be a useful adjunct to the clinical exam in patients with glaucoma or other optic neuropathies.

The flash VEP waveform is recorded as N75, the first trough; P100, the first peak; and N135, the second trough. These are analogous to the multifocal VEP waveform where you find an initial trough (C1) followed by a peak (C2).

**Indications**

The multifocal VEP is used to rule out functional vision loss and diagnose optic neuropathies. It is particularly useful in following those with multiple sclerosis, but the repeatability does allow one to monitor the progress of other optic neuropathies. It can be helpful in early detection and monitoring of patients with glaucoma.\textsuperscript{22} Multifocal VEP is also valuable in those who are unable to perform a reliable visual field.

**Procedure**

The multifocal VEP can be performed using the same equipment used for multifocal ERG testing, but the analysis is very different. The patient fixates a point in the center of a dartboard pattern. It is important to assure patient fixation throughout the test, as eccentric fixation will result in reduced amplitude in the central region. The test is performed monocularly on an undilated patient. The patient should wear their best corrected near prescription. Electrodes are placed in 3 areas: 4 cm above the inion (active electrode), at the inion (reference electrode), and
on the forehead (ground electrode). Some practitioners place two additional active electrodes, each 1 cm above and 4 cm lateral to the inion.\textsuperscript{21} This allows for detection of retrochiasmal disorders that cannot be detected if only one central electrode is used.

**Interpretation**

Because VEP amplitudes can vary from one person to the next, it is helpful to compare hemisphere readings from the same person.\textsuperscript{19} It is also valuable to compare inter-eye symmetry.\textsuperscript{21} Similar to the visual field analysis, 2 to 3 contiguous abnormalities are generally necessary to verify that a defect exists.

Figure 8 shows responses from a multifocal VEP. Probability plots, similar to that used with the Humphrey Visual Field, compare the VEP amplitude to normal controls (Figure 9). An intraocular comparison of amplitudes (Figure 9C) may be a more sensitive indicator of damage.\textsuperscript{21} These readings take the ratio of the amplitudes in each eye and compare this to control groups to obtain the significance levels.
Figure 8: Multifocal VEP responses. The right eye responses are shown in blue and the left eye responses are shown in red.

A.                                                B.                                                 C.

Figure 9: Multifocal VEP probability plots for the left (A), right (B), and both (C) eyes. Darker, more saturated colors indicate a defect with greater than 1% significance level. The less saturated, lighter colors are significant at the 5% level. The red colors indicate areas that the left eye is worse than the right eye. The blue colors indicate areas where the right eye was worse than the left eye.

While VEP measurements can be helpful if determining the presence of optic nerve disease, it is not always helpful in determining the cause. The P100 latency is prolonged in most optic nerve disease, but you can also get decreased amplitude. With optic neuritis the multifocal VEP appearance varies. Either or both the amplitude and implicit time may be affected. Ischemic optic neuropathy, however, will cause decreased amplitude but normal latency with multifocal VEP. VEP amplitude is reduced in those with optic nerve meningiomas, and the waveform is delayed with optic nerve gliomas. In cases of dominant optic atrophy and Leber hereditary optic neuropathy, the VEP responses are delayed. The amplitude can also be affected in
more severe cases of dominant optic atrophy. There is an amplitude reduction and lengthened implicit time with toxic or nutritional optic neuropathy.\textsuperscript{17} Papilledema will not cause VEP abnormalities.\textsuperscript{18} If a VEP abnormality is present in a patient with papilledema, you should suspect that the VEP readings are a result of the underlying cause of the papilledema or due to secondary optic atrophy. VEP amplitude is reduced after stroke.\textsuperscript{19} A delay in the VEP latency is seen in patients with Parkinson disease.\textsuperscript{24} This is reversible with L-DOPA therapy.

Multifocal VEP can also be a useful tool in the objective measure of progression in advanced glaucoma, particularly for those who are unable to perform a visual field.\textsuperscript{5} It can also detect damage prior to visual field loss.\textsuperscript{25} Generally, the amplitude is decreased, but there is no change in implicit time.\textsuperscript{22} Comparison between the two eyes is helpful in glaucoma patients.

The multifocal VEP results should be compared to the Humphrey Visual Field printout. The multifocal VEP shows good repeatability and correlation with visual field defects in those with glaucoma and compressive optic neuropathy.\textsuperscript{21,23} The multifocal VEP can be used to verify the visual field loss or to pick up loss that was not detected by the visual field.\textsuperscript{10}

A normal VEP is helpful in cases of functional vision loss, but an abnormal VEP does not necessarily mean an optic neuropathy is present.\textsuperscript{19} An abnormality can occur due to macular disease, improper refractive error, media opacity, or poor compliance.\textsuperscript{23} A flash VEP may be more useful if the patient has media opacities, poor fixation, or is not cooperative.
Conclusion

Electrophysiological testing can play an important part in the care of our patients. The multifocal ERG is particularly helpful in detecting subtle retinal disease. If the multifocal ERG results correspond with the visual field loss it is very likely that the patient’s vision loss is related to the retinal defect. Both the pattern ERG and multifocal VEP can be helpful in detecting glaucoma prior to visual field loss and with following the condition. Combining the multifocal ERG with the multifocal VEP will help establish an organic cause for vision loss and confirm the extent of the visual field loss. The multifocal VEP is additionally useful in those with multiple sclerosis, optic neuropathies, or glaucoma.

References


