

ISCEV standard for clinical electro-oculography (2010 update)

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Abstract The clinical electro-oculogram (EOG) is an electrophysiological test of function of the outer retina and retinal pigment epithelium (RPE) in which changes in electrical potential across the RPE are recorded during successive periods of dark and light adaptation. This document presents the 2010 EOG Standard from the International Society for Clinical

Electrophysiology of Vision (ISCEV: www.iscev.org). This revision has been reorganized and updated, but without changes to the testing protocol from the previous version published in 2006. It describes methods for recording the EOG in clinical applications and gives detailed guidance on technical requirements, practical issues, and reporting of results. It is intended to promote consistent quality of testing and reporting within and between clinical centers.

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<http://www.iscev.org>.

Keywords Arden ratio · ISCEV standards · Clinical electrophysiology · Electro-oculogram (EOG) · Light adaptation · Retinal pigment epithelium (RPE)

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Abbreviations

ERG Electroretinogram
FO Fast oscillation
RPE Retinal pigment epithelium

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This Standard is one of a series of ISCEV Standards and Guidelines for clinical electrophysiology of vision [1–8] available for download from www.iscev.org. This Standard supersedes previous versions of the ISCEV Standard for Clinical Electro-oculography first issued in 1993 and most recently revised in 2006 [1, 2]. This current Standard has been reorganized for greater clarity and to a format consistent with other ISCEV standards, and it contains updated information without changes to the 2006 testing protocol.

Clinical and research users of the EOG are encouraged to use the current Standard wherever possible, to achieve consistency of results within and between test centers. Where a method is used which deviates from the Standard, the deviations should be described together with any normative or reference data.

What is the EOG?

Electrophysiology of the outer retina in dark and light

There is a difference in electrical potential between the front and back of the eye, sometimes called the corneo-fundal potential or standing potential. This potential is mainly derived from the retinal pigment epithelium (RPE), and it changes in response to background levels of retinal illumination. The potential decreases for 8–10 min after switching to darkness. Subsequent retinal illumination causes an initial fall in the standing potential over 60–75 s (the fast oscillation), followed by a slow but larger rise over 7–14 min (the light response). These phenomena arise from ion permeability changes across ion channels in the basal RPE membrane that are controlled (at least in part) by the bestrophin gene. The clinical EOG measures indirectly the amplitude of the standing potential in the dark and then again at its maximum amplitude in the light. This is usually expressed as a ratio of the maximum (peak) amplitude in the light to the minimum (trough) amplitude in the dark, which is referred to as the light/dark ratio or Arden ratio. The behavior of the corneo-fundal potential in the normal eye is predictable in defined conditions, such as those described in this Standard. However, changing from prolonged darkness to light actually initiates a more extended series of changes in this potential that last for about 2 h in the form of a damped sinusoidal oscillation.

Diseases affecting the light response of the EOG

The light response is affected in diffuse disorders of the RPE and the photoreceptor layer of the retina including some characterized by rod dysfunction, chorio-retinal atrophy, and by inflammation. In most

of these disorders, there is correlation between effects on the EOG and on the electroretinogram (ERG), with the notable exception of disorders of the bestrophin gene, including Best vitelliform maculopathy, autosomal recessive bestrophinopathy, and autosomal dominant vitreoretinopathopathy (ADVIRC) in which the clinical EOG can be highly abnormal even in the presence of a normal ERG. The EOG may also be markedly depressed in acute zonal occult outer retinopathy (AZOOR).

Principles of clinical EOG measurement

The electrical potential across the RPE causes the front of the eye to be electrically positive compared with the back. As a result, potentials measured between electrodes at each side of an eye will change as the eye turns horizontally. The EOG method is widely used to record the eye movements, on the assumption that the corneo-fundal potential has a fixed amplitude. In the clinical EOG, we use defined eye movements to monitor changes in the corneo-fundal potential. If the test subject looks alternately at targets separated by a fixed angle, the potential recorded from electrodes near the canthi will resemble a square wave; the amplitude of this square wave will be a fixed proportion of the corneo-fundal potential (see Fig. 1). During a light/dark cycle, changes in this indirectly measured potential are directly proportional to the source potentials across the RPE.

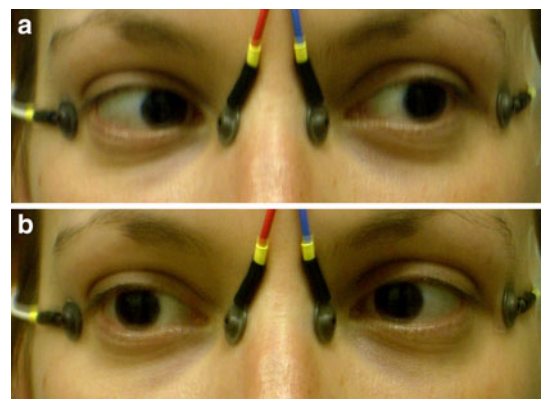


Fig. 1 Electrode positions for Standard EOG recording. **a** looking left makes left electrodes cornea positive. **b** looking right makes right electrodes positive

The standard method

Technical requirements

Electrodes

These should be relatively nonpolarizable skin electrodes, such as standard medical EEG or ECG electrodes, of a size appropriate for attachment to the side of the nose and near the outer canthi. If baseline drift is excessive, less polarizable electrodes may be necessary.

Stimulator

The EOG should be performed using a full-field (Ganzfeld) dome. The Ganzfeld stimulator should have a comfortable head/chin rest and two red fixation lights located 15° left and right of center. The fixation lights should be bright when the light adapting background is on, and dim (to be just visible) in the dark.

Light and dark

The dark phase should take place in total darkness, with the fixation lights dimmed to the minimum necessary to enable fixation.

The light phase requires even lighting throughout the dome. This adapting light should appear white and have a luminance of 100 photopic cd/m^2 as measured with a photometer equipped with a photopic filter. To account for minor variability in equipment and calibration, a tolerance of $\pm 10\%$ (0.05 log units) is acceptable within the standard. Calibration of the Ganzfeld stimulator should be carried out periodically, e.g., once a year. Modest room lighting may be turned on during the light phase as long as ambient luminance is less than that in the bowl.

Note that adapting light sources of different types, such as tungsten, halogen, LED, and fluorescent, have different spectral characteristics and the color may change with brightness. This makes the definition of standard lighting inherently imprecise, although for practical purposes, most “white” light of the correct luminance will give very similar results. We suggest that reports indicate the type of light source.

Amplification and filtering

Amplifiers should have a band pass between either 0 (d. c.) and 30 Hz or 0.1 and 30 Hz to make recordings of saccadic eye movements appear as square waves. For a 30° saccade, the typical EOG amplitude is between 250 and 1,000 μV with an essential frequency content of 0–30 Hz. In theory, the ideal recording technique is d. c. amplification but this is generally impractical because of base line drift. Thus, we recommend a.c. recording with a 0.1 Hz high-pass filter (i.e., a filter that passes only frequencies above 0.1 Hz). If the high pass filter frequency is higher (e.g., 0.5 Hz), it will distort the square waves, making identification of overshoot and stepped saccades very difficult (see Fig. 2). Setting the low-pass filter above 30 Hz serves only to show more noise in the response (which may affect automatic cursor placement regimes).

The operator should be able to see the saccadic recordings as they occur. This monitoring ensures there are no artifactual signals, no problems such as

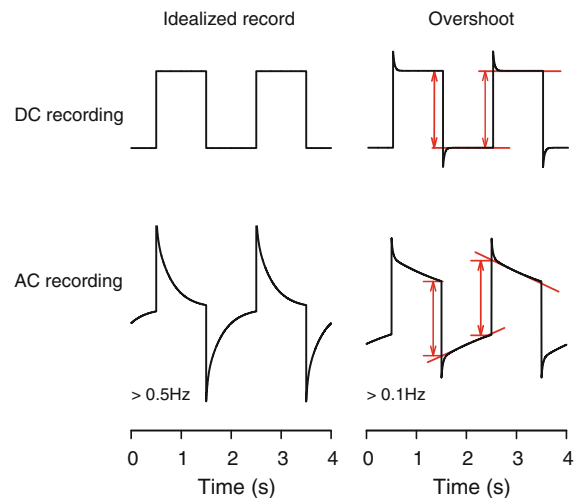


Fig. 2 Idealized saccadic recording with d. c. amplification (*upper*) and a. c. amplification (*lower*). The d. c. records show ideal square waves (*left*) and square waves with modest overshoot (*right*). The amplitude of the latter should be measured from the plateaus (*red arrows*) not the peaks. A. c. records have less drift, but the square-wave shape of the responses gets distorted progressively as lower frequencies are filtered out. Filtering at 0.5–30 Hz (*left*) distorts square waves too much for amplitude measurement or for recognition of overshoot. Filtering at 0.1–30 Hz (*right*) distorts square waves only slightly, so that plateaus and amplitudes can still be accurately recognized and recorded (*red arrows*)

amplifier saturation (that can be corrected by adjusting amplifier gain) and that subjects are compliant with the task.

Preparation of the test subject

Pupils

The pupils should be dilated maximally before testing and their size recorded. If full pupil dilation is impossible or undesirable, an attempt should be made to increase the adapting luminance so that the same retinal illumination is maintained. The amount of light passing through the pupil (measured in Trolands) is simply the product of luminance (cd/m^2) and pupil area (mm^2). For example, to produce the same effect upon the retina, twice as much dome luminance is required with a 5 mm pupil (roughly 20 mm^2) than with a 7 mm pupil (roughly 40 mm^2).

The report should describe any deviations from the Standard.

Electrodes

After suitable skin preparation, place recording electrodes close to the outer and inner canthi of each eye as in Fig. 1. Connect the electrodes from each eye to separate channels of a differential amplifier. A ground electrode should be placed at an indifferent point, e.g., on the forehead. The impedance between any pair of electrodes should not exceed $5 \text{ k}\Omega$. The electrodes, amplifier, and impedance meter must be approved for medical use.

Pre-exposure to light

The test subject should be in ordinary room illumination for as long as possible before the test, ideally upwards of an hour. We advise that examinations such as indirect ophthalmoscopy and fundus photography be avoided during this period, but if such examinations have been performed, a recovery time of at least 30 min is required. As near as is practical, the pre-test light exposure should be the same for all subjects.

Explanations

Explain the procedure fully, noting that the head position should not change, the eyes should move

without head movement, and the alternation of the fixation lights should not be anticipated. Practice the procedure with the recording system to check on the stability and quality of the recorded saccades.

Clinical recording

Recording of saccades

Fixation lights should alternate once per second, for 10 s out of every minute. The EOG potentials are recorded only during this period. There should be a warning, verbal or automatic, of the impending start of each recording period to ensure readiness of both test subject and operator. However, there should be no auditory cues at each alternation of the fixation lights, to avoid triggering eye movements without actual fixation.

Dark phase

Maintain total darkness for 15 min, except for the dim fixation lights. EOG recordings should be made once a minute (for 10 s, as specified in the preceding paragraph). The operator should have a concurrent view of the recordings to check for patient compliance and for errors such as noise or overshoot.

Light phase

The dome background light of $100 \text{ photopic cd}/\text{m}^2$ should be turned on to “trigger” the initial light phase response and should remain on for the duration of the light phase. However, if photophobia is severe, it is recommended that the operator increases the luminance gradually over a short period (e.g., 20 s). Longer ramps (e.g., lasting minutes) will alter the responses. Continue the recording for 10 s out of every minute (as above) for at least 15 min to register the presence or the absence of a light peak. Ensure the test subject is seated with the forehead forward in the headrest of the Ganzfeld dome for the duration of the test, with eyes open.

Patient compliance

Test subjects will have difficulty performing saccadic movements if they cannot fixate reliably because of poor central vision, diplopia, or ocular motility problems (including nystagmus). Patients with diplopia may be advised to look between the pair of

images, or one eye can be patched if the suspected retinal disorder is bilateral. Patients who are very young or those with learning disabilities may not be able to perform an EOG. Physical disabilities may prevent proper positioning.

Even for “normal” subjects, compliance can vary from fatigue or inattention. Common problems are drifting of the head back from the dome, irregular eye movements during the recording, or eye closure during the light phase. These can be minimized by watching the patient and by having a real-time view of the EOG recording. Monitoring the patient’s eyes via an infrared camera is useful if available, but direct observation can suffice during the light phase. In most cases, gentle coaching and reminders will remedy difficulty with the task.

Unreliable performance makes the interpretation of records difficult, but it does not necessarily mean that useful information cannot be obtained. Just one or two reliable records near the times of the dark trough and light peak may be enough to demonstrate whether there is a light rise or not. This is particularly important with children, since compliance is often variable, but by age 7 or 8, many children can cooperate sufficiently to give valid information.

Analysis and reporting

Saccadic amplitude

Measure the EOG amplitude in μV , either manually or by a computer algorithm. Overshoot or irregular (artifactual) saccades should not be measured or included in calculations (see Fig. 2). The average of the measurable amplitudes should be calculated within each 10 s recording period. If a computer algorithm is used, it is important to ensure that the values returned represent true EOG amplitudes and not artifactual records. Particular causes of unreliability are overshoot (see Fig. 2), stepped saccades, missing saccades, inverse saccades (eye movements opposite to the direction of the fixation lights), or eccentric fixation in which the saccade length may switch between two and more values. When measured manually, these difficulties are fairly obvious.

Dark trough and light peak: smoothing

The average EOG amplitude calculated from each 10 s trial should be plotted. However, there is always

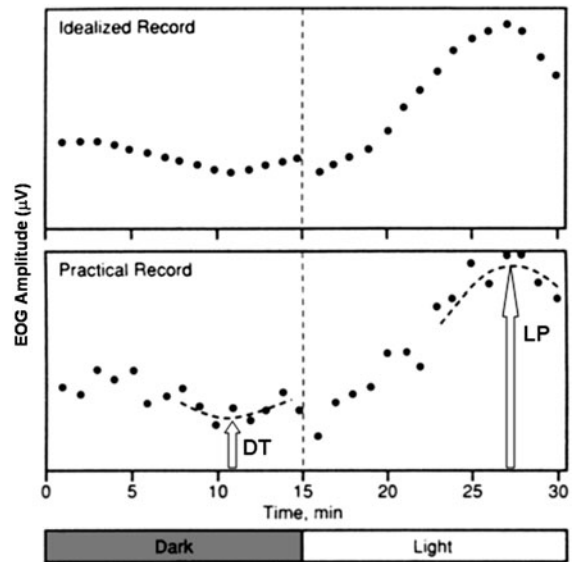


Fig. 3 Idealized (*upper*) and realistic (*lower*) EOG amplitude versus time curves for a healthy subject. The realistic curve has noise and variability, but it is not difficult to estimate the underlying physiologic curve (*dashed lines*). *Arrows* show the dark trough (DT) and light peak (LP), which should reflect the physiologic curve rather than individual points that might be higher or lower

“noise” in real-life recordings, and the goal of EOG measurement is to record the physiologic trough and peak, rather than lowest or highest numerical points that may represent artifact or noise or occur at an unlikely point in time (Fig. 3). Thus, the first critical step is that the underlying physiologic curve be recognized and drawn to derive a meaningful trough and peak. This may use a curve-fitting algorithm, a ‘flexicurve’ (curve-fitting ruler) or just a practiced hand (see Fig. 3), and it relies on knowledge that both trough and peak are most likely to occur in the vicinity of 10 min after the change in lighting. It is helpful if uncertain or artifactual values can be identified and marked at the time of recording, so that they can be ignored later when curve fitting.

Standing potentials

This Standard recommends reporting the minimum standing potential (i.e., the EOG amplitude at the dark trough). This value is not often used in diagnosis, but if it is abnormally low, it may indicate an inactive retina (e.g., total retinal detachment), and a calculated Arden ratio will be invalid because of the

small size of the denominator. Normal values for the minimum standing potential should be established, but as a guide, standing potentials less than 150 μV are most likely to produce unreliable Arden ratios.

Arden ratio calculation

The Arden ratio (light/dark ratio) is the ratio between the light peak and the dark trough of the smoothed (physiologic) EOG record (Fig. 3).

Reporting

Clinical reports should state the Arden ratio, the dark trough amplitude in μV , the time from start of the light phase to the light peak (if present), the pupil size, and the type of adapting light source. The report should also state whether any difficulties were encountered during the test session which may affect confidence in the results, such as head movements or inconsistent saccadic eye movements.

Normative data

No fully authenticated normal reference data are available at present for the Standard EOG. However, from a review of existing published data, Arden ratios <1.5 are generally reported as abnormally low, and those >2.0 are generally reported as normal; ratios between 1.5 and 2.0 may be reported as borderline. Users are strongly urged to establish their own norms over time.

Interaction between eyes

The EOG potentials from one eye can contaminate the response from the other. The magnitude of this effect is approximately 15% with electrodes placed on each side of the nose close to the inner canthi. This effect rises to about 40% if the electrodes touch (i.e., act as a common central electrode on the bridge of the nose). This crosstalk can give misleading results in cases of an electrically inactive eye (e.g., total retinal detachment), or absent eye, because the defective eye will appear to have the same Arden ratio as for the fellow eye, albeit on a much smaller standing potential. An even more confusing situation can occur when the eyes have similar standing potentials but different Arden ratios. In these cases, the measured Arden ratio

from the better eye is enhanced at the expense of that from the weaker eye, which can in fact have a measured Arden ratio of less than 1.0, solely due to crosstalk.

Deviation from standard

This Standard represents a basic minimum clinical procedure. If a laboratory chooses techniques that vary from the Standard, it is important to cite this document and specify any deviations, such as a different luminance level for the adapting light.

Additional test: fast oscillation

Some centers also measure the fast oscillation (FO), in conjunction with the clinical EOG. This response has the opposite polarity to the EOG. Light onset causes an initial decrease in the standing potential, the light trough (LT), that recovers after 30–40 s. This is caused by a drop in intracellular chloride that alters ion transport across the basolateral RPE membrane, resulting in a hyperpolarization. Light offset causes an initial increase in the standing potential, the dark rise (DR).

The FO is recorded using the same technical specifications as the clinical EOG (amplifier, electrode placement, fixation targets, background luminance, and 1 per second saccades). To record the FO, saccades and the recording is continuous without interruption for the duration of the test. The FO test protocol consists of light (100 cd/m^2) and dark periods alternated every 60 s to induce the FOs, which have a near sinusoidal appearance. During each light interval, a light trough (LT) develops and begins to rise again after 30–40 s. The subsequent interval of darkness results in a dark rise (DR) at 30–40 s following the onset of darkness. The total number of light–dark intervals should be at least 4, making a total test time of 8 min. Pre-adaptation does not affect the FO, and so this test can be performed either independently or in conjunction with the clinical EOG.

Figure 4 shows an idealized representation of the FO cycles. The ratio of DP to LT of the FO should be reported. The normal DP/LT amplitude ratio is typically between 1.05 and 1.30. It should be noted that high blood glucose levels increase the FO amplitudes.

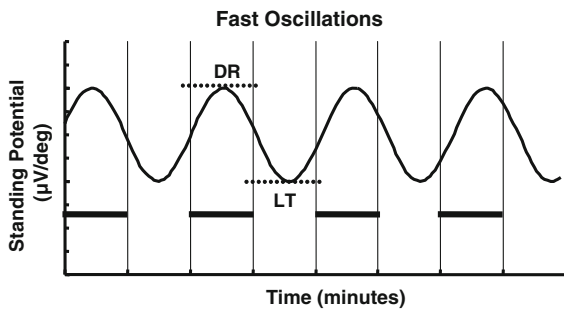


Fig. 4 Idealized representation of fast oscillations (FO). In the dark intervals (*black bars*), the standing potential increases to a dark rise maximum (DR). Following light onset, the standing potential falls to a light trough (LT). The FO ratio of the DR:LT standing potentials should be recorded

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