

ISCEV Standard for Clinical Electro-oculography (EOG) 2006

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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 the change in the electrical potential between the cornea and the ocular fundus is recorded during successive periods of dark and light adaptation. This document sets out a Standard Method for performance of the test, and also gives detailed guidance on technical and practical issues, and on reporting test results. The main object of the Standard is to promote consistent quality of testing and reporting within

and between centres. This 2006 Standard, from the International Society for Clinical Electrophysiology of Vision (ISCEV: www.iscev.org), is a revision of the previous Standard published in 1993, and reviewed and re-issued in 1998.

Keywords Arden ratio · Clinical standards · Electro-oculogram · Light adaptation · Retinal pigment epithelium

Abbreviations

ERG Electroretinogram
FO Fast oscillation
RPE Retinal pigment epithelium

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Purpose and use of this Standard

This Standard is one of a series of Standards and Guidelines for electrophysiology of vision [1–8] available for download from www.iscev.org, and is a revision of the ISCEV Standard for Clinical Electro-oculography (first issued 1993 – re-approved 1998) [1, 2], which provides a Standard Method for measurement of the electro-oculogram (EOG). Also included is advice on possible variations on the Standard Method, additional tests, and comment on the procedures recommended. The major change in this current

standard compared with the earlier EOG standards is that it recommends one single standard testing protocol and measurement strategy.

Clinical and research users of the clinical EOG are encouraged to use the current Standard Method where possible, to achieve consistency of results within and between test centres. Reports of EOG recordings performed to the Standard Method given here should cite this 2006 Standard. Where a method is used which deviates from the Standard Method, the deviations should be stated, together with any normative or reference data. Where the method used conforms to a previous EOG Standard, this may be cited instead.

EOG origins, pathological effects, and principles of measurement

Electrophysiology of the RPE in dark and light adaptation

The eye has a standing electrical potential between front and back, sometimes called the corneo-fundal potential. The potential is mainly derived from the retinal pigment epithelium (RPE), and it changes in response to retinal illumination. The potential decreases for 8–10 min in darkness. Subsequent retinal illumination causes an initial fall in the standing potential over 60–75 s (the fast oscillation (FO)), followed by a slow rise for 7–14 min (the light response). These phenomena arise from ion permeability changes across the basal RPE membrane. The clinical electro-oculogram (EOG) makes an indirect measurement of the minimum amplitude of the standing potential in the dark and then again at its peak after the light rise. This is usually expressed as a ratio of ‘light peak to dark trough’ and referred to as the Arden ratio. The behaviour of the corneo-fundal potential in the normal eye is predictable in defined conditions, such as those described in this Standard, but changing from dark to light actually initiates a triggered response extending for about 2 h in the form of a diminishing 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 characterised by rod dysfunction, or chorio-retinal atrophic and inflammatory diseases. In most of these there is correlation with the electroretinogram (ERG), except notably in the case of Best’s vitelliform maculopathy, in which the clinical EOG is usually highly abnormal in the presence of a normal ERG.

Measurement of the clinical EOG

The potential across the RPE causes the front of the eye to be electrically positive compared to the back. As a result, potentials measured between two electrodes placed on the skin at each side of an eye will change as the eye turns from left to right. The EOG method is used widely to record eye movements, on the assumption of unchanging corneo-fundal potentials. In the clinical EOG described here, we use defined eye movements to monitor the changes in corneo-fundal potential. If the test subject looks alternately at targets a fixed angle apart, the potential recorded from the skin resembles a square wave whose amplitude will be a fixed proportion of the corneo-fundal potential. During a light/dark cycle, this indirectly measured potential will change in the same way as the source potentials, so that the Arden ratios (and timing of peaks etc.) will be a close approximation to the average changes occurring across the RPE.

The Standard Method

This section outlines the Standard Clinical EOG method, definitions, explanations, and instrument specifications. Further notes regarding testing strategies are given in later sections.

Pupils Apply dilating drops before any other action to allow pupil dilation to be relatively complete by the start of the test (see notes

below). Their size should be checked at the start and end of the test and recorded at the end of the test.

Electrodes After suitable skin preparation, place small recording electrodes, close to the canthi of each eye as in Fig. 1. Connect the electrodes from each eye to separate channels of a differential amplifier. The ‘ground’ electrode can be placed on the forehead. The impedance between any pair of electrodes should not exceed 5 k Ω . The electrodes, amplifier and impedance meter must be approved for medical use.

Amplifier This should have a band pass of either 0 (d.c.) to 30 Hz, or 0.1 to 30 Hz, to provide recordings of the saccades which appear as square waves.

Full field (Ganzfeld) stimulator This should have a comfortable head/chin rest, and two red fixation lights 15 degrees left and right of centre. The fixation lights should be bright when the light adapting background is on, and as dim as practical in the dark.

Pre-adaptation The test subject should be in stable indoor lighting for as long as possible before the test, and should not be exposed to any large changes in lighting (lighter/darker) during this period, such as indirect ophthalmoscopy. As near as is practical, the pre-test light exposure should be the same for all test subjects.

Preparing the test subject Explain the procedure including, ‘chin/head on rest/restraint in stimulator, 15 min dark, 15 min light, fixation

lights alternate in simple rhythmic manner, for 10 s each minute, when lights change, move eyes in single sweep to next one, do not turn head, do not anticipate the changes’. Practice the procedure with the recording system on and coach the subject if there is head movement, overshoot, stepping, or anticipation.

Dark phase In total darkness for 15 min, except for the dim fixation lights, alternate the fixation lights every 1 s for 10 s every 1 min, and record the resulting EOG potentials. The test subject should remain looking into the stimulator the whole time if possible, and should be warned of the start of each measurement sequence to ensure attention. The operator must have an instant view of the recordings to check for patient compliance, and errors such as overshoot.

Light phase Bring on the ganzfeld background light of 100 photopic cd/m². If necessary, bring this on gradually over a short period (e.g. 20 s) for patient comfort, especially in cases of photophobia. Continue recording every 1 min as above. Keep the test subject forward in the stimulator bowl for the whole time and with eyes open.

This completes the procedure for the test subject.

Measure the amplitude of the EOG Taking care to remove the effects of overshoot (see Fig. 2 and notes below) and stepped saccades, measure the EOG amplitude in μ V, either manually or by a computer algorithm. Calculate the average of the amplitudes in each 10 s trial.

Plot the change in the responses Plot the average amplitude of the EOG in μ V on a graph representing the 30 min of the test. Ignore any points known to be incorrect (e.g. subject did not follow the fixation lights properly), and identify the underlying curve (see notes) as in Fig. 3 (lower panel).

Calculate the Arden ratio This is the ratio between the peak and trough of the *underlying curve*, not the maximum and minimum recorded values.

Report As a basic factual report state the Arden ratio, the first (dark) trough amplitude in μ V, the time from start of the light phase to the peak (if present), the pupil size, and the type of adapting light source. The report should also state

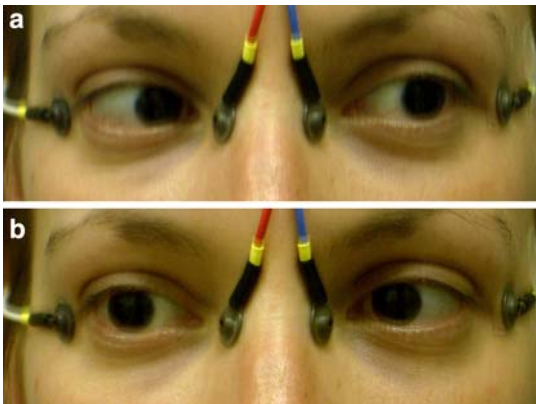


Fig. 1 (a and b). Recording electrode positions

Fig. 2 Idealised saccadic recording with d.c. amplifier (top) and example a.c. coupled amplifier with high pass filter at 0.5 Hz and 0.1 Hz. Overshoot is hard to recognise using 0.5 Hz

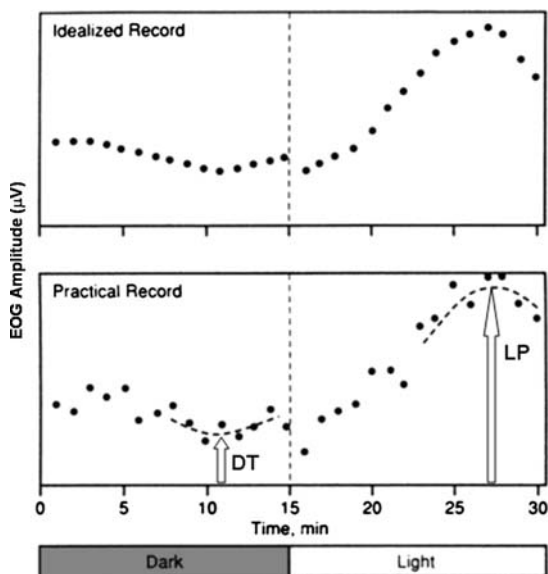
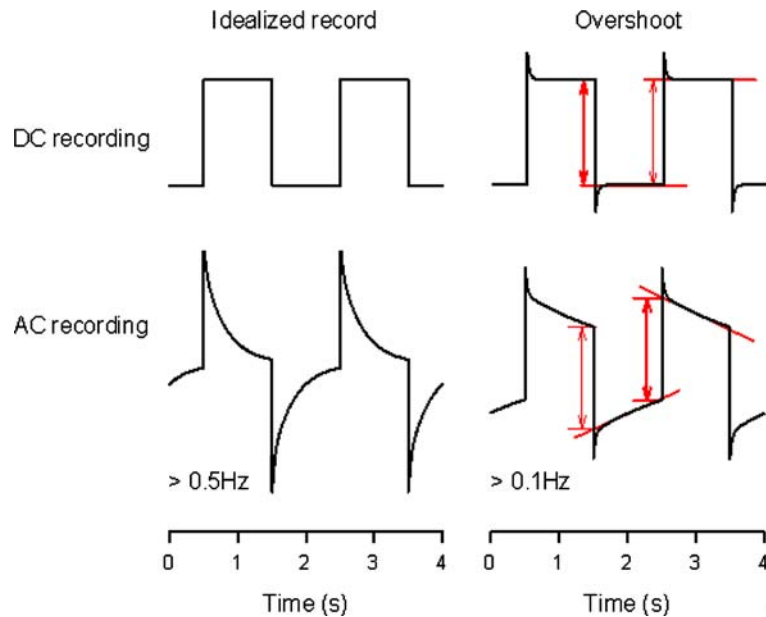


Fig. 3 Idealised (underlying) EOG response (top) and practical response with noise and trial/trial variability. Arrows show the dark trough (DT) and light peak (LP). The underlying curve must be estimated before recording the Arden ratio (LP/DT)

any difficulties which were encountered during the test session which may affect confidence in the results, such as the test subject's difficulty in performing the test.

Deviation from the Standard

This Standard represents a basic or core procedure. If a laboratory chooses a procedure which varies from the Standard Method above, it is critical to cite this Standard, but specify the deviations from the Standard Method, such as different luminance level for the adapting light. If a statistical report is given, then this must be supported by reference data obtained under the same conditions.

Additional tests

Some centres measure the 'Fast Oscillation' (FO), often in conjunction with the Clinical EOG.

The fast oscillations:

The fast oscillations (FOs) have the opposite polarity to the light rise of the Standard Clinical EOG. At light onset there is a decrease in the standing potential that recovers 30–40 s after light onset. This decrease, the 'light-trough' (LT), is caused by a decrease in intracellular Cl^- that results in a decrease of Cl^- transport across the

basolateral membrane resulting in a hyperpolarisation of the RPE basal membrane.

The FO is recorded using the same parameters as for the clinical EOG (amplification, electrode placement and stimulus light intensity). However, recordings should be made continuously as the subject executes regular horizontal saccades at 1/s. Alternating light and dark for 60 s each induces the FOs, which have a near sinusoidal appearance. During the 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 next interval of light induces another light trough. The total number of light-dark intervals should be at least 4 with 60 s periods of light and dark, 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, provided pre-adaptation conditions for the latter are consistent within the lab.

Figure 4 shows a schematic idealised representation of the FO cycle, from which the ratio of DP:LT should be reported. The normal amplitude ratio is typically between 1.05 and 1.30. However, at present each laboratory should obtain and use their own reference data. It should be noted that high blood glucose levels increase the FO amplitudes.

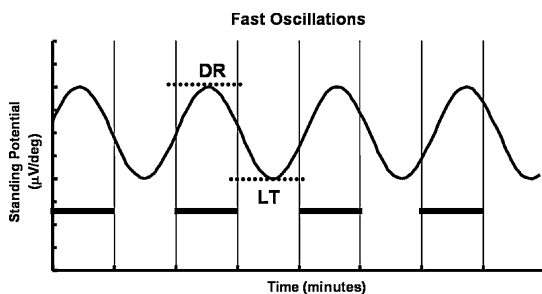


Fig. 4 Idealised representation of fast oscillations (FO). In the dark intervals (black bars) the standing potential increases to a dark rise maximum (DR). Following light onset the standing potential falls to a light trough (LT). The FO ratio of the DR:LT standing potentials should be recorded

Practical notes, instruments and definitions (alphabetical)

Amplifiers For a 30 degree saccade, the typical EOG amplitudes are between 250 and 1000 μV with essential frequency content of 0 to 30 Hz. With such signal amplitudes, no special shielding nor interference protection should be necessary. Medical grade amplifiers intended for human physiological recording are required to be ‘electrically isolated’ to prevent any risk of electric shock to the patient via the recording electrodes. Laboratory grade amplifiers may not have this protection. To obtain recordings of saccadic movements as a ‘square wave’ (the ideal) requires a d.c. amplifier (i.e. no high pass filter) but there are operational penalties in terms of base line shift due to electrode polarisation and movement, which can be partially eliminated by the use a high pass filter (e.g. 0.1 Hz). If a higher frequency is used (e.g. 0.5 Hz) there is considerable ‘droop’ of the square wave, making identification of overshoot and stepped saccades more difficult (see Fig. 2). For the low pass filter, 30 Hz is sufficient. Including higher frequencies adds noise to the response (e.g. EMG) and since most automatic cursor placement regimes find the lowest and highest parts of the wave, this exaggerates the recorded amplitudes. Since both the peak and the trough amplitudes will be equally exaggerated the Arden ratio will be underestimated. For guidance on verifying amplifier performance, see reference [3].

Amplifier saturation EOG potentials measured during saccadic eye movements as in the Standard Clinical Method can vary by about 5:1 in amplitude between subjects, which, with the light rise, may mean a total amplitude range of up to 15:1. Thus, the operator must be able to see the recordings of the saccades to ensure saturation does not occur, and to adjust the amplifier gain settings accordingly.

Arden ratio Using the Standard clinical EOG method described here, the Arden ratio is the peak EOG amplitude occurring in the light phase, divided by the minimum amplitude during the dark phase. The peak and trough values must be measured from the ‘underlying curve’ as shown on Fig. 3, not from individual measurements.

Compliance of the patient Test subjects will have difficulty performing the saccadic movements if they do not have good central vision, or suffer from diplopia or dysconjugate eye movements, have nystagmus, are very young, or are infirm and are unable to take up the physical positions required for the duration of the tests. Some patients also suffer claustrophobia or fear of the dark, and so the testing must be performed in such a way as to minimise these fears. Real-time view of the EOG potentials, and infrared camera view of the patient's eyes, are very useful in ensuring full compliance. In most cases, coaching under observation can remedy poor co-operation. A common issue is the patient closing eyes during the light phase, which can be seen by a camera.

The cost of unreliable performance is that the margins of error are widened. This does not mean that no information can be gleaned. If the suspected disorder is one with a clear test outcome, it may be possible to make the diagnosis on one or two reliable trials performed near the time of the trough and the peak, to ensure that there is indeed a light rise of some amplitude, or not.

Diplopia Test subjects often find the fixation lights too near for them to achieve convergence. The subject may be advised to look between the pair of images in cases of intractable diplopia. Subjects with ocular motility problems are likely to give unreliable results. If the suspected retinal disorder is bilateral, it is acceptable to patch one eye to perform the tests (see the notes on interaction between eyes below).

Electrodes Recording the EOG is relatively undemanding as regards the electrodes. These should be relatively non-polarisable such as standard medical EEG or ECG electrodes, of a size appropriate for attachment to the side of the nose. If baseline drift is excessive, less polarisable electrodes may be necessary.

Fixation targets These should be small, red, and adjustable in brightness so that they can be seen clearly by all subjects above the background illumination, and to be dim (just visible to the test subject) in darkness.

Full field (Ganzfeld) stimulator This should be as large as practicable to allow adequate distance

from eye to fixation lights. It should have a chin rest and forehead bar to ensure stable head position, and it should have fixation lights 15 degree each side of centre. The background intensity should be stable and 'visibly white' (see notes on Light below).

Interaction between eyes The EOG potentials from one eye will contaminate the response from the other. This is approximately 15% with electrodes placed on each side of the nose close to the inner canthi, rising to about 40% as they come close together and then touch (e.g. becoming a common central electrode placed on the bridge of the nose). This can give misleading results in cases of an electrically inactive (e.g. total retinal detachment), or absent eye, in which case the defective eye appears to have the same Arden ratio as for the fellow eye, albeit on a much smaller apparent standing potential. More confusing is 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 appear to have an Arden ratio of less than 1.0, solely due to interaction.

Light

Luminance For the light phase the luminance of the full field adapting light should be 100 photopic cd/m^2 as measured with a photometer (photopic filter) with a traceable calibration (see also notes on pupil dilation below). The calibration of the ganzfeld stimulator should be carried out periodically, e.g. once a year, and corrective action applied (see ref [3] for guidance). Modest room lighting may be turned on during the light phase when the impact on the effective luminance in the bowl should be negligible with the test subject looking into the bowl.

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

Colour There are several possible sources of adapting light such as tungsten, halogen, LED, and fluorescent. For a commercial recording system, the type will be stated in the manufacturer's

literature. Spectrally these are quite different, and the spectra for tungsten and halogen also change with brightness. This issue makes the definition of a single Standard Method for recording the clinical EOG difficult at present, and therefore all reports should state the type of light source used. If the user has additional data, such as colour temperature, or scotopic luminance, then this should be stated.

Normative data/reference range At present there is no standard international reference range for the clinical EOG. With the introduction of this Standard (The Standard Clinical EOG Method 2006) there is a greater possibility of developing and comparing normative data (see notes on reporting).

Photophobia The EOG ‘light rise’ is a ‘triggered’ response, and is assumed to start from the onset of the light phase. Some test subjects will find the light too bright and it may be necessary to bring the adapting light up gradually over, say, a 20-second period. If so, this variation should be stated. If the adapting light is brought on very slowly (e.g. minutes), the response is changed.

Plotting The average EOG amplitude calculated from each 10-second trial should be plotted (see Fig. 3). The first critical step is that the underlying physiologic curve is recognised and drawn for derivation of the trough and peak. This may require a curve fitting algorithm or a traditional ‘flexicurve’ (curve fitting ruler) on paper. Only then should the Arden ratio be calculated. It is helpful if any uncertain values have been identified and marked at the time of recording, so that they can be ignored when identifying the underlying curve.

Pupil dilation Having dilated pupils means less variability in the light entering the eye. There may be occasions when full pupil dilation is impossible or undesirable. If pupils are not artificially dilated, then the report should state this. An attempt should be made to adjust the adapting luminance to accommodate smaller or variable pupils, and this luminance should be quoted (it is usual to try to achieve the same value in Trolands, as for dilated pupils). In many cases useful diagnostic information can be obtained without dilated pupils, especially with extreme

results (no light rise, strong light rise). Intermediate results for the Arden ratio will obviously be of less value with undilated and therefore variable pupil sizes.

Reporting

Basic factual report This should include the Arden ratio, the first (dark) trough amplitude in μV , the time from the start of the light phase to the light peak (if present), the pupil size at the end of the test, and the type of adapting light source.

Statistical report This should show how the calculated Arden ratio relates to a quoted reference range. If the reference range was obtained with any different test parameters, this should be explained.

No fully authenticated normal reference data is available currently for the Standard Clinical EOG method given above. However, from a review of existing published data, Arden ratios <1.5 are reported as being abnormally low, and those >2.0 are reported as probably normal, and in between as borderline. This guidance may be useful in the absence of local normative data, but the values do not constitute validated diagnostic criteria.

Saccade measurement Use a scale or electronic calliper to measure the change in EOG potential resulting from each saccade, and calculate an average for each 10 second trial. The average should include only those measurements judged to be reliable. Alternative measurement methods may be used, including computer algorithms.

If a computer algorithm is used there is a need to ensure that the values returned properly represent the true EOG amplitudes. Each algorithm is likely to make some mistakes. Fortunately, the final dark/light response curve will form an ‘average of averages’ in which the influence of a few errors should be swamped by the remaining data.

Particular causes of unreliability are overshoot (see Fig. 2), stepped saccades, missing saccades, inverse saccades (eyes go opposite way to fixation lights), and eccentric fixation in which the saccade length switches between two or more values. When measuring manually, these difficulties are fairly obvious.

Standing potentials This Standard recommends the reporting of the minimum standing potential (dark trough minimum), taken from the underlying response curve, *not* the minimum recorded value. This value is not often used in diagnosis at present, but if the value is abnormally low it may indicate an inactive retina (e.g. total retinal detachment), and the calculated Arden ratio may be unreliable because of the low value of the divisor in the ratio. Normal values for the minimum standing potential should be established, but as a guide, minimum standing potentials less than 150 μV should be treated as low, and more likely to produce unreliable Arden ratios.

Warning of start of each trial There should be a warning, verbal or automatic, of the impending start of each trial, to ensure readiness of both test subject and operator. Some users have sounds (beeps) to co-incide with the alternations of the fixation lights. However, it may be better to rely solely on the visual stimuli, to avoid the possibility of alternation without actual fixation.

History and acknowledgements

This Standard forms part of series of Standards, Recommendations and Guidelines prepared by the International Society for Clinical Electrophysiology of Vision (ISCEV):

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