Principles and Practice of Clinical Electrophysiology of Vision

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A Year Book Medical Publishers imprint of Mosby-Year Book, Inc.

Mosby-Year Book, Inc.
11830 Westline Industrial Drive
St. Louis, MO 63146

1 2 3 4 5 6 7 8 9 0 CL CL MV 95 94 93 92 91

Library of Congress Cataloging-in-Publication Data
Principles and practice of visual electrophysiology / [edited by]
John R. Heckenlively, Geoffrey B. Arden.
p. cm.
Includes bibliographical references.
Includes index.
ISBN 0-8151-4290-0
1. Electroretinography. 2. Electrooculography. 3. Visual evoked response. I. Heckenlively, John R. II. Arden, Geoffrey B. (Geoffrey Bernard)
[DNLM: 1. Electrooculography. 2. Electrophysiology. 3. Electroretinography. 4. Evoked Potentials, Visual. 5. Vision Disorders—physiopathology. WW 270 P957]
RE79.E4P75 1991 91-13378
617.7 1547—dc20 CIP
DNLM/DLC
for Library of Congress

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Clinical Application of Direct Coupled Recording of the Electroretinogram c-Wave and of the Fast and Slow (Light Peak) Oscillations

Sven Erik G. Nilsson

As was discussed in Chapter 42, the c-wave of the electroretinogram (ERG) represents the sum of a cornea-positive potential (P_I) generated in the pigment epithelium (PE) and a cornea-negative potential (slow P_{III}) originating in the Müller cells, both arising as responses to a light-evoked decrease in extracellular potassium concentration in the photoreceptor layer. The PE response is generally the bigger one and gives rise to a positive c-wave (Fig 68–1,A). There is a sizable interindividual variation, however, and it is known that a few individuals with seemingly healthy eyes have a "flat" c-wave, i.e., the two components appear to be equal in size. The reason may possibly be variations in membrane surface area of the PE and Müller cells. Thus, c-wave amplitudes must be judged with some caution. The safest conclusions can be drawn from comparisons of the right and the left eye in an individual with a uniocular disease.

The still slower variations of the voltage across the eye, the fast and slow (light peak) oscillations, also represent PE activity, the first one being potassium dependent and the second one being dependent upon a transmitter substance (a light peak substance) from the neuroretina (see Chapter 42). Instead of recording the light peak (the response to continuous light following dark adaptation) and dark trough (the response to darkness following light adaptation) indirectly as the electro-oculogram (EOG), both potential changes can be recorded directly from the cornea together with the fast oscillation (see below) by using the direct coupled (DC) technique employed for c-wave recordings (see Chapter 42).[14, 20] This is particularly advantageous in patients who cannot cooperate in ERG and EOG recordings but must be anesthetized, e.g., small children. Furthermore, such dc recordings are necessary in animal experiments.

The dc recordings of the ERG c-wave and of the fast and slow oscillations may be valuable in clinical diagnostic work regarding PE disease. The Arden index[2] used for EOG evaluation may also be calculated from DC recordings.

THE c-WAVE OF THE HUMAN ELECTRORETINOGRAM

The Normal c-Wave

The c-wave amplitude is linearly related to the stimulus intensity in humans, at least within the range of intensities studied (3.5 to 5.5 log relative units above the b-wave threshold).[22] With increasing stimulus duration, the c-wave amplitude and implicit time both increase.[29] The c-wave amplitude shows cyclic variations with time[23] in such a way that the c-wave amplitude follows that of the slow oscillations, i.e., the c-wave amplitude is largest at a

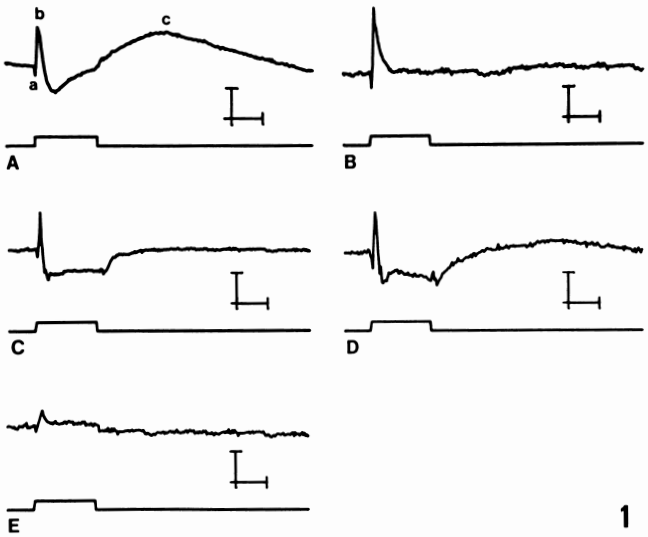

FIG 68–1.
dc recorded human ERGs (a-, b-, and c-waves indicated) in response to a 1-second light stimulus *(lower line)* 4.0 log relative units above the b-wave threshold (amplitude calibration, 200 μV **[A, C, D]** or 100 μV **[B, E];** time calibration, 0.5 seconds). **A,** normal subject. **B,** Best's disease. **C** and **D,** choriocapillaris atrophy, right and left eye, respectively. **E,** retinitis pigmentosa (for details, see the text). (From Nilsson SEG, Andersson BE: *Doc Ophthalmol* 1988; 68:313–325. Used by permission.)

time that coincides with the maximum of the light peak and is smallest when the transocular potential (standing potential) thereafter goes negative.[14] This is best demonstrated when the ERG is superimposed upon the slow oscillation of the transocular potential (monkey).[30] Such a recording from a human subject is shown below. Solvents such as ethanol,[19] toluene, styrene,[21] trichlorethylene, methylchloroform, and halothane[5] have been shown to influence the c-wave amplitude.

The c-Wave in Some Diseases Affecting the Pigment Epithelium

Best's disease (vitelliform or vitelliruptive macular degeneration) is now known to be a disease affecting the PE across the entire fundus, with the most advanced changes located in the macula.[17] It seems that the PE is the primary site of the changes and that the photoreceptors degenerate over the areas with the most pronounced PE lesions. The a- and b-waves are normal,[4] whereas the EOG is highly pathological.[8] In accordance with these findings, we[11, 15] found that in the families we studied the a- and b-waves were within normal limits but the c-wave was missing (Fig 68–1,B) or, in a few cases, extremely small and present only under certain stimulus conditions.

Choriocapillaris atrophy may be regional or diffuse and involves degeneration of the PE and the choroidal capillaries as well as the overlying photoreceptors. Figure 68–1,C and D show the dc ERGs of the right and left eye, respectively, of a patient with a fairly early stage of choriocapillaris atrophy.[12] The a- and b-waves are larger in amplitude for the left eye, but they are also within normal limits for the right eye. There is no c-wave for the right eye, but the left eye shows a small c-wave. These ERG findings agree very well with the EOG results (Arden index 140 and 183 for the right and left eye, respectively) and with the clinical findings (right eye ophthalmoscopically more affected than the left eye; visual acuity 0.9 [18/20] for the right eye and 1.0 [20/20] for the left eye).

Retinitis pigmentosa (RP) in its classic form is characterized by early rod degeneration followed later by cone degeneration. The PE does not seem to be affected primarily. Figure 68–1,E demonstrates a dc ERG from a patient with RP. Small a- and b-waves are often found at early stages, at least in the dominantly inherited forms. In our RP patient data, we have never seen a c-wave.[12]

Central retinal artery occlusion was shown to reduce not only the ERG b-wave but also the c-wave in humans (Fig 68–2)[28] as well as experimentally in monkeys.[30] This was surprising since vascular support for the PE is from the choriocapillaris. Thus, the positive PE component of the c-wave ought to be normal. Furthermore, blocking of the retinal circulation should damage Müller cells, which would reduce the negative Müller cell component of the

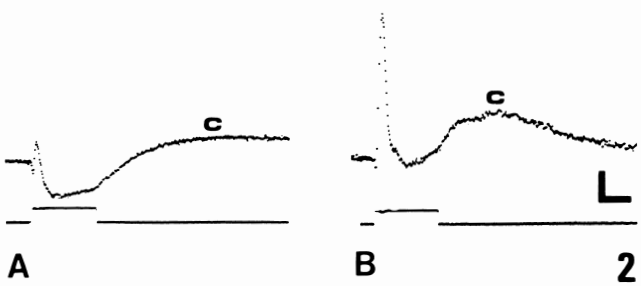

FIG 68–2.
dc ERG recordings from a human eye with occlusion of the central retinal artery **(A)** and from the healthy fellow eye **(B).** The b-wave and the c-wave (indicated) are both reduced in the eye with central retinal artery occlusion (stimulus duration, 1 second [indicated on *lower line*]; stimulus intensity, 130 cd/m^2; amplitude calibration, 100 μV; time calibration, 0.5 seconds). (Adapted from Textorius O: *Acta Ophthalmol* 1978; 56:827–836.)

c-wave. As a consequence, one would expect the c-wave to be increased. The reduction in the c-wave may possibly reflect changes in neuroretinal extracellular potassium concentration that are caused by inner retinal damage.

Clinical use of the c-wave amplitude is limited to a certain extent by its fairly large interindividual variability, also in normal subjects, which seems to be due to the fact that the c-wave is built up by two components from two different cell types. The question is whether there are ways of testing the PE component of the c-wave alone without involving the Müller cells. Experimental work on an isolated retina-PE-choroid preparation[18] showed that choroidal hyperosmolarity hyperpolarized the basal PE membrane and decreased the amplitude of the light-evoked c-wave. Further work will show whether this hyperosmolarity response of the c-wave can be of clinical use.

THE "OFF c-WAVE"

After light adaptation or light stimulation and when the light is turned off, the extracellular potassium concentration in the photoreceptor layer increases,[26, 27] which gives rise to the "off c-wave."[3, 16] The off c-wave (named the h-wave by us) was studied further in our laboratory in normal humans (Fig 68–3) and in monkeys.[24, 25, 31, 32] The off c-wave (h-wave) was found to behave in exactly the same way as the c-wave regarding stimulus intensity-amplitude relationship, cyclic variations with time, and response to ethanol.

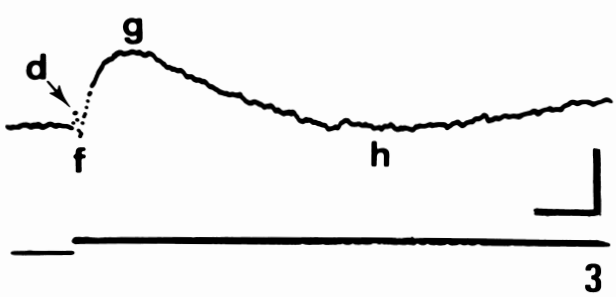

FIG 68–3.
Off-responses of the human dc recorded ERG after the termination of an illumination of 60 lux (average of two recordings). The "h-wave" in our terminology corresponds to the "off c-wave" (Amplitude calibration, 100 μV; time calibration, 1 second). (From Skoog K-O, Welinder E, Nilsson SEG: *Vision Res* 1978; 18:1041–1044. Used by permission.)

FAST AND SLOW (LIGHT PEAK) OSCILLATIONS

The dark trough and light peak are generally recorded indirectly as the EOG.[1, 2, 7, 9] However, these slow oscillations, together with the fast oscillations, may very well be recorded directly from the cornea with a dc technique, which is basically the same as the one used for c-wave recordings (see Chapter 42).[14, 20] This is valuable, especially in patients who require general anesthesia (e.g., small children) for electrophysiological tests. In addition, dc recordings of this kind are necessary for the evaluation of PE health in animal models of hereditary diseases of the PE and retina.[10, 13]

Figure 68–4 shows a direct recording of the fast oscillation and the light peak in a normal subject as compared with a recording from a patient with RP. The latter recording, which shows almost no response, corresponds to an almost flat EOG.

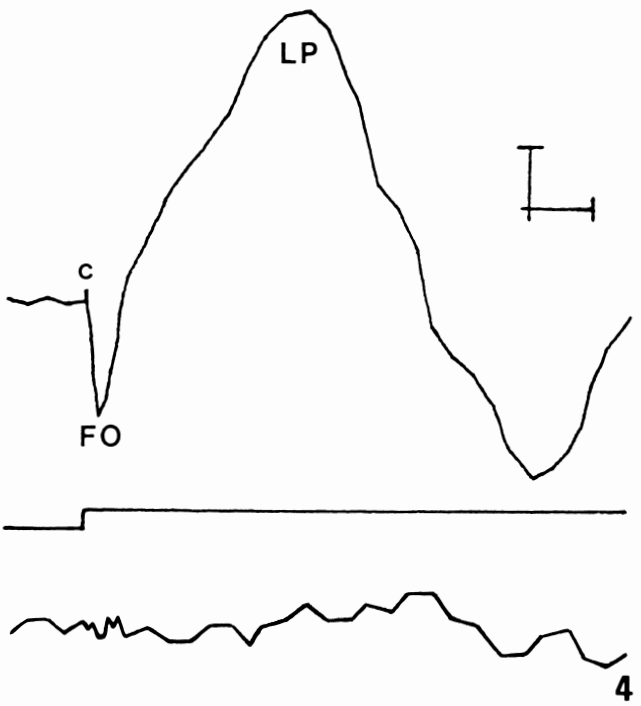

FIG 68–4.
The *upper trace* shows a direct corneal dc recording of the ERG (only the c-wave is seen), the fast oscillation *(FO)*, and the light peak *(LP)* (slow oscillation) in a normal subject. The *bottom trace* shows the same kind of recording from a patient with RP. The latter response is essentially flat. The onset of a 16-lux light stimulus is indicated between the two recordings (amplitude calibration, 1 mV; time calibration, 3 minutes).

The light peak can be evoked not only by continuous light but also by repeated flashes of light. In such a recording, the a- and b-waves of the ERGs are too fast to show up, but the ERG c-waves are superimposed upon the light peak (Fig 68–5). (For further details regarding the measuring procedure, see Chapter 42.) In this way, it is easily seen that the c-wave amplitude follows that of the light peak, i.e., it is largest at the time of the maximum of the light peak. (The fast oscillation does not show up with 2-minute intervals between recordings.)

The hyperosmolarity response mentioned above has been used clinically regarding the effect on the transocular potential (standing potential), as reflected in the EOG or in direct dc recordings of the transocular potential. Intravenous administration of a hypertonic solution decreases the transocular potential.[33] The hyperosmolarity response was reported to be suppressed or absent in eye diseases involving the PE (e.g., RP and advanced diabetic retinopathy with breakdown of the blood-retinal barrier). The explanation was given by Shirao and Steinberg.[18] Choroidal hyperosmolarity hyperpolarized the basal membrane of the PE and decreased the transtissue potential in an isolated retina-PE-choroid preparation (corresponding to the transocular potential in the intact eye). Yonemura and Kawasaki[33] also found that acetazolamide given intravenously decreased the transocular potential in EOG studies or in direct dc recordings. The acetazolamide response was normal in RP, however. Kawasaki et al.[6] reported that acetazolamide on the choroidal side of an isolated PE-choroid preparation hyperpolarized both the basal and apical PE membrane, the basal more than the apical one, thus decreasing the transepithelial potential.

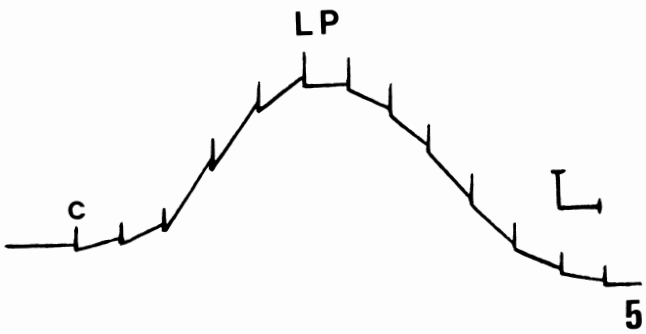

FIG 68–5.
Light peak *(LP)* evoked by repeated light flashes. The ERG c-waves are seen to be superimposed upon the LP. The c-wave amplitude is largest at the time of the maximum of the LP (amplitude calibration, 0.5 mV; time calibration, 2 minutes).

CONCLUSIONS

The ERG c-wave can be dc recorded clinically and, when using averaging technique, with fairly stable results. The c-wave amplitude is one of a number of valuable parameters regarding PE health. However, it should be used with some caution since the interindividual variability is fairly large and since a few individuals with healthy eyes actually do not show a c-wave. It is possible that the hyperosmolarity response of the c-wave may be a way of getting away from this problem in the future.

Direct dc recordings of the fast and slow (light peak, dark trough) oscillations can be obtained clinically without difficulty. Such recordings are of particular value when general anesthesia has to be used and when the EOG cannot be employed.

Acknowledgment

This investigation was supported by the Swedish Medical Research Council (Project No. 12X-734).

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