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Full-field electroretinography examinations of the human eye with the eye diagnostic device PEP-2000 – First results

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Abstract: Full-field electroretinography (full-field ERG) forms the diagnostic basis for numerous pathologies of the eye. For this reason, fast and accurate diagnostics in the field of ophthalmology are essential. Two examination techniques, full-field ERG and pupillometry were combined in a diagnostic device developed by ICM e.V. to reduce the examination process for both examiners and patients. In this paper, the device is examined for the quality of the full-field ERG measurements. A feasibility study with 12 healthy subjects (3 f, 9 m, 36.33 ± 11.94 years) was conducted to evaluate the device. The results showed that the peak times for both light- and dark-adapted measurements were within the range of the researched literature values. However, the amplitudes were markedly lower in both measurements compared to the averaged literature values (dark-adapted about 8.5-fold and light-adapted about 5.5-fold) and are clearly outside the range of values researched. The main reason for this is the use of cup electrodes, which were placed on the skin of the lower eyelid. Nevertheless, plausible and comparable analysis values could be obtained with the eye diagnostic device PEP-2000. Further studies with wire electrodes will be performed.

Keywords: Full-field electroretinography, Ophthalmology, Human eye, Analysis methods, Cup electrode

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Figure 1: PEP-2000 diagnostic device as stationary and hand-held unit. (Source: ICM e.V.)

1 Introduction

Due to diseases up to blindness of the eye, affected persons lose a large part of their quality of life. The diseases often progress slowly and are diagnosed very late, so the effects have a strong impact on the organism and leave permanent damage, even after the disease has been fought. Some diseases, such as high-pressure glaucoma, are even accompanied by severe pain [1].

For this reason, rapid and meaningful diagnostics are essential in the field of ophthalmology. In most cases, numerous time-consuming individual examinations are necessary before a diagnosis can be made, and the patient can be helped [2]. In order to shorten the examination process for examiners and patients as well as to reduce costs, the PEP-2000 ophthalmic diagnostic device was developed (see Figure 1). It combines pupillometric and electrophysiological examination techniques in one device setup and can be used stationary as well as mobile [3]. The core of the device is the

removable head section, in which a stimulation module is integrated. By means of two LED rings inserted behind the eyecups, flash color, frequency and brightness, as well as background color and brightness can be varied and a wide range of applications can be covered [3]. In this work, the developed examination device shall be compared with literature values in the field of full-field ERG. The evaluation and interpretation of the ERG depend on the existence of valid standards or guideline values. It is not possible to rely solely on published data, because the measured parameters are strongly influenced by the device itself and the accessories used [4].

2 Methods

A study design with corresponding subject information and a data protection statement was developed for conducting the feasibility study. Furthermore, the method full-field ERG is presented and its evaluation methods and literature values are listed. Finally, the experimental procedure is explained in detail.

2.1 Study design

Suitable subjects were selected by the following exclusion criteria: psychological pre-diseases, recent eye surgeries or ophthalmological pre-diseases, refractive errors above ± 3 dpt, current or previous abuse of addictive substances, neurological diseases, conspicuous reactions (e.g., circulatory collapse, "fainting") to stress-inducing situations, regular intake of medication, allergies/ hypersensitivities of the skin, smoking of nicotine-containing products, and epilepsy.

A two-part data collection form is used to record the key data of the subjects. In the first part of the data collection form, the physical characteristics of the subjects are recorded, and previous diseases are queried in order to detect possible exclusion criteria. In the second part of the data collection form, the subject's current daily condition is queried. The subjects also receive a written information sheet explaining the test procedure, pointing out exclusion criteria and the dangers of the test. From the 25 volunteers, 12 subjects (3 females, 9 males, mean age: 36.33 ± 11.94 years) could be selected for the feasibility study.

2.2 Full-field ERG

The ERG is used to record and evaluate the electrical potentials generated by the retina [5]. The ERG is derived using three electrodes. The active electrode is placed centrally on the lower eyelid, the reference electrode on the forehead and the grounding electrode at the temple [2]. When using cup electrodes, a low electrode-skin impedance is required. It must be less than or equal to 5 kΩ at a frequency between 10 Hz and 100 Hz [2,4]. For all types of ERGs, the placement of the electrodes, the general conditions and the permissible examination modes are defined and standardized by the International Society for Clinical Electrophysiology and Vision (ISCEV). This ensures the reproducibility of the results [4]. The potential change recorded by means of electrodes in response to a light stimulus shows a defined progression in healthy persons. Waves are formed whose amplitudes and peak times are used for diagnostics. The most important analysis parameters form a- and b-wave (Amp_a and Amp_b) with the corresponding peak times (Lat_a and Lat_b) [4]. The a-wave corresponds to the amplitude of the first negative peak, which results from the hyperpolarization of the photoreceptors [6]. The subsequent first positive peak of the potential curve arises from the depolarization of non-neuronal glial cells and is referred to as the b-wave [4]. In the further progression of the potential response, further peaks can be detected. These are usually not needed for diagnosis in clinical practice [6,7]. The typical shape of an ERG with the corresponding labelling of the waves and peak times can be seen in Figure 2.

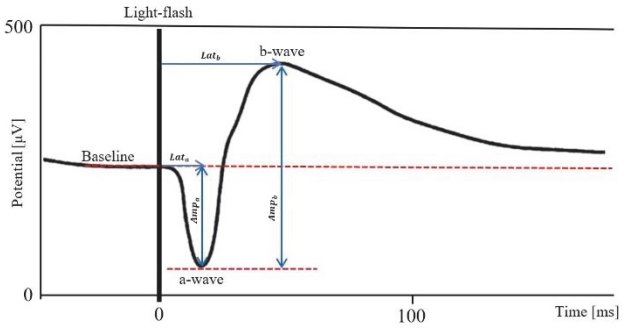

Figure 2: Time progression of the ERG waves, based on [4].

The a-wave amplitudes are always measured starting from the baseline, the b-wave from the maximum amplitude of the a-wave to the maximum of the b-wave, and the peak times are measured from the onset of the stimulus to the maximum amplitude of the peak [6,7]. Normal values for amplitudes and peak times of the a- and b-wave have been determined in various studies, but these show a dependence on age, gender, as well as the device and electrodes used. Table 1 lists typical literature values [6,8,9].

Table 1: Analysis values for electroretinography [6,8,9]. (MV – mean value)

Analysis parameter	photopic	scotopic
a-wave amplitude	20–50 µV (MV 35 µV)	190–300 µV (MV 245 µV)
a-wave peak time	14–20 ms (MV 17 ms)	20–26 ms (MV 23 ms)
b-wave amplitude	90–180 µV (MV 135 µV)	400–700 µV (MV 550 µV)
b-wave peak time	14–20 ms (MV 17 ms)	40–60 ms (MV 50 ms)

2.3 Execution of experiment

The tests are performed with the PEP-2000 diagnostic device in a darkened room. First, the device position is set for the respective subject. The position of the eyes is checked on the laptop via the real-time display of the device cameras. After the placement of the three cup electrodes, the electrode-skin impedance is checked (Impedance $\leq$ 5 kΩ). First, the dark-adapted ERG measurement is performed at a flash strength of 3 cds/m^2. According to ISCEV standards, a total adaptation time of at least 20 minutes is required. Then the ERG recording begins. Five stimuli are performed in the form of light flashes (inter stimulus interval: 10 s). For each stimulus, an ERG derivative is recorded. During the measurement period, the subjects are instructed to sit as quietly as possible in order to minimize interferences. After rechecking the electrodes, the light-adapted ERG measurement is performed at 3 cds/m^2. In this part of the experiment, the adaptation period (light intensity: 25 cd/m^2) is ten minutes, which is performed directly on the device. The intervals between the light flashes are 0.5 s. For each subject, at first, a measurement in the dark-adapted state and then a measurement in the light-adapted state is performed.

2.4 Data Analysis

The a- and b-waves were preprocessed internally in the device. For this purpose, a mean curve was formed within the device for each subject from the individual five ERG curves. The waves were linearly interpolated and filtered (bandpass 1-300 Hz). Optionally, the data can be filtered with a notch filter. This was not applied in this feasibility study. The mean value and standard deviation for the a- and b-wave amplitude and for the a- and b-wave peak times are calculated from the 12 subject values of the subjects. This procedure is performed for both the dark-adapted and the light-adapted measurement.

3 Results

The dark- and light-adapted ERG measurements are shown in figures 3 and 4. It can be seen that the ERG curves for both test methods of all subjects are approximately in the same range in the anterior section up to about 60 ms. This section of the curve contains the a- and b-waves, which will be analyzed in the following. In the further progression of the curve, the curves deviate more strongly from each other. Only the curve of subject 2 from the light-adapted ERG measurements also shows larger deviations in the first curve section.

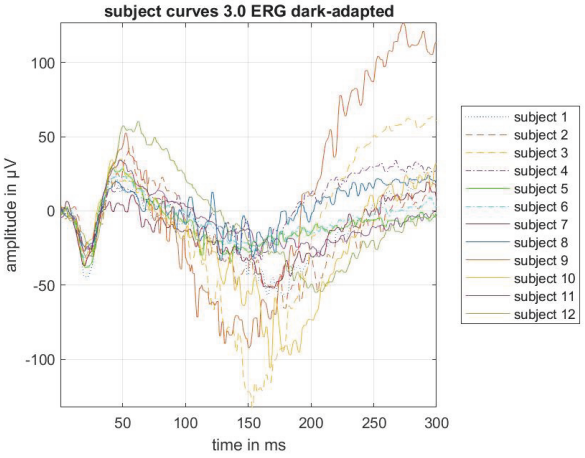

Figure 3: Individual curve shapes of the dark-adapted (scotopic) ERG of all subjects.

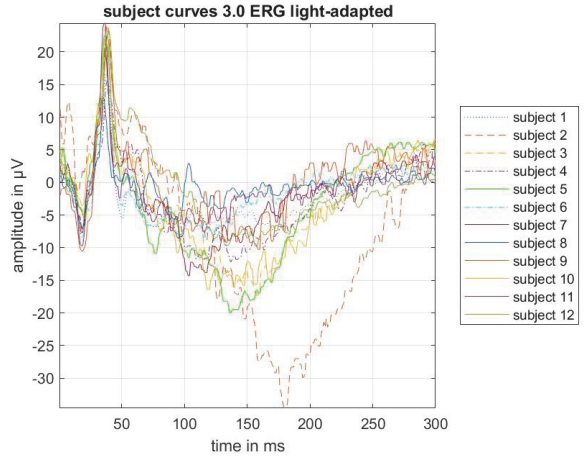

Figure 4: Individual curve shapes of the light-adapted (photopic) ERG of all subjects.

Statistical values were calculated for each of the four analysis parameters and summarized in Table 2 for dark-adapted and Table 3 for light-adapted ERG measurements. The scotopic values show a higher scatter range compared to the photopic values. The peak times, on the other hand, show a small scatter range for both methods. In contrast, the standard

deviations of the a-wave amplitude (6.14 µV) and b-wave amplitude (12.40 µV) in the photopic ERG are particularly large. Nevertheless, the comparison of the determined analysis parameters (see Table 2 and 3) with the literature values (see Table 1) for both measurements shows that the peak times of the a- and b-wave agree very well and these are in the range of the researched literature values [6,8,9]. The amplitudes, on the other hand, are markedly lower in both measurements (dark-adapted about 8.5-fold and light-adapted about 5.5-fold) compared to the averaged literature values and are thus clearly outside the researched value range [6,8,9]. The main reason for this is the use of cup electrodes instead of wire electrodes [6]. Due to the better acceptance compared to the wire electrodes by the subjects as well as the easy handling, the use of cup electrodes was chosen in order to prove the basic working principle of the PEP-2000. Another factor influencing the measurement results is the small number of subjects. Due to various exclusion factors (see 2.1), the majority of the intended subjects (25 volunteers) had to be excluded from the study, resulting in a very small study group (n = 12).

Table 2: Statistical values of the analysis parameters of the dark-adapted (scotopic) ERG. (SD - Standard deviation)

Analysis parameter	Mean value	SD
a-wave amplitude	31.73 µV	6.14 µV
a-wave peak time	20.83 ms	2.41 ms
b-wave amplitude	59.48 µV	12.40 µV
b-wave peak time	48.08 ms	4.98 ms

Table 3: Statistical values of the analysis parameters of the light-adapted (photopic) ERG. (SD - Standard deviation)

Analysis parameter	Mean value	SD
a-wave amplitude	6.81 µV	2.60 µV
a-wave peak time	18.00 ms	1.21 ms
b-wave amplitude	25.96 µV	3.87 µV
b-wave peak time	37.00 ms	1.21 ms

4 Conclusion

In this paper, it could be shown that the developed eye diagnostic device PEP-2000 for full-field ERG provides plausible analysis parameters which are comparable with the literature. The determined analysis parameters should provide the basis for further investigations in the form of guideline values. However, the quality of the measured values needs to be improved. When performing ERG measurements, the use of other types of electrodes, preferably Gold-Foil electrodes, should be considered to increase signal quality and cause stronger potential changes. Furthermore, the bio signal amplifier should be integrated directly into the diagnostic device for simplified handling. An application of the PEP-2000 in the veterinary field is also currently being investigated.

Author Statement

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References

[1] Leydhecker W. Glaukom: Ein Handbuch. Springer-Verlag, 2013.
[2] Augustin A. Augenheilkunde, 4th ed. Kaden Verlag; 2019.
[3] Biedermann J, Walther S, Grundmann A. Entwicklung eines mobilen Diagnosegerätes, welches das Ganzfeld-Elektroretinogramm (Ganzfeld- ERG) und die Pupillographie vereint. Patent DE102018005084A1, 2018.
[4] Marmor MF, Fulton AB, Holder GE, Miyake Y, Brigell M, Bach M. International Society for Clinical Electrophysiology of Vision. ISCEV Standard for full-field clinical electroretinography (2008 update). Doc Ophthalmol 2009;118(1):69-77.
[5] McCulloch DL, Marmor MF, Brigell MG, Hamilton R, Holder GE, Tzekov R, Bach M. ISCEV Standard for full-field clinical electroretinography (2015 update). Doc Ophthalmol 2015;130(1):1-12.
[6] Kimme S. Voraussetzungen für die Entwicklung eines Screening-Gerätes zur Bestimmung der Retinafunktion. Bachelorarbeit, Erst-Abbe-Fachhochschule Jena, Jena 2014.
[7] Bergström AL, Cordes H, Zsurger N, Heegaard PM, Laursen H, Chabry J. Amidation and structure relaxation abolish the neurotoxicity of the prion peptide PrP106-126 in vivo and in vitro. J Biol Chem 2005;280(24):23114-21.
[8] Grehn F. Untersuchungsmethoden des Ophthalmologen. Augenheilkunde. Springer, Berlin, Heidelberg, 2015.
[9] Fishman GA, Sokol S. Electrophysiologic Testing, 3rd ed. San Francisco, CA, American Academy of Ophthalmology, 1990.