MULTIFOCAL ELECTRORETINOGRAPHY. GLAUCOMA DIAGNOSIS BY MEANS OF THE WAVELET TRANSFORM

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ABSTRACT

A summary is given of the multifocal electroretinography technique. Particular stress is laid on the application of the wavelet transform, a technique little explored hitherto, for obtaining markers that might be useful in the early detection of glaucoma. Possible future research lines are also sketched out.

Index Terms— Multifocal Electroretinogram, m-sequence, Wavelet Transforms, Glaucoma.

1. INTRODUCTION

The traditional techniques for clinical analysis of the retina are based on indirect methods (measurement of the intraocular pressure, visual inspection of the eyeground, campimetric tests, etc). Their main drawback is that they do not give objective information on the functioning of the retinal photoreceptors, essential elements in the perception of light energy. A new technique has recently been developed for obtaining this retina-functioning information in a quick and reproducible way; this technique is known as the multifocal electroretinogram (mfERG). The mfERG enables a functional exploration to be made of the light sensitivity of the retinal cells and also the spatial distribution of this sensitivity. The mfERG basically involves recording the variations in retinal potential evoked by a light stimulus and then mapping out the results in a 3D diagram showing those regions that respond to the visual stimuli (Sutter & Tran 1992).

The mfERG technique allows simultaneous recording of local responses from many different regions of the retina, building up a map of its sensitivities. As in the conventional electroretinogram (ERG), also called the full-field electroretinogram, the potential is measured as the sum of the electric activity of the retina cells. In the full-field ERG, however, the signal recorded comes from the whole retina surface, so it is hard to detect smaller one-off defects that do not affect the whole retina. The mfERG, by contrast, gives detailed topographical information of each zone and can therefore detect small-area local lesions in the retina and even in its central region (fovea).

From the technical point of view, equipment is needed for capturing the visually evoked potentials at retina level (presented as a set of hexagons of varying sizes and intensities). Due to the low amplitude of the signals generated (at nanovolt level), the technique calls for suitable hardware equipment (recording electrodes, instrumentation amplifiers, digitalisation, etc) and also signal processing algorithms (filtering, averaging or smoothing procedures, rejection of artefacts, etc) to ensure that the results are clinically useful.

This paper gives a description of the recording and arrangement of the signals we have used in our research, the signal analysis by the Wavelet transform for recording possible glaucoma markers; it also mentions possible future research lines.

2. METHODS

2.1. Obtaining the Signal Databases

Fifty six patients diagnosed with open angle glaucoma as well as an identical number of healthy subjects were included in our mfERG record database using the VERIS 5.1 multifocal recording system (Electro-Diagnostic Imaging, San Mateo, USA). The stimulus consisted of an m-sequence applied to a group of 103 hexagons, as shown in figure 1, displayed on a 21-inch monitor and covering a 45º arc of the retina. The local luminance of each hexagon was 100 cd/m^2 in the on phase and less than 1.5 cd/m^2 in the off phase, determined by the pseudorandom sequence.

The monitor frequency was 75 Hz and the m-sequence was modified so that each step thereof comprised 4 frames in the following order: flash-dark-flash-dark. In the flash fames all the hexagons were illuminated with a maximum luminance of 200 cd/m^2, with a minimum luminance of less than 1.5 cd/m^2 in the dark frames. The background

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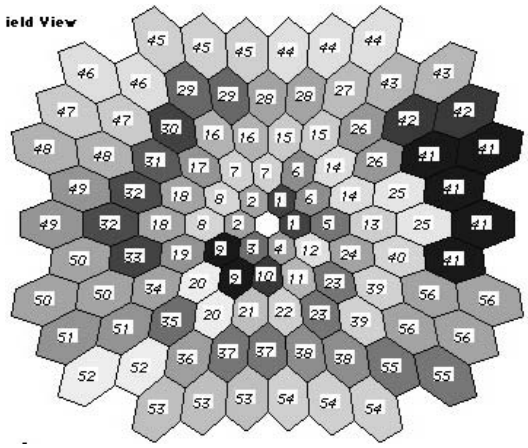

Fig.1. Geometry of the multifocal stimulus and regrouping of the hexagons.

luminance of the rest of the monitor surface surrounding the hexagons was kept constant at 100 cd/m^2. This stimulation protocol is especially adapted for obtaining responses from the retinal ganglion cells and their axons. It is based on the effect of the focal responses (M) on the following global stimulus (F), which amplifies the signals coming from the ganglion cells. Basically, the protocol (M-F-O-F-O) consists of five steps. In the first step (M) each hexagon follows a luminous stimulation (100 cd/m^2) determined by a pseudorandom binary m-sequence. In the second step the whole area is illuminated (200 cd/m^2) (F), followed by a dark sequence (O) (<1.5 cd/m^2), followed by another global flash (200 cd/m^2) (F) and then darkness again (O) (<1.5 cd/m^2). This stimulation will give us an acceptable signal-to-noise ratio and also ensures a reasonably short recording time (9 minutes).

The stimulus was displayed through pharmacologically dilated pupils using a Burian-Allen bipolar contact lens (Hansen ophthalmics, Iowa City, IA). The residual spherical refractive error was corrected by the VERIS™ autorefractor, mounted on the stimulation monitor. The alignment of the patient's pupil with the monitor optic and the fixation stability are controlled by an attached infrared camera. The signals are amplified with a Grass Neurodata Model 15ST amplification system (Grass Telefactor, NH), with a 50,000 gain, filters with 10-300 Hz bandwidth and a sampling interval of 0.83 milliseconds (1200 Hz).

The signals obtained from the 103 hexagons were regrouped and averaged to build up a new 56-sector map as shown in figure 1. The purpose of this regrouping was to simplify the analysis and to improve the signal-to-noise ratio. A 56-sector topography was therefore chosen, similar to that studied in automated campimetry, the clinical ¨gold-standard¨ for evaluating the visual field. Two databases were created, one called "abnormal" and the other "normal". The abnormal database comprised a collection of 56 of the aforementioned sectors. Not all the sectors making up a map belong to a single patient; the map groups together 56 clearly glaucoma-identified sectors belonging to different patients diagnosed with the same symptom. Following a similar procedure, a map comprising the normal database was built up, this time on the basis of healthy individuals.

2.2. Analysis of the signals by the Wavelet Transform

The great drawback of the Fourier transform-based analysis is that the time information is forfeited when the signal is transformed into the frequency domain. The drawback is particularly telling when the signal to be analysed is transitory in nature or of finite duration, as in the case of mfERG signals, whose frequency content changes over time. The discrete wavelet transform (DWT) gets over this drawback by analysing the signal in different frequencies with different resolutions, using regions with windowing of different sizes and obtaining a two-dimensional time-frequency function as a result. Wavelet analysis uses finite-length, oscillating, zero-mean wave forms, which tend to be irregular and asymmetrical. These are the windowing functions called mother wavelets. In principle there may be an infinite number of possible waves that are eligible for use as wavelets, but in practice a more limited number of wavelets are used, of well-known characteristics, efficacy and implementation: Haar, Daubechies, Coiflets, Mexican Hat, Symlets, Morlet, Meyer, etc. In the study we are dealing with here a great number of them were explored; it was with the Bior3.1 wavelet that the best subjective results were obtained for visual identification of certain markers that help us to differentiate normal mfERG signals from those belonging to subjects with glaucoma.

The signal to be analysed is decomposed on the basis of shifted and dilated versions of the mother wavelet or analysing wavelet that we have decided to use; this is all done by means of the correlation between the signal to be decomposed and the abovementioned versions of the mother wavelet. Mathematically, the discrete wavelet transform (DWT) is defined as:

$$C(j,k) = \sum_{n \in z} f(n) 2^{-j/2} \psi(2^{-j} n - k) \qquad (1)$$

where the resulting C(j,k) is a series of coefficients indicating the correlation between the function f(n) to be decomposed and the wavelet ψa,b(t) dilated to a scale a=2^j and with a shifting b=k2^j, with j,k Є Z. The resulting C(j,k) includes time and frequency information of the function f(n), according to the values of j and k, respectively. In practice we obtain two sets of time-function signals, one of them made up by the signals A_1 to A_n which represent successive approximations of increasing smoothness or declining frequency of the signal f(n), and the other by D_1 to

D_n which represent the successive details, also of falling frequency.

The signals were analysed by applying up to 5 levels of wavelet decomposition to each one of the different sectors and for two different time windows: one from 10 to 190 ms and another from 60 to 90 ms. The first contains the global response to the multifocal stimulus used here and the second contains the most important information on the induced response generated by this type of stimulus. Several superimposed records were obtained from different sectors to obtain an overview of the markers that might differentiate normal signals from abnormal signals.

3. RESULTS

The bottom graph of figure 2 shows superimposed the D4 details of the Wavelet decomposition, between 10 and 190 ms and it displays a window only from 10 to 140 ms from ten different sectors corresponding to different healthy individuals. The top graph of the same figure shows a similar representation for ten sectors affected with glaucoma and with an identical topographical position to the former. It immediately stands out that the signals corresponding to individuals affected by glaucoma show their greatest negative edge at about 45 ms, while signals in healthy sectors tend to bottom out at about 70 ms. The efficiency of this marker was quantified against a time window running from 25 to 90 ms, looking for the greatest negative edge. When this edge came in the first half of the window the signal was classified as affected by glaucoma, while if it came in the second half it was classified as healthy.

Figure 3 (top) shows superimposed the A2 approximations corresponding to the Wavelet decomposition between 60 and 90 ms of ten different sectors belonging to different healthy individuals. The lower part of this figure shows a similar representation for ten sectors affected with glaucoma and with the same topographical position as those above. In this case a trough appears at about 73 ms for healthy subjects, coming slightly later for abnormal subjects. Since there might be more troughs, the efficiency of this second marker is quantified against a time window running from 65 to 87 ms, in which said trough is sought. When the trough came in the first half of the window the signal was classified as healthy, while if it came in the second half it was classified as affected by glaucoma.

Table 1 shows the results, using both markers separately, of true and false normal and abnormal findings from a set of 56 sectors belonging to different healthy individuals and 56 with glaucoma.

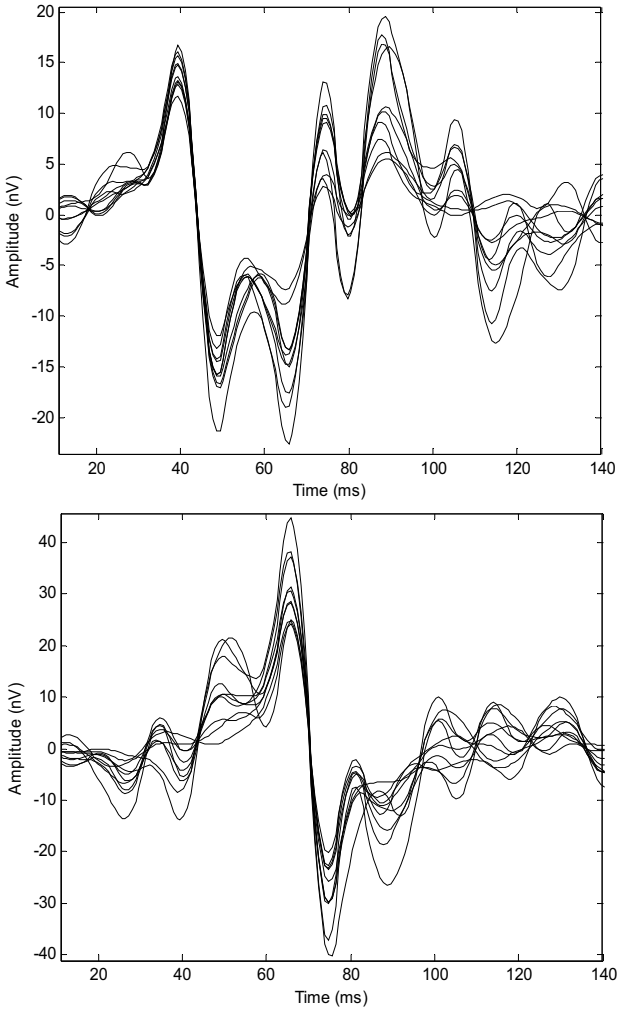

Fig.2. Detail D4 of the wavelet decomposition for 10 healthy sectors (bottom) and 10 with glaucoma (top).

Table 1. Results using both markers separately.

Marker	True healthy	False glaucoma	True glaucoma	False healthy
A2	55	1	48	8
D4	54	2	51	5

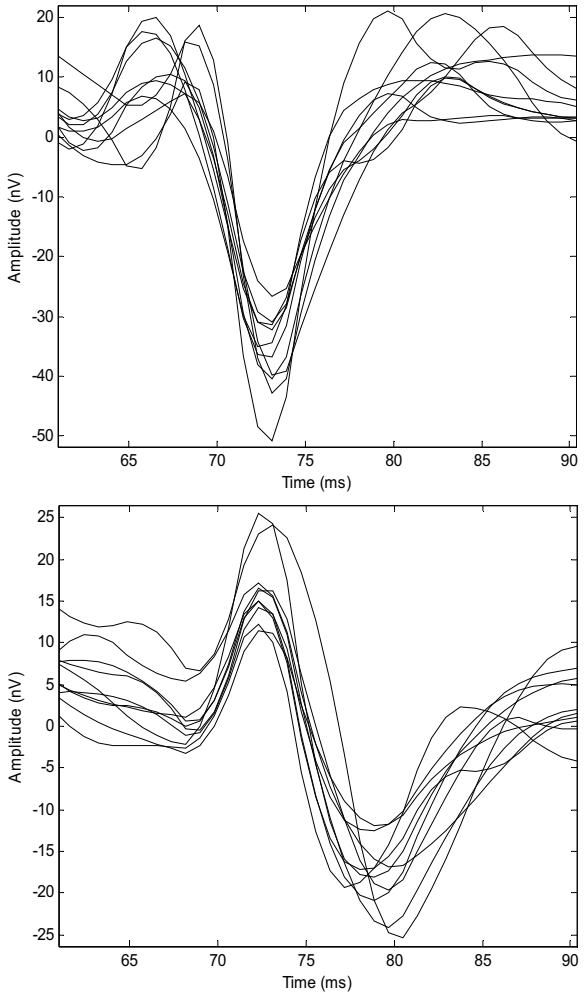

Fig.3. A2 approximation of the wavelet decomposition for 10 healthy sectors (top) and 10 with glaucoma (bottom).

4. DISCUSSION

The morphology of the signals recorded in each hexagon varies according to the position that this hexagon occupies in the retina and the type of stimulus used. It is also known that the optic nerve head component (ONHC) is the main cause of the asymmetries in the records [1,7], whereby said component arrives in each hexagon with a different time-lag depending on the distance between the hexagon and the optic nerve. This will enhance or cancel out some components as a result of the different retina levels below the hexagon under study. Loss of the ONHC has already been mooted as an early indicator of glaucoma [5], so there is obviously a need for adjustment of the various time windows and types of markers used in this study, according to the position of the hexagon in the retina map, to optimise and fine tune the results obtained herein.

A more in-depth investigation needs to be carried out to ascertain the most efficient markers, depending on the retinal quadrants and rings to which the sector under study belongs, in view of the abovementioned hexagon dependency.

The type of markers used herein and the tool used to obtain them, the Wavelet transform, make it impossible a priori to establish any association with a specific physiological origin, since there are no precedents to go on. It does not fall within the remit of this study to establish a physiological cause-effect relationship for the marker but rather to search for technical tools to help experts to diagnose glaucoma in humans in its early stages of development.

5. ACKNOWLEDGMENTS

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6. REFERENCES

[1] Brad Fortune, Marcus A. Bearse, Jr, George A. Cioffi, and Chris A. Johnson, "Selective Loss of an Oscillatory Component from Temporal Retinal Multifocal ERG Responses in Glaucoma", *IOVS Vol. 43, No. 8*, Association for Research in Vision and Ophthalmology, pp. 2638-2647, August 2002.

[2] D. C. Hood, J. G. Odel, C. S. Chen, and B. J. Winn, "The Multifocal Electroretinogram", *J Neuro-Ophthalmol, Vol. 23, No. 3*, pp. 225-235, 2003.

[3] Dorit Raz, Ido Perlman, Christine L. Percicot, George N. Lambrou, and Ron Ofri, "Functional Damage to Inner and Outer Retinal Cells in Experimental Glaucoma", *IOVS Vol. 44, No. 8*, Association for Research in Vision and Ophthalmology, pp. 3675-3684, August 2003.

[4] M. F. Marmor, D. C. Hood, D. Keating, M. Kondo, M. W. Seeliger, and Y. Miyake, "Guidelines for basic multifocal electroretinography (mfERG)", *Documenta Ophthalmologica*, Kluwer Academic Publishers, Vol. 106, pp. 105-115, 2003.

[5] Nalini V. Rangaswamy, Wei Zhou, Ronald S. Harwerth, and Laura J. Frishman, "Effect of Experimental Glaucoma in Primates on Oscillatory Potentials of the Slow-Sequence mfERG", *IOVS Vol. 47, No. 2*, Association for Research in Vision and Ophthalmology, pp. 753-767, February 2006.

[6] Sutter EE., "Imaging visual function with the multifocal m-sequence technique", *Vision Res. Vol. 41*, pp. 1241-1255, 2001.

[7] Wei Zhou, Nalini Rangaswamy, Periklis Ktonas, Laura J. Frishman, "Oscillatory potentials of the slow-sequence multifocal ERG in primates extracted using the Matching Pursuit method", *Vision Research 47*, Elsevier, pp. 2021-2036, March 2007.