Application of Synchronous Detector techniques for electroretinographic studies in patients with retinitis pigmentosa

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A description is given of the application of the Synchronous Detector technique for electroretinographic (ERG) measurements (cone function) in patients with retinitis pigmentosa. The results obtained, in terms of average amplitudes and average "delay time," are compared with the results obtained by conventional waveform averaging processes. Time delay measurements with the Synchronous Detector system are relatively independent of amplitude and precise waveform definition, and provide a convenient means of differentiating normal and abnormal responses. Very small signals can be measured with this system, and estimates of delay time can be obtained at levels where the usual (waveform) averaged responses have poor definition. A correlation of visual field loss with abnormal delay time is noted. The relationship of this method of signal analysis to the usual ERG interpretation is discussed briefly.

Key words: electroretinogram, Synchronous Detector, amplitude, phase, frequency, delay time, visual fields, cone function.

The electrical response of the outer layers of the retina to light stimulation may be measured by means of the electroretinogram (ERG). A great deal of work has gone into the evaluation of what may be described as the "traditional ERG," and different laboratories have established their own standards and methods of interpretation. Until recent years most ERGs were measured on a single-flash basis, or sometimes repeated ERGs were superimposed photographically to give some enhancement. Signals which were too small to be recorded by this means were described usually as "extinguished." Computer techniques are now available for increasing the signal-to-noise ratio of small signals, and thus enable signals to be measured which previously were regarded as too small to be detected satisfactorily. Averaging techniques work well here, so that a waveform often can be defined for a small repetitive signal. If the signal has similar characteristics to a larger single-flash ERG waveform, then presumably the interpretation may be carried out in the

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usual manner. However, as the signals become very small their waveform may change, so that the interpretation often is not immediately apparent. There has been some interest in the time delay characteristics of the waveform, but a basic problem here involves the definition of time delay, particularly with low signal-to-noise ratios. First, it must be decided whether or not a signal is present. If a small signal is present, then one faces the problem of defining the time delay to some part of the signal, usually when the waveform duration is relatively long compared with the delay time.

With the above problems in mind it was thought that a somewhat different method of data processing might be a useful adjunct to the traditional ERG technique. For many years now a method termed “synchronous detection” has been in use in the physical sciences for the detection of small repetitive signals buried in a large “noise” background; it has not been used widely with biological systems. (One possible contributing reason for this is that suitable instruments for clinical use have not been available commercially. Princeton Applied Research Company of New Jersey is a major manufacturer of Synchronous Detectors, and with relatively minor modifications some of their instruments could be used. A commercial instrument of appropriately limited but suitable application for ophthalmological use still awaits production.) When applied to ERG measurements the method may be regarded as a means of measuring the average amplitude and phase of the retinal response to flicker stimulation at different frequencies. The phase measurements are used to plot a phase-frequency graph, which usually gives a good approximation to a linear plot over a certain frequency range. The slope of this linear plot is proportional to the “delay time” of the system. (While this may not be apparent immediately, the fact that the delay time is proportional to the rate of change of phase with frequency is a fundamental concept.) An advantage of this system, when small signals are involved, is that one does not have to be too specific about the waveshape of the signals. In addition, the relative phase measurements which are used to obtain the “delay time” are not very sensitive to variations of the amplitudes of the signals. The “delay time” thus can be estimated and used as a measure of retinal function in cases of opaque media or in somewhat uncooperative patients, where the amplitudes of the signals may be varying considerably.

As emphasized by Gouras, it is desirable for the rod and cone function to be separated by some technique. The results to be described here have been obtained with white-flash stimulation, the patient in a normal state of light adaptation, in a room with background illumination of approximately 15 foot candles. The stimulation frequency has been in the range from approximately 20 to 60 or 80 cycles per second, so that mainly the cone response is being measured. A red stimulus may be used, but the stimulus energy available is limited under these conditions with an electronic flash as the source, and consequently, the signals become smaller. For measurement of rod response, lower frequency blue-flash stimulation in the dark is used. A different type of response with a longer delay time is obtained by this means, but this will not be discussed further here.

It may be argued that data processing techniques have a limited place in the usual ERG measurement routine. This is partially a matter of equipment cost and complexity, together with questions of ease of measurement and interpretation of the results. The traditional ERG measurements rely heavily upon interpretation of waveshape and signal amplitudes, and the inherent variation in responses is often largely ignored. Measurements often are not made in the light-adapted state, as the signal-to-noise ratio in normals is low. Abnormal signals usually are decreased in
size, so that the problems of measurement and interpretation become more pressing. When the media are not clear, or the pupils are very miotic, the interpretation of the traditional ERG becomes even more difficult. As such cases often are the ones of clinical interest it seemed that a method which bypassed some of these difficulties would be of use at times. In order to illustrate the application of the method, patients with retinitis pigmentosa were chosen, as they often have evident visual function even when their electrical responses are very small or nonmeasurable.

Test procedure and equipment
Some details of the system have been given before.11 The stimulus used has been provided by the Grass PS-2 Photo Stimulator, with the intensity set at No. 2, and the lamp placed at two feet from the patient's eyes. The integration time was ten seconds in most cases. The responses from both eyes usually are recorded simultaneously, with one channel being processed while the other channel is stored on magnetic tape for later evaluation. The output of the system is displayed in polar form on an X/Y plotter, so that as the signal builds up during the integration time a radial line is plotted. This procedure gives the total amplitude of the signal and a direct indication of its phase angle automatically. The phase angle shifts with change in frequency of stimulation, so that when the outputs are plotted from a common center point the over-all result is a star-shaped pattern. The phase angles obtained from this pattern are plotted against frequency on standardized scales, and the "delay time" is obtained from the slope of the resulting plot. This procedure may be illustrated with the use of a relatively large calibration signal with a specified delay time. When such a signal is processed, a linear phase-frequency plot is obtained with a slope which corresponds to the specified delay time. When the signal is not a well-defined symmetrical waveform, the interpretation is not as immediately evident, but the same principles apply.

In order to illustrate how the Synchronous Detector method compares with the more familiar signal waveform averaging techniques, some of the recorded signals were averaged to display their waveforms with a Hewlett Packard No. 3721A Correlator in the averaging mode.

Normal values. As the traditional ERC data for normal subjects could not be used directly to establish normal results for this method of data processing, it was necessary to establish the range of normal results experimentally. The usual clinical and functional criteria were taken as the basis of "normal." Unprocessed retinal signals from a normal eye are shown in Fig. 1. The top trace shows the retinal baseline when no stimulus is present, while the lower three traces show in succession the unprocessed responses to white-flash stimuli at 27, 47, and 67 cycles per second. Although the signals for the lower two frequencies are evident upon inspection, the signal-to-noise ratio is too low for the noise to affect the waveform of the response to a considerable degree. An obvious improvement is obtained in the signal-to-noise ratio by averaging 128 sweeps, as shown in Fig. 2, for 27 cycles per second stimuli. Fig. 3, A shows the output of the Synchronous Detector system when these same signals are processed. The almost horizontal straight line is a 27 cycle per second calibration signal with an amplitude of 3 μv (rms.). Fig. 3, B illustrates the linear phase-frequency plot obtained from these measurements, with a delay time of 24 msec.

The amplitudes of the retinal signals are a function of the amount of light entering the eye. It was determined that maximum dilation of the pupil allowed the signal amplitude to increase by a factor of approximately two. The average amplitudes vary with frequency, and have a rather wide distribution. For example, measurements from 200 normal eyes (obtained mainly from subjects in the clinic population of a large hospital) with dilated pupils, at 27 cycles per second, gave an average value of 3.75 μv with a standard deviation of 1.7 μv. The actual distribution has a range of approximately 20 decibels, or equivalently a 10 to 1 voltage range. The normal delay times (from 276 normal eyes over an age range of 3 months to 80 years) are not dependent upon age, have a mean value of 24 msec, and a standard deviation of...
of 2.2 msec. The distribution is approximately symmetric, and the normal range in practice is approximately 18 to 29 msec. The results indicate that the variation of normal delay times is considerably smaller than the variation of normal signal amplitudes.

**Application to patients with retinitis pigmentosa.**

The results of ERG measurements from patients with retinitis pigmentosa have been described extensively. The ERGs often have been described as "extinguished," but with the introduction of waveform averaging techniques it was found that small signals sometimes could be obtained from such patients. However, eventually a point is reached at which no significant signal can be obtained, this usually corresponding to the clinical condition where the patient has extreme loss of visual field. Early or suspect cases of retinitis pigmentosa present a rather different picture. The history and retinal appearance may be equivocal, and the changes in the ERG may not be large. The following three patients are discussed briefly in order to illustrate the results obtained with cases of increasing severity of degeneration.

**Case 1: R. M. (No. 887).** This 16-year-old Caucasian boy had a family history of retinitis pigmentosa. One older brother had advanced retinitis pigmentosa, and it was reported that one older deceased brother may have been...
blind in one eye from retinitis pigmentosa at the time of his accidental death at age 25. The father was reported to have had difficulty with night blindness, but no definite details could be obtained. What little was known of the mother's history was unremarkable. Examination demonstrated the best vision in each eye to be 20/50. The media were clear and the discs appeared to be normal. The arterioles were slightly thin, but there was no typical pigmentation present, in fact only one or two isolated spots of pigment could be seen. Fields were difficult to measure in a repeatable fashion, but appeared to be constricted in normal illumination. Dark adaptation curves and flicker perimetry were reported as typical for retinitis pigmentosa of medium severity (courtesy of Dr. E. Wolf, Massachusetts Eye and Ear Infirmary).

The test conditions were as described previously (i.e., white-flash stimulation in the light-adapted state). The resulting signals were difficult to detect reliably on single sweep presentation, but they became much more evident after the summation of 128 sweeps. Fig. 4 shows such averaged signals obtained from the left eye at 22 cycles per second. The output of the Synchronous Detector is given in Fig. 5, A, and the corresponding phase-frequency plot in Fig. 5, B. It is clear from the latter figure that the "delay" of the signal may be specified over two frequency ranges, above and below approximately 37 cycles per second. For lower frequencies, the delay is approximately 34 msec, while for the higher frequencies it is approximately 5 msec. This is to be compared with the "normal" single linear segment of Fig. 3, B for the signal outputs shown in Fig. 3, A.

Fig. 4. Averaged waveform for 128 sweeps at 22 cycles per second. Patient R. M. (No. 887). Left eye. Vertical calibration 10 μv, horizontal calibration 10 msec.

Fig. 5. (A) Synchronous Detector output for patient R. M. (No. 887). Left eye. (B) Phase-frequency plot for patient R. M. (No. 887). Left eye.
Case 2: E. H. (No. 941). This patient was a 55-year-old Caucasian lady with obvious retinitis pigmentosa. Her family history was unremarkable. Best vision in the right eye was hand motion at one foot, and in the left eye, counting fingers at two to three feet. The media were clear, and the fundus appearance was typical of retinitis pigmentosa with a somewhat thin distribution of pigmentation. Fields were markedly decreased in each eye, and she became essentially blind with decreased illumination levels. In this case, the unprocessed retinal signals from each eye showed no detectable response. The results obtained from the left eye at 27 cycles per second by averaging 128 sweeps are shown in Fig. 6. The output of the Synchronous Detector is given in Fig. 7, A, and the phase-frequency plot in Fig. 7, B. The lower-frequency portion of the plot is not well defined, due to the very small signal amplitudes at these frequencies. For frequencies of 30 cycles per second and higher the plot is almost horizontal.

Case 3: J. I. (No. 851). This patient was a 35-year-old Caucasian lady with an advanced case of retinitis pigmentosa. What little was known of her family history was unremarkable. The diagnosis was first made at age 16, with progression which had been worse in the right eye.
eye than in the left eye. Her best vision was inaccurate light projection in each eye. The media were clear, and the fundi showed the typical appearance of advanced retinitis pigmentosa. Clinically it was not possible to say that one eye differed from the other, but the patient was certain that vision had always been much better with the left eye than with the right eye. Measurements from the left eye showed no detectable signal on the single-sweep presentation, while the result of summing 128 sweeps was very similar to that shown in Fig. 6 for Case 2. Processing the signals in the Synchronous Detector system gave small signal outputs for the left eye, with a phase-frequency plot which was flat. The signals from the right eye of this patient were indistinguishable from noise even after waveform averaging for 128 sweeps, as shown in Fig. 8, for 27 cycles per second stimulation. The Synchronous Detector output is shown in Fig. 9, and it is evident that no distinct phase-frequency plot can be obtained. The right eye thus provides an example for which the results can only be described as "noise" or "extinguished," even after the signals have been processed by either the waveform averaging technique or the Synchronous Detector.

Results

Association of loss of visual field with abnormal retinal delay times. Some generalizations may be made from consideration of the records obtained from 950 patients tested in the last few years. The normal retina gives the typical star-shaped pattern shown in Fig. 3, A. When the visual receptor elements undergo degeneration, as in the early stages of retinitis pigmentosa, the phase angles move around in a clockwise direction for the lower frequencies. The delay time changes correspondingly from a normal range of approximately 18 to 29 msec., to an abnormal value which becomes smaller for the higher frequencies. The amplitudes of the signals also decrease in general, although reasonable signal amplitudes may be obtained at times even when the delay time is grossly abnormal. Further degeneration results in eventual loss of the signal. The clinical course of such patients typically is one of increasing field loss, often while retaining sharp central visual acuity. For this group of patients it is interesting to consider if there is a correlation between the abnormal delay times and the extent of the field loss. Such a correlation is somewhat hindered because of lack of an effective simple numerical description of field loss. Without being too dogmatic, one may describe markedly constricted fields as those in which the central field is decreased approximately to the 5° isopter, as measured by the usual tangent screen technique with a white object (3 mm. in diameter) at one meter. A somewhat arbitrary division of the abnormal delay times also may be made, as listed in Table I. This table represents a summary of the results obtained from 72 eyes of patients with a diagnosis of retinitis pigmentosa. In five cases the retinal responses could be described only as "noise," and no delay time could be associated with them. In the other 67 cases the retinal
Table I. Visual field loss versus retinal delay time in eyes with retinitis pigmentosa

<table>
<thead>
<tr>
<th>Fields</th>
<th>Retinal delay time (msec.)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T&lt;3</td>
<td>3&lt;T&lt;=10</td>
</tr>
<tr>
<td>No information</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Markedly constricted</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>Some field loss</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>33</td>
</tr>
</tbody>
</table>

delay times have been divided into three abnormal categories and one normal category, namely greater than 18 msec. It is clear from the table that the markedly constricted fields are associated with the lower retinal delay times. (Although not discussed here this same association of constricted fields with abnormally low retinal delay times has been observed in many other patients. For those patients whose fields could be checked effectively, there has been no instance of a grossly abnormal retinal delay time and an intact field.)

Discussion

The stimulation frequency must be kept in mind when comparing the results obtained from abnormal retinas with this system with the results given by the conventional ERG methods. In the latter case, an increased delay time is associated often with abnormal retinal function, while with the Synchronous Detector system (for cone function) the abnormal delay times usually are decreased below the normal range. The phase-frequency plots indicate how this apparent discrepancy arises, as the traditional ERG refers to the lower-frequency end of the plot, for example one cycle per second or lower; while the Synchronous Detector system described here refers usually to frequencies of approximately 20 cycles per second and higher. The phase-frequency plot of the abnormal retina may be described in simple terms as follows:

1. the flatness of the higher-frequency response;
2. the steepness of the lower-frequency response;
3. the frequency at which one response changes into the other.

The higher-frequency response corresponds to a minimal delay time, and the signal amplitudes usually are quite small. The lower-frequency points usually indicate a delay time which is greater than the normal, and the points often show marked irregularities. The two segments of the phase-frequency plot intersect at a frequency which tends to decrease as the extent of the degeneration becomes more severe and widespread. As this occurs, the initial portion of the plot becomes steeper, and, consequently, the low-frequency delay time becomes longer. A point is then reached at which the low-frequency portion of the curve is not well defined, usually at approximately 17 to 20 cycles per second. Under such conditions, the measurements then show only the high-frequency straight line segment and indicate a markedly reduced delay time. The appearance of such signals on the X/Y plot is characteristic. Instead of the usual star-shaped pattern the responses all tend to be grouped close to each other in angle, covering one small sector of the plot.

The question often arises of the relationship of the Synchronous Detector output to the usual presentation of the ERG waveform, in terms of the “a” and “b” waves. Obviously, the two are representations of the same physical phenomena, but while the presentation of the usual ERG waveform is now accepted almost
intuitively, the relative strangeness of the processed Synchronous Detector output presents obvious difficulties in acceptance. If the usual ERG waveform is regarded as being produced at a certain repetition rate, for instance one cycle per second, or 20 cycles per second, then the resulting waveform may be subjected to Fourier analysis in the usual mathematical sense. A fundamental component will then be obtained at the basic frequency, together with higher harmonics. Each of these components will have an amplitude and phase angle associated with it, and the output of the Synchronous Detector is a measure of the amplitude and phase angle of the fundamental component. If one inspects the waveforms of the ERG signals at frequencies of 20 cycles per second and higher, it is at once clear that the usual ERG interpretation is not entirely appropriate, and that the main bulk of the waveform may be regarded as a photopic b-wave component. Thus, the output of the Synchronous Detector is a measure of this repetitive photopic b-wave, with the amplitudes dependent mainly upon the size of the wave, and the phase angle dependent to some extent upon the shape of the wave. As the waveform narrows, the phase relations change too, and the phase-frequency plots illustrated in this paper assume a different slope. The derivation of delay time from the phase angles obtained at different frequencies has no direct analogy in the usual ERG interpretation. When the phase-frequency plots show two distinct slopes, for example with the transition frequency at 30 cycles per second, the question arises as to whether this can be interpreted in terms of the "a" or "b" wave changes in the usual ERG sense. For the reasons outlined above this is difficult to do, particularly as in the instances where these transitions occur the signals usually are abnormal and the amplitudes are small. With the testing conditions specified, i.e., light adapted and with white-flash stimuli, the signal-to-noise ratio is usually low enough so that it is very difficult to discuss small a-waves.

The three examples given show that parameters such as "delay time" often can be derived even under conditions where the averaged waveform still has poor definition. The delay time does vary with the illumination level, but fortunately this is not a very sensitive function. "Normal" delay times have been obtained from subjects with closed lids, dense cataracts, and vitreous hemorrhages, so that variations in delay time due to variations in the retinal illumination level must be of little significance within the normal range described.

The fact that the test parameters involve the frequency of stimulation provides an additional means for separating the rod and cone function, in addition to the color and intensity of the stimulus and the background illumination. As mainly cone function is being tested under the conditions described, it is reasonable to consider that a field defect may exist when the delay time is abnormal. The results given in Table I show that there is such an association in a gross sense. Consequently, objective information often can be gained about field loss on a receptor dysfunction basis. (This also applies in cases with opaque media.) Although only patients with retinitis pigmentosa have been described here, this association of field loss and abnormal retinal delay time has been found to hold with other degenerative retinal states.

The average amplitude of the signals also may be used to differentiate normal from abnormal signals, although this is much less sensitive because of the wide range of normals. In addition, of course, the effect of opacities of the media becomes important again, as with the traditional ERGs. Tests carried out with patients with different conditions, for example injured eyes, detached retinas, and a variety of degenerative conditions, allow one to hazard some broad generalizations. It is not possible usually to obtain specific histologic evidence, except for some
traumatic cases, but it may be speculated that the amplitudes of the signals represent a measure of the number of functioning receptor elements, while an abnormal delay time characterizes an average change or loss of function of the existing elements.

The cases described briefly above have been used to illustrate the application of the Synchronous Detector method to patients with a well-recognized disease entity. In these cases it is evident that this method provides a simple direct numerical description of retinal (cone) function, even in states of advanced degeneration. Theoretically, the sensitivity of the system could be increased further by lengthening the integration time, but other factors such as patient cooperation and the time available for testing provide a practical limitation to this. Traditional ERG techniques, without any computer averaging, obviously run out of effective signals at much higher signal-to-noise ratios and can only report extinguished ERGs. Waveform averaging techniques may be used to recover these smaller signals, but some basic limitations still exist. The waveform averaging devices are more susceptible to interference, and they also involve relatively sophisticated computer techniques and equipment. In addition, their waveform output is not always ideal for time delay measurements, particularly when the resulting signal is quite small in amplitude. The Synchronous Detector process is much simpler from the point of view of instrumentation and, by its method of operation, is able to function even with a relatively large degree of interference. In addition, one avoids the direct problem of specifying a waveshape in order to measure delay time, and this applies even when the media are opaque. The Synchronous Detector process is much simpler from the point of view of instrumentation and, by its method of operation, is able to function even with a relatively large degree of interference. In addition, one avoids the direct problem of specifying a waveshape in order to measure delay time, and this applies even when the media are opaque. The Synchronous Detector process is much simpler from the point of view of instrumentation and, by its method of operation, is able to function even with a relatively large degree of interference.

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