Quantitative evaluation of photopic ERG waveforms

Candace M. Anderson, Arne Troelstra, and Charles A. Garcia

Quantitative, computer-based ways of representing photopic ERG waveforms are investigated and related to over-all retinal condition in a group of normal subjects and a group of patients with diagnosed retinitis pigmentosa. Sinusoidal stimulation and a Fourier series response representation have been selected. This combination provides a few parameters which facilitate waveform comparison, and it naturally lends itself to generalization if more detailed features of ERG recordings are to be included. On the basis of this type of waveform characterization, the over-all photopic retinal condition of any individual eye can be represented by a single number or by its location in various cluster diagrams and its distance from the normal cluster. As exemplified by the results herein described, such an automated approach can be particularly useful in screening large populations for retinal degenerations or in quantitatively following the progression of retinal degeneration over long periods of time.

Key words: ERG, retinitis pigmentosa, photopic, sinusoidal stimulation, computerized analysis, cluster diagrams

The specific aims of this paper are to investigate ways to more precisely characterize the photopic electroretinogram (ERG) response and to thoroughly test the feasibility of any such characterization method in a clinical environment.

In clinical applications a few general parameters are presently used to characterize prominent features of the ERG waveform. Very common among these are the peak-to-peak amplitude (A) and implicit time (T) for the single-flash ERG or the peak-to-peak amplitude and pseudo phase shift (P) for the ERG evoked by repetitive flashes. Measured in the manner shown in Fig. 1, these two parameters provide important information and have been successfully used by Berson to diagnose and classify many retinal degenerations. However, there is no way to estimate how accurately these general parameters capture the essential characteristics of the ERG waveform, or what other features of the response might be significant. Basically, one would like (1) a small number of parameters to represent the ERG waveform, (2) a convenient way to determine these parameters in a clinical situation, (3) a measure of the error in a particular representation, and (4) a method for reducing this error by including additional parameters. In this paper we shall look at parameters which satisfy these criteria. In addition, an attempt will be made to derive quantitative measures from these parameters that allow one to more precisely follow the progression of retinal degenerations or other retinal diseases.

Methods

Subjects chosen for evaluation. This study is based upon the quantitative comparison of photopic ERGs from a group of normal subjects with
those obtained from patients with retinal pathology. Baseline normal data were first collected from both eyes of 20 volunteers ranging in age from 18 to 75 years. Then the same protocol was used to test a group of 63 patients referred to the Electrodiagnostic Clinic of the University of Texas Medical School at Houston because of symptoms and/or family history of retinitis pigmentosa (RP). This particular disease was selected for study because of (1) the availability of a significant number of individuals with similar abnormalities, (2) the willingness of these patients to return for periodic evaluation, and (3) the accessibility of clinical information, including results from standard diagnostic tests. Of the total abnormal group, the diagnosis of RP has been confirmed for 59 individuals. The four remaining patients, lacking signs and symptoms consistent with the classic pattern of the disease and having more nearly normal retinal function, are referred to as "pseudo RPs" throughout the remainder of this investigation.

**Stimulus selection and response characterization.** A Sylvania R1131C glow modulator tube is used as a light source. With some additional electronics, this tube can produce a variety of light outputs when driven by an external generator such as a computer. With a simple optical arrangement, a homogeneous circular light spot approximately 15 mm in diameter is projected onto a white translucent scleral ERC contact lens worn by the subject. The pupil is dilated and completely covered by the illuminated portion of the translucent lens. Consequently, the light stimulus entering the eye is well diffused and always perceived in ganzfeld mode by the subject. For all experiments described in this paper, the stimulus color is "white".

Any type of quantitative evaluation of the ERG should be done with response waveforms that have the lowest possible noise contamination. Be-

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**Fig. 1.** Upper tracing, measurement of peak-to-peak amplitude (A) and implicit time (T) for a single flash ERG response; lower tracing, measurement of peak-to-peak amplitude (A) and pseudo phase shift (P) for a periodic ERG response. The 100 μV vertical calibration applies to both recordings, and each represents a duration of 83.3 msec.
cause of the noise characteristics of blinks, eye movements, electrode polarization drift, etc., a common way to improve the signal-to-noise ratio is to average many responses evoked by repeated stimulation under identical conditions. If the stimulation is a brief flash repeated at low frequencies, the response has basically all the attributes of a single-flash ERG and could be quantitatively characterized in either the time domain by a number of sample points or in the frequency domain by its frequency spectrum. The choice usually depends on personal preference and computer capability. In either case, the number of parameters would be rather large, dependent on the faithfulness of the characterization required. A representation using amplitude and implicit time seems more practical, since measurements can be made directly from records without the need for a computer and it is possible to ignore noise such as baseline drift and blinks. However, as mentioned before, these parameters are not suitable as a starting point for quantitative characterizations.

As an example of averaged ERGs recorded with different types of periodic stimulation, let us consider...
Consider the waveforms in Fig. 2. The light stimulus presented is a flash, a square wave, or a sine wave, and the repetition frequency varies from 5 to 54 Hz. Note that, in general, the responses are less detailed for square-wave stimuli than for flash inputs and that they become even smoother for sinusoidal stimulation. Also, the complexity decreases when the repetition frequency increases.

On the basis of a comparison of the three types of periodic ERGs, we now decide upon (1) a particular temporal pattern of light stimulation, (2) a specific type of response approximation, and (3) a quantitative error criterion to measure how well our response approximations resemble the actual ERG recordings. Obviously, these choices are not independent. We have selected the Fourier series approximation primarily because virtually all computer software packages contain subroutines to perform the necessary calculations. Since this approach is based upon the summation of sine waves, the smoother the response, the fewer the number of terms needed in a Fourier series to meet a given error criterion. Therefore sine wave stimulation has been selected as the type of light input. The error criterion in a Fourier series approximation is the mean square error.

Excluding the DC component from all our periodic ERG signals, the time-varying portions of these waveforms can be represented by a Fourier series of the form:

$$\sum_{n=1}^{N} A_n \cos(2\pi n f t + P_n)$$

where $A_n$ and $P_n$ represent the amplitude and phase of each harmonic, $N$ is the number of harmonics included in the approximation, $f$ is the frequency of stimulation in Hz, and $t$ is time in seconds. The coefficients $A_n$ and $P_n$ are determined in such a way that for any number of terms $N$, the series approximation is the best in a least-square-error sense.

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**Fig. 3.** For a signal $x(t)$ the power is defined as $S = \frac{1}{M} \sum_{m=1}^{M} (x_m - x_0)^2$, where $M$ is the number of signal samples in one period, $x_m$ is the value of the $m$th sample, and $x_0$ is the mean value of the signal. Values of $(x_m - x_0)$ are shown as vertical bars in the top portion of the figure. For a signal approximation $y(t)$, the error power is defined as $E = \frac{1}{M} \sum_{m=1}^{M} (y_m - x_m)^2$, where $y_m$ represents the value of the $m$th approximation sample. Vertical bars in the lower portion of the figure indicate values of $(y_m - x_m)$. In this particular case, the signal is a 20 Hz ERG flash response, and the approximation is the fundamental harmonic.
ERG RESPONSE TO 20 Hz FLASH STIMULATION

Fig. 4. ERG response to 20 Hz flash stimulation is approximated by an increasing number of harmonics. The ratio S/E of signal power to error power is given for each approximation.

To see how well ERG waveforms can be approximated by a Fourier series, a quality criterion the ratio of signal power to error power (S/E) is selected as illustrated in Fig. 3. This ratio is inversely related to the mean square error and provides essentially the same information. Although S/E = 1 would mean that the signal and error had equal power, increasing values for S/E indicate successively better approximations of the waveform.

In Fig. 4, a periodic flash ERG waveform of 20 Hz has been approximated by the fundamental only (N = 1), the fundamental and the second harmonic (N = 2), the sum of the first three harmonic components (N = 3), and the sum of the first four components (N = 4). In each case the value of S/E has been calculated. Having inspected many such characterizations, we have noticed that S/E >50 gives an excellent waveform approximation and S/E >10 means that the most general aspects of the response are represented.

For a small number of harmonics, characterizations of the flash, square wave, and sine wave responses are now compared on the basis of S/E. For each of the three stimulus types, the value of this ratio is shown in Fig. 5 at various frequencies for N = 1, 2, 3, and 4. It is apparent from this figure that at most frequencies, the highest value of S/E for the fewest number of harmonics is achieved when the stimulus is sinusoidal. At frequencies lower than 10 Hz, this improvement becomes very significant.

Using only the magnitude and phase of the fundamental response component, we limit ourselves in this initial study to two-parameter characterizations. One advantage of this simple approach is that variations in a pair of parameters can be conveniently visualized in a two-dimensional cluster diagram. As can be seen from Fig. 5, characterizations based solely upon the fundamental are only practical for frequencies larger than 20 Hz and even then only capture the general, over-all shape of the response. More detailed waveform features are contributed by higher harmonics and thus reflect nonlinear ERG behavior not considered in a two-dimensional (linear) approximation.
Fig. 5. Contribution to the S/E ratio by each of four harmonics at five different frequencies. Each contribution is indicated by different shading as shown on the right. Each group of three bars represents three types of periodic stimulation. Left bar, repetitive flash; middle bar, square wave; right bar, sine wave.

In our experimental protocol, the mean light level of the stimulus is made sufficiently high to saturate the rod system. In addition, the high frequencies ensure that only photopic activity contributes to the response. This has been experimentally verified for a rod achromat who showed a normal scotopic ERG but a totally extinguished response for the types of stimulations considered clinically in this paper.

Operating system implementation. The operating system is composed of two functionally different parts: a data-acquisition section and a data-analysis section. The computer configuration used for both sections consists of a central processor with 4K of memory and a number of standard peripheral units such as analog-to-digital converters, digital-to-analog converters, a magnetic tape storage unit, an oscilloscope display, and a control panel.

A block diagram of the data acquisition section is shown in Fig. 6. The amplifier has variable gain (maximum = 10,000), DC offset, and a time constant which is sufficiently high to ensure a flat frequency response (both magnitude and phase) in the range from 2 to 200 Hz.

For each eye tested, a total of 19 responses is collected and saved on magnetic tape. For reference purposes, the first stimulus presented is a light "flash" which has a peak intensity of 13.3 ft-lamberts and a duration of 100 msec. The remaining 18 inputs are sine waves of mean intensity 6.7 ft-lamberts and modulation of about 98%. The frequency is varied in the range of 2 to 54 Hz. As indicated by the order of sinusoidal stimuli specified in the first column of Table I, a two-pass

Table I. Summary of the standard protocol used for measuring ERG responses to periodic stimulation (total time required for actual recording approximately 3.7 min)

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>No. Averaged</th>
<th>Time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>16</td>
</tr>
<tr>
<td>12</td>
<td>64</td>
<td>11</td>
</tr>
<tr>
<td>20</td>
<td>128</td>
<td>13</td>
</tr>
<tr>
<td>24</td>
<td>128</td>
<td>11</td>
</tr>
<tr>
<td>32</td>
<td>128</td>
<td>8</td>
</tr>
<tr>
<td>42</td>
<td>128</td>
<td>6</td>
</tr>
<tr>
<td>54</td>
<td>128</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>10</td>
<td>64</td>
<td>13</td>
</tr>
<tr>
<td>16</td>
<td>128</td>
<td>16</td>
</tr>
<tr>
<td>20</td>
<td>128</td>
<td>13</td>
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<tr>
<td>28</td>
<td>128</td>
<td>9</td>
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<td>36</td>
<td>128</td>
<td>7</td>
</tr>
<tr>
<td>48</td>
<td>128</td>
<td>5</td>
</tr>
</tbody>
</table>
MEMORY  
4K
CENTRAL
PROCESSOR
SINE WAVE
GENERATION
LIGHT
STIMULATOR
EYE
AMPLIFIER
START
RESPONSE
AVERAGING
STORE
TAPE
DISPLAY

Fig. 6. Data acquisition section. The double-lined blocks are part of the computer system, which in our case is a DEC PDP-12. However, any small computer or microprocessor can provide the same capabilities.

procedure is followed in order to make sure that no gradual changes in light adaptation occur during the course of the experiment. The values listed in the second and third columns of Table I show the number of two-period segments averaged and the length of the recording interval required at each frequency. In addition to automatically changing the stimulus and the number of responses to be averaged, the computer also displays each averaged response according to patient number, stimulus number, and left or right eye. The operator has to perform only two operations: to initiate the averaging process for each new stimulus and to decide whether to store the averaged response on tape. Once the electrodes are in place and the light source is positioned, data acquisition requires only about 5 min per eye with this automated procedure.

As illustrated by the block diagram shown in Fig. 7, data analysis is also performed by computer. The three distinct operations which are involved in this section are referred to as step I, step II, and step III.

In step I, the Fourier transform is determined for each of the two periods of a response. By so doing, each period is represented by the magnitude and phase of its fundamental, the magnitude and phase of its second harmonic, and so on, up to and including the thirtieth harmonic. The resulting 120 parameters per response are then stored on tape and are available for use in step II.

ERGs obtained under clinical conditions are frequently low in amplitude. Furthermore, because many patients have difficulty in maintaining steady fixation and suppressing blinking, their responses are often not as reproducible as normal recordings and tend to be more contaminated with unwanted disturbances. In order to determine when a stimulus-related signal is present, each response is therefore tested for reproducibility and magnitude. This evaluation is formulated in quantitative terms by calculating a reproducibility factor $R$ for each response as follows:

$$R = 100 \frac{\sum \limits_{n=1}^{4} K_n \cos(\Delta P_n)}{A}$$  \hspace{1cm} (1)

The subscripts 1 through 4 in the above equation refer to the first four harmonic components of the response. The phase difference between the first and second periods of the $n$th harmonic represented by $\Delta P_n$. The coefficients $K_n$ are found from the following expression:

$$K_n = \frac{A_n}{A_1 + A_2 + A_3 + \ldots + A_{30}}$$

for $n = 1, 2, 3, 4$.

Each $A$ in the above equation represents the magnitude of the harmonic indicated by the subscript and averaged over the two periods of the response. If any $A_n < 0.7 \mu V$ referred to the original ERG input signal, then that particular $K_n$ is set to zero.

The value of $R$ varies between 0 and 100 depending on the quality of the response. For waveforms where $K_n \cos(\Delta P_n) = 0$ for $n$ equal 1 through 4, $R$ has the minimum value of zero. On
the other hand, the maximum value of R is achieved if (1) a response is completely characterized by its first four harmonics, (2) each of the nonzero components has a peak-peak amplitude greater than 0.7 μV, and (3) the corresponding phase angles for the first and second cycles are exactly identical. “Perfect” reproducibility is thus described by:

$$\Delta P_1 = \Delta P_2 = \Delta P_3 = \Delta P_4 = 0$$

and

$$R = 100 \left[ K_1 + K_2 + K_3 + K_4 \right] = 100$$

Decreasing from a maximum value of 1 for $\Delta P_n = 0$ to a minimum of zero for $\Delta P_n = \pm 180$ degrees, the function $\cos \left( \Delta P_n \right)$ serves as a weighting factor in the computation of R described in equation 1. The cosine is used because it is an even function and thus assigns equal weights to positive and negative phase discrepancies. The eighth power ensures a rapid decrease for increasing values of $\Delta P_n$, and thus only those harmonics whose two response periods are most nearly in phase contribute significantly to the total value of the reproducibility factor, R. Although many weighting functions with similar properties are possible, this particular one has been empirically determined to produce values for R which seem closely related to visual appreciation of responses. This is illustrated in Fig. 8, where several 32 Hz responses obtained from patients are shown with corresponding values of the reproducibility factor R.

With $R = 20$ used as a cutoff value, ERGs whose computed reproducibility factor falls below this threshold are deemed nonrecordable. A response can be so classified for any one or more of the following reasons. (1) The signal is too small in amplitude ($<0.7 \mu V$) for adequate resolution. (2) There is too much variation in the phase angles of corresponding harmonics in the two periods of the response. (3) Not enough of the signal is represented by the first four harmonics because the response contains excessive high-frequency noise contamination. Recordable ERG responses for which $R \geq 20$ are evaluated on the basis of the average of their two periods.

The final stage in the data analysis procedure, step III, involves the determination of a single quantitative index to characterize a series of responses from any one eye. Since there are strong...
Fig. 8. Responses of RP patients to 32 Hz sinusoidal light stimulation. Recordings shown represent the average of 128 two-period response segments. These waveforms are reproduced on different scales, and the peak-peak amplitude in microvolts is shown in the left column. In the right column the value of the reproducibility factor R is given for each response. As explained in the text, this factor indicates how closely the two periods in each response resemble one another.

Table II. Mean peak-peak amplitude and mean phase of the fundamental frequency in response to sinusoidal stimulation for the group of normals tested

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Amplitude (μV)</th>
<th>Phase angle (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>39 ± 9*</td>
<td>125 ± 12</td>
</tr>
<tr>
<td>24</td>
<td>47 ± 11</td>
<td>94 ± 11</td>
</tr>
<tr>
<td>28</td>
<td>57 ± 15</td>
<td>59 ± 13</td>
</tr>
<tr>
<td>32</td>
<td>57 ± 16</td>
<td>25 ± 13</td>
</tr>
<tr>
<td>36</td>
<td>57 ± 18</td>
<td>-20 ± 15</td>
</tr>
<tr>
<td>42</td>
<td>44 ± 14</td>
<td>-72 ± 17</td>
</tr>
<tr>
<td>48</td>
<td>30 ± 11</td>
<td>-117 ± 14</td>
</tr>
<tr>
<td>54</td>
<td>20 ± 6</td>
<td>-149 ± 18</td>
</tr>
</tbody>
</table>

*Mean value ± 1 S.D.

Table III. Subdivision of RP patient group into three categories according to response characteristics (total number of eyes = 118 (59 patients) for each frequency)

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Category 1 (recordable)</th>
<th>Category 2 (extinguished)</th>
<th>Category 3 (unreliable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>52</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>24</td>
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<td>48</td>
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</tr>
<tr>
<td>54</td>
<td>29</td>
<td>68</td>
<td>21</td>
</tr>
</tbody>
</table>

Absolute value of the difference in degrees between the fundamental phase angle P and the normal mean m is computed. (2) For any responses labeled as nonrecordable in step II, a maximum phase difference of (P - m) = 180 degrees is assigned. (3) For each of the sample frequencies from 20 to 54 Hz, the number of standard deviations by which the phase differs from the normal mean is expressed as $d = (P - m)/\sigma$. (4) The average phase deviation D is determined in accordance with the following equation:

$$D = \frac{1}{9} [d(20) + d(20) + d(24) + d(28) + \ldots + d(32) + d(36) + d(42) + d(48) + d(54)]$$

The numbers in parentheses in the above expression denote the frequency of sinusoidal stimulation. If for a particular eye, the phase of the fundamental response component exactly coincided with the normal mean at all nine frequencies, then every d(f) in equation 2 would equal zero, and
Fig. 9. Polar plot cluster diagrams of normals, pseudo RPs, and RP patients at two frequencies of sinusoidal stimulation: 24 and 54 Hz. Peak-peak magnitude of the fundamental is plotted radially on a log scale, and the inner and outer circles represent 0.75 and 96 μV, respectively. The phase angle is plotted linearly from 0 to ±180 degrees. Normals are depicted as filled squares, pseudo RPs as open squares, and RP patients with recordable ERGs as + signs.
consequently D would have the minimum value of zero. At the opposite extreme, the maximum value of D is obtained when a patient has no recordable ERG at any of these high frequencies. In this, the worst possible case, each \( d(f) = \frac{180}{\sigma} \), where \( \sigma \) represents the standard deviation in the normal phase at that particular frequency.

**Clinical procedures.** Once computed for each abnormal eye, the photopic ERG index D is compared with standard clinical test results, including visual acuity, color vision, visual fields, and the electro-oculogram (EOG). The best corrected visual acuity is determined in the standard manner. Color Vision is evaluated on the basis of the Farnsworth 100-hue test. Visual fields are measured with the Goldmann perimeter (Haag-Streit; Model 940-K3) using three isopters: \( V_4 \), \( I_4 \), and \( I_2 \). With islands of vision and ring scotomas taken into account, the approximate visual field radius in degrees is estimated for each isopter. The mean of these three radii is then computed, and the resultant value is called the average visual field radius. The EOG ratio is determined in the conventional way as the light-peak/dark-trough ratio.

Other patient data such as degree of retinal pigmentation and hereditary pattern are also noted. Retinal pigmentation is classified as mild, moderate, considerable, or heavy. Hereditary pattern is categorized as sex-linked, dominant, or recessive, and those patients with no known family history of RP are included in the recessive group.

**Results**

Comparisons made in this section are based on results obtained from 20 normal subjects, 59 RP patients, and four individuals categorized as pseudo RPs. In all cases both eyes of each subject were tested.

In Table II the mean peak-peak magnitude and the mean phase of the fundamental frequency in response to sinusoidal stimulation are given for the normal subjects. The mean magnitude reached a maximum of 57 \( \mu \)V around 32 Hz, and the phase decreased
Fig. 11. Polar plot cluster diagrams at 20 and 32 Hz. Normals are indicated as filled squares. The small + signs represent both eyes of RP Patient J tested three times at 6-month intervals, and the large ones represent those of RP Patient K tested two times 6 months apart.
Fig. 12. Top portion, Visual acuity plotted as a function of the photopic sinusoidal ERG index D. Lower portion: Farnsworth 100-color test score plotted as a function of ERG index D. A score of less than 100 is considered normal, and the higher the score, the more severe the color vision abnormality.

steadily from +125 degrees at 20 Hz to −149 degrees at 54 Hz.

Recordable ERGs were obtained from all 40 normal and eight pseudo RP eyes for each of the nine sample frequencies. Table III shows how at each frequency of stimulation, the total of 118 RP eyes divided into three categories. The numbers listed in category 1 passed the reproducibility test and are the only ones to appear in subsequent plots. Those in the other two categories were deemed nonrecordable either because the amplitude was too low (category 2) or because there was too much variability in the record-
came so low in magnitude at higher frequencies that they moved inside the 0.75 \( \mu V \) circle and therefore no longer passed the reproducibility test.

Since RP is nearly always bilateral, it is of interest to see how the right and left eyes of each patient are plotted. In Fig. 10, which is a replica of the top portion of Fig. 9, the corresponding eyes of most RP patients are encircled. Note that the two members of each of these pairs are usually located close to one another. Exceptions include the unlabeled single eyes for which the corresponding eye did not pass the reproducibility test because of too much variability in the recording. Patients whose two eyes appear rather far apart in the RP cluster in Fig. 10 are labeled A, B, and C. For Patient A, the eye which is further away from the normal cluster did indeed have more significantly affected visual fields and color vision. The same is true for the visual fields of Patient B, but to a lesser degree. Although no particular differences between the two eyes of Patient C could be corroborated, the results of the various clinical tests were not too reliable in this case because of the presence of visual problems not directly related to the RP condition.

Fig. 11 exemplifies results obtained from two patients retested at intervals of approximately 6 months. Polar plot cluster diagrams similar to those introduced in Fig. 9 are shown for frequencies 20 and 32 Hz. The normals, again plotted as black squares, are included for reference. Patient J, represented by the small + signs, was tested three times, resulting in 6 points (one for each eye) in both polar plots. The four large + signs which also appear in the two plots represent Patient K, who was tested twice. As can be seen in both the upper and lower portions of the figure, the points for each of these subjects stayed fairly close together over long periods of time. Similar results have been obtained for many other patients tested repeatedly. The 6- to 12-month intervals are probably much too short to show significant progression in retinal degeneration and resultant movement of points within the RP cluster.

In the previous section, a photopic sinusoidal ERG index D was introduced, which reflects the average number of standard deviations by which the fundamental phase angle of an abnormal eye differs from the normal mean. Recall that D = 0 would be a perfect normal, whereas the maximum value D = 12.7 is assigned when no high frequency response is recordable. This latter value is obtained by substituting \( d(f) = 180/\sigma \) for all nine frequencies in equation 2 and using the standard deviations given in Table I.

In Figs. 12 and 13, the outcome of clinical
Table IV. Relationship between degree of retinal pigmentation in RP patient group and the ERG index D (total number of eyes = 118 (59 patients))

<table>
<thead>
<tr>
<th>No. of RP eyes</th>
<th>Retinal pigmentation</th>
<th>Mean D ± 1 S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>Mild</td>
<td>8.6 ± 0.8</td>
</tr>
<tr>
<td>58</td>
<td>Moderate</td>
<td>9.7 ± 0.4</td>
</tr>
<tr>
<td>14</td>
<td>Considerable</td>
<td>10.1 ± 1.0</td>
</tr>
<tr>
<td>18</td>
<td>Heavy</td>
<td>10.5 ± 0.6</td>
</tr>
</tbody>
</table>

Table V. Relationship between hereditary patterns in RP patient group and the ERG index D (total number of eyes = 118 (59 patients))

<table>
<thead>
<tr>
<th>Hereditary pattern</th>
<th>No. of RP eyes</th>
<th>Mean D ± 1 S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex-linked</td>
<td>2</td>
<td>7.6 ± 0.5</td>
</tr>
<tr>
<td>Dominant</td>
<td>16</td>
<td>9.0 ± 1.0</td>
</tr>
<tr>
<td>Recessive</td>
<td>100</td>
<td>9.9 ± 0.4</td>
</tr>
</tbody>
</table>

tests quantified in the manner described in the methods section is plotted as a function of the sinusoidal ERG index D. In all cases there was a large spread in the data points, but a general trend could be clearly recognized. With increasing values of D, the visual acuity became worse, color vision deteriorated, and the average visual field radius decreased. The EOG ratio seemed to decrease only slightly when D changed drastically, but it was below normal for the whole range of D. In all four graphs of Figs. 12 and 13, there are points from different eyes which would fall on top of each other, especially for D = 12.7. In those cases, points are displaced vertically by a small amount in order to distinguish them from one another.

The relationship between retinal pigmentation and the ERG index D is illustrated in Table IV. Again there was a general trend of increasing D with this clinical observation.

The relationship between hereditary pattern and ERG index D is illustrated in Table V. In this instance, the number of RP eyes in two of the three categories was so small that no meaningful conclusion could be made.

Discussion

In this paper a particular type of light stimulation (sinusoidal) and frequency range (≥20 Hz) has been investigated and tested for its usefulness in clinical electroretinography, especially in cases of RP. The sine wave stimulus is utilized because the response waveforms it elicits are somewhat less complex in appearance than those observed using other types of periodic stimulation, such as flashes and square waves. The rather high-frequency range has been selected in this initial study because normal ERGs can be approximated by only two parameters (magnitude and phase of the fundamental component) without prohibitively large errors.

Periodic stimulation has been tested before in similar clinical situations. However, the current study is different in that the emphasis has been on (1) computer-controlled test procedures, (2) automated evaluation of responses and categorization as recordable, extinguished, or unreliable, (3) computer display of cluster diagrams showing normal clusters and those made up of RP eyes with recordable responses, and (4) derivation of a sinusoidal ERG index to capture the over-all photopic retinal condition with one single number.

Our findings are very encouraging in that the cluster diagrams exhibit many properties one would like to see in this type of data presentation. Normal eyes cluster together; RP eyes fall into a separate extended cluster; eyes of the same subject are usually located close together; and repeated testing over long time intervals does not change the location of a particular abnormal eye in the RP cluster (cf. Figs. 9, 10, and 11). Results could be made to look even better by improving the experimental conditions in the following ways: (1) perform tests only at frequencies ≥20 Hz and average more responses, (2) use an amplifier configuration with a shorter time constant suitable for these higher frequencies, (3) alter the stimulus intensity to correct for differences in dilated pupil size, and (4) improve the scleral ERG lens to ensure that the illuminated portion of translucent mate-
Fig. 14. Same polar plot cluster diagram at 24 Hz as top portion of Fig. 9. Values of the sinusoidal ERG index D are indicated for various eye pairs (encircled). A pseudo RP patient (open squares) has been included to illustrate the low value of D when eyes are close to normal. Values for D of 3.8 and 8.4 correspond to Patient A of Fig. 10 (not encircled). Values of D of 5.7 and 9.6 correspond to patient B of Fig. 10 (not encircled).

rial always covers the pupil completely. If such changes were implemented, one would expect the normal clusters such as those shown in Fig. 9 to become smaller, the plots of two eyes of a subject to move even closer together in the RP cluster (Fig. 10), and the long-term stability illustrated in Fig. 11 to improve. Furthermore, the present detection threshold of less than 1 μV could be made even lower. Thus some responses now classified as being extinguished would move into the category of recordable responses, and the RP clusters plotted would contain more eyes.

It should be noted that in the polar plot cluster diagrams shown in Figs. 9, 10, and 11, a clockwise movement of points indicates an increasing phase lag. When at a fixed frequency points are displaced clockwise as are the RP eyes compared to the normal eyes in the top portion of Fig. 9, this indicates longer delay times and/or greater sluggishness in the system dynamics for the abnormals. The fact that there are always some delay and dynamical sluggishness causes both normal and RP clusters to rotate clockwise when the frequency of stimulation is increased—as in the lower portion of Fig. 9 relative to the upper portion. When the cluster diagrams in these two portions of Fig. 9 are compared, it appears that a "spiraling tail" RP cluster at 24 Hz becomes a "radial tail" RP cluster at 54 Hz. Cluster diagrams at intermediate frequencies show that this is a very gradual process. It means that the increase in phase lag with increasing frequency of stimulation oc-
curs at a slower rate for RP subjects than for normal subjects. A similar finding has been reported by Fricker.10

The ERG amplitude decreases rapidly in RP cases, and we have been fortunate to have such a large group of patients with a measurable response (about 40% of the RP patients, see Table III). If one had to select one particular frequency of stimulation at which to obtain a quick evaluation of the photopic ERG, 32 Hz would be a good choice. At this frequency, the response is well represented by its fundamental frequency only (Fig. 5), there is a maximum in the amplitude of the normal response (Table II), and a correspondingly large number of RP patients have recordable responses (Table III).

The photopic sinusoidal ERG index D is basically a measure of how far away a particular eye is located from the normal mean in a number of cluster diagrams; it is expressed in standard deviations phase lag averaged over nine frequencies from 20 to 54 Hz. This index varies from 0 to 12.7, and comparison with clinical information shows that larger values of D generally correspond to a more severely abnormal retina. Figs. 12 and 13 and Tables IV and V support this finding, although the large spread in the points should caution us when drawing conclusions from these data. We believe that this spread is not caused as much by uncertainty regarding the value of the deviation index D as by the variability in the clinical test results or the fact that certain of these tests are not directly related to over-all photopic retinal activity.

To illustrate how the location in RP cluster at a particular frequency is related to the index D and consequently to the over-all retinal condition, a number of D values are indicated in Fig. 14 (a replica of the top portion of Fig. 9). It is clear that the farther a point is removed from the normal cluster, the higher the value of D. However, there is no monotonic increase in over-all index value with distance, since D is calculated from information at nine frequencies from 20 to 54 Hz and a cluster diagram depicts information at only one frequency. It is interesting to note from Fig. 14 that Patients A and B whose eyes are rather far apart in the RP cluster of Fig. 10, also have quite different D values (D = 3.8 and 8.4 for A, and D = 5.7 and 9.6 for B). Again, the larger values of D correspond to the eyes more severely affected.

It should again be emphasized that the present study is concerned exclusively with the photopic behavior of the over-all retina. Another aspect of this activity is reflected in the responses to sinusoidal stimulation at frequencies below 20 Hz. In our experimental arrangement it has been demonstrated with a rod achromat that for frequencies from 2 to 6 Hz there is some contribution from the scotopic system. In order to isolate photopic behavior at such low frequencies, it may be necessary to include a background adaptation light to suppress the scotopic response. Also, it can be seen from Fig. 5 that responses to sinusoidal variations slower than 20 Hz cannot be accurately represented by the fundamental component only and that additional harmonics must therefore be taken into account. A complication is thus introduced, since two-dimensional clusters like the ones introduced in Fig. 9 are no longer adequate and higher-dimensional representations have to be considered.

The scotopic system can be tested with the same protocol described in this paper for photopic evaluation. To do so, the stimulus color is changed to blue, the average light level is decreased considerably, slower input frequencies are used, and subjects are completely dark-adapted before beginning the experiment. Because the scotopic responses thus elicited by sinusoidal stimulation are quite simple, they too can be represented by fundamental magnitude and phase only without too much of an error. Cluster diagrams similar to that shown in Fig. 9 can therefore be constructed.

This study has demonstrated that if one wants a fast and accurate assessment of retinal condition, a sinusoidal ERG test may be an excellent choice. Such evaluation is objective and can be used to directly compare any retinal condition with normals and patients with retinal pathology. If only one test could be performed for screening a large
photopic ERG waveforms

population, this procedure has definite advantages because of its convenient application and the wealth of information which can be obtained.

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REFERENCES


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