Effect of Decreased Retinal Illumination on Simultaneously Recorded Pattern Electroretinograms and Visual-Evoked Potentials

Jeffrey Froehlich* and David I. Kaufman†

Sixteen normal subjects and three patients with optic neuritis were studied to determine the effect of decreased retinal illumination on simultaneously recorded pattern electroretinograms (PERG) and visual-evoked potentials (VEP). Using neutral-density filters (NDF), it was found that linear modeling is an excellent fit for VEP/PERG amplitudes and latencies as log functions of retinal illumination, both for individual eyes and averages of pooled data. Within narrow statistical limits, regression slopes show that mean PERG B-wave and VEP P100 latencies are affected almost identically by decreased illumination, leaving the mean retinocortical time (RCT) virtually unchanged. However, mean B-wave amplitude was greatly reduced at retinal illuminations at which P100 amplitude was unaffected. Of clinical significance was that these latency and amplitude effects were found in each eye tested, whether normal or pathologic. In particular, the RCT in normal subjects was never found to be statistically abnormal due to decreased retinal illumination, and it faithfully represented the optic nerve lesion in the patients with optic neuritis. This result was applied to a population of eight patients with uncomplicated cataracts. The significance of these results is discussed.

The visual-evoked potential (VEP) is often used in the diagnosis of optic nerve lesions (ONL).1-4 Unfortunately, nonneurologic factors such as refractive error5-7 and volitional manipulation,8-9 and retinal problems such as maculopathy23 can produce a VEP with abnormal P100 latencies in patients without ONL. Previous work has shown that a simultaneously recorded pattern electroretinogram (PERG) is useful in detecting these factors. In particular, the greater sensitivity of the PERG over the VEP to disruption by ocular or nonneurologic problems implies that a normal PERG eliminates these problems as the etiology of an abnormal VEP.6-9 In the case of early maculopathy, a normal retinocortical time (RCT), the interlatency period from the PERG B-wave to the VEP P100, places the etiology of a prolonged VEP in the retina.3,4

In this report we used neutral-density filters (NDF) to study the effect of decreased retinal illumination on the VEP/PERG. We show that PERG B-wave latency changes account for most of any prolongation induced in the VEP by the NDF. The RCT is relatively unchanged and remains normal even when the P100 latency exceeds statistical limits of normal. This makes the PERG a clinically important adjunct to the VEP in any ocular condition creating opacities to the transmission of light, eg, cataracts or uveitis. Using the simultaneous VEP/PERG in known cataract patients who are otherwise normal, the PERG and RCT calculated from it resolve the ambiguity surrounding an abnormal VEP in such patients.

In addition, in two patients with known unilateral optic neuritis, decreased retinal illumination affected VEP/PERG latencies and amplitudes in the affected eye to the same extent as in the normal eye. As with normal eyes, the RCT was constant in the affected eye with decreased retinal illumination. A third patient with bilateral optic neuritis was also studied. In a similar study on five normal subjects, Tobimatsu et al10 suggested that the RCT is not changed significantly by decreased retinal illumination. By increasing the sample size and both the number and total range of luminances tested, we established the relative constancy of the RCT more precisely, both for individuals and for population means, and the linear relationship between log (luminance) and VEP/PERG latencies and amplitudes. A differential effect of decreased retinal illumination on VEP and PERG amplitudes was also found.

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Materials and Methods

Sixteen subjects with normal neuro-ophthalmologic examinations and two patients with unilateral optic neuritis and abnormal VEP in the affected eye were used to study the effect of decreased retinal illumination on the simultaneously recorded VEP/PERG. A third subject with bilateral optic neuritis was also studied. The diagnosis of optic neuritis was based on the presence of ocular pain aggravated by movement, visual loss over several days with a cecocentral scotoma, no evidence of mass by magnetic resonance imaging, and normal funduscopic. Eight patients with early cataracts, minimal acuity changes, and otherwise normal neuro-ophthalmologic examinations were referred to our Neuro-Visual Unit to be tested for concomitant ONL. These patients, aged 55-75 yr, provided an impetus for this study because their cataracts acted partly as filters to incoming light. The age range for the control subjects and the patients with optic neuritis was 20-48 yr. All subjects consented to testing after being informed of its experimental nature. The patients with optic neuritis were chosen because, at the time of testing, 10 days to 4 weeks after the acute visual loss, they had recovered normal visual acuity despite their ONL, and their VEPs were well defined, although with delayed P100 peaks.

Details for recording the VEP/PERG are described elsewhere.4 The PERG were recorded with the use of bipolar Burian-Allen contact lens electrodes. After lens placement, each normal eye tested, and the affected eye of the patients with optic neuritis, was refracted to at least 20/20 acuity. The cataract patients were refracted to at least 20/60 acuity. The visual stimulus consisted of a checkerboard pattern of 30' checks subtending a total visual angle of 30° at a distance of 85 cm. The pattern was reversed at 1.8 reversals/sec. Total screen luminance was 34 footlamberts with a contrast of 94%.

The VEP was recorded from a midoccipital electrode (MO) referenced to a frontal electrode (Fz). Ground was at the vertex (Cz).

Using this setup, retinal illumination was decreased during testing by introducing NDFs directly in front of the properly retracted eye. The strength of an NDF is measured as log(Ij/If), where Ij is luminance of incoming light and If luminance of the light after passing through the filter. The VEP/PERG were done with a sequence of NDFs needed for the following log-unit decreases in retinal illumination: 0.0, 1.0, 1.3, 0.6, 1.6, and 0.0. The repeat of the control (0.0) test was to eliminate the possibility of decremental responses due to the length of the test, approximately 20 min per eye. Decremental responses did not occur. Staggering the NDFs used ensured that the results of the data analysis were not just secondary to systematic or monotone changes in test luminance.

For 10 of 46 eyes, the B-wave amplitude for the 1.6 log-unit test was too small (less than 0.3 μV) to locate the peak accurately. In two eyes, the 1.3 log-unit reduction in retinal illumination made the B-wave too small to locate.

All eyes tested had pupil sizes greater than or equal to 5 mm, except for two of the cataract patients. Before lens placement for VEP/PERG testing we did a regular VEP. This served the dual purposes of checking the VEP before lens placement for later consistency and allowing a 15-25-min period for adaptation before doing VEP/PERG testing. Hence, luminance changes secondary to small pupil sizes were not a problem.10,11

Visual acuity was also measured while using the 1.6 log-unit filter. Although the resulting acuity was lower than originally tested, it never was worse than 20/50 for any normal subject or patient with optic neuritis. This acuity was sufficient for VEP/PERG recording with 30' checks. With a 1.0 log-unit filter, acuity was only slightly altered. Thus we believe our results are not due to poor fixation or acuity problems.

All VEP/PERG tracings were the result of 100 inputs averaged with a minicomputer. Inputs were recorded at a low band pass of 1 Hz and a high band pass of 100 Hz. In addition, all PERG input was monitored continuously to eliminate the possibility that amplifier saturation in recording epochs subsequent to artifact rejection of large blink artifacts was causing amplitude reduction during the tests. We found this artificial reduction of amplitudes can be a problem even for normal controls12 and believe this to be a major cause for the variability of the PERG13 and the low limits of normal for B-wave amplitudes often reported.14 Detection of this problem followed by appropriate patient instruction makes PERG recording much more reliable.

A-wave and B-wave peaks of the PERG and the N70 and P100 peaks of the VEP were labeled with a standard program, which also measured P100 and B-wave latencies and amplitudes. Our convention was to define B-wave amplitude as the voltage difference between A-wave and B-wave peaks, the P100 amplitude as the voltage difference between N70 and P100 peaks, and the RCT as the interlatency time between PERG B-wave and VEP P100 peaks. Positive deflection is up for the PERG and down for the VEP.

Amplitude differences between duplicate tracings were never greater than 15% of the larger value and rarely greater than 10%. Duplicate waveforms were
then averaged off line before analysis. All values reported for the subjects in this study were compared with normal limits used in our laboratory based on 45 different controls (age range, 18–45 yr) (Table 1). For comparison with the age group of our cataract patients, 55–75 yr, 5 msec was added to the normal upper limit for P100 latency.

**Statistical Analysis**

For each eye tested and for the averages of all measured quantities, linear-regression lines and slopes for B-wave latency and amplitude, and P100 latency and amplitude as functions of log-unit decreases in retinal illumination were calculated by standard procedures. Amplitudes normalized as a fraction of the control (0.0 log filter) were also analyzed in this way. Because of the statistical effects of intereye correlation, one eye was chosen randomly from each subject for analysis of the pooled data. This was also done for the normals in Table 1. For the cataract patients, only the eye for which the patient was referred was used for analysis.

Coefficients of determination (the square of what would be the correlation coefficients if the retinal illumination were a random rather than an independent variable) for regression lines were at least 0.85 and, in 80% of all determinations, greater than 0.92. In general, the coefficient of determination, which is the fraction of the total variance of the dependent variables (eg, latencies and amplitudes) accounted for by the regression line approximation, varied from 0–1. A value of 1 means that a linear model fits the data perfectly. The values obtained in this study show that linear modeling was excellent for these data, both for individuals and for the averages of the pooled data.

*Fig. 1. Effect of decreased retinal illumination on one subject's VEP/PERG. Duplicate recordings of the PERG on left and the VEP on right are shown for the indicated log luminance reductions in (a); their offline averages are superimposed in (b). Data for 1.6 log reduction are also shown in (b). One unit on horizontal axis is 25 msec; one unit on vertical axis is 1.25 nV for the PERG, 5.0 nV for the VEP. VEP/PERG landmarks for the control (0.0 log reduction) are marked in (b).*

**Table 1. Normal values for 30° VEP/PERG: comparison with cataract patients**

<table>
<thead>
<tr>
<th></th>
<th>Normals (n = 45) (mean [SD])</th>
<th>Normal limit*</th>
<th>Cataract patients (n = 8) (mean [SD])</th>
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<tbody>
<tr>
<td><strong>B-wave</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (msec)</td>
<td>48.1 (3.5)</td>
<td>57.5</td>
<td>60.3 (3.4)</td>
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<tr>
<td>Amplitude (μV)</td>
<td>4.1 (1.1)</td>
<td>1.8</td>
<td>1.34 (0.7)</td>
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<tr>
<td><strong>P100</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency (msec)</td>
<td>99.1 (4.1)</td>
<td>109.5</td>
<td>117.3 (4.2)</td>
</tr>
<tr>
<td>RCT (msec)</td>
<td>51.0 (4.2)</td>
<td>61.4</td>
<td>57.0 (3.4)</td>
</tr>
<tr>
<td>Amplitude (μV)</td>
<td>10.1 (3.9)</td>
<td>0.3</td>
<td>7.2 (3.3)</td>
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</tbody>
</table>

* Mean + (2.5 × SD) for latencies; Mean – (2.5 × SD) for amplitudes. Add 5 msec to the P100 latency limit for comparison with the 55–75 age range of our cataract patients.

This was also found by Chiappa, who looked at P100 latencies similarly, using NDFs to reduce retinal illumination.

Univariate statistics were done with standard spreadsheet software. Regressions were calculated with a programmable calculator equipped for linear-regression analysis of variance on ordered pairs of input. Confidence limits for the slopes of the means of the data pooled were calculated from the standard deviations of the individual points and the formula for the slopes, using standard methods.

The use of at least five test points for each graph for least-squares analysis represents a necessary improvement over the method of using only three employed by Tobimatsu et al. With only three luminance values the least-squares weighting for determining the regression slope essentially ignores the middle value,
the resulting slope being determined by just the largest and smallest luminance data.

Results

Figure 1 shows the effect of NDFs on the VEP/PERG in one subject's right eye. Figure 2 contains plots of the relevant latencies and amplitudes for the subject illustrated in Figure 1. The least-squares regression slopes for this subject are reported in Table 2 (subject 1, right eye [OD]) along with the calculated slopes for all 16 controls tested. Note the near equivalence of the B-wave and P100 latency slopes (18.1 msec/log unit versus 19.0 msec/log unit) for this subject's right eye. This is reflected in the small variation in the RCT over the whole range of retinal illumination (Fig. 2). In the entire study, not one VEP/PERG recorded from our normal subjects had an abnormal RCT due to reduction of retinal illumination, if there was sufficient B-wave amplitude to locate a B-wave peak at all (Table 2, last column).

Plots analogous to Figures 1 and 2 were done for each eye listed in Table 2. Similar to the eye in Figure 2, P100 latencies for each normal eye exceeded limits of normal when retinal illumination was reduced by greater than 0.6 log units.

Regarding amplitude changes, Table 2 reports regression slopes for the raw data in μV (amplitude, column A) and for the data normalized to the control value (column B). Normalizing means dividing each amplitude by the control amplitude to determine the fraction of initial amplitude remaining at each luminance. Thus for the subject illustrated in Figures 1 and 2, a fractional slope of −0.54 means that each tenfold decrease in retinal illumination decreased the B-wave amplitude by 54% of the initial value.

For each eye tested, Table 2 shows approximate equality of the B-wave and P100 latency slopes. In particular individuals either the B-wave or P100 slope could be larger, although the difference was never large enough to produce an abnormal RCT (greater than 61.4 msec, Table 1) in our normal subjects. In addition, the normalized B-wave and P100 amplitude slopes show that the B-wave amplitude is much more affected than the P100 amplitude by decreased retinal illumination for every eye tested. Figure 1 was a typical example of this result.

Averages over all normal eyes tested are listed in the middle of Table 2. Note the small average slope for the RCT and the nearly equal average slopes for B-wave and P100 latencies (15.9 versus 16.6 msec/log unit).

A better analytic appreciation for the effects of decreased retinal illumination can be obtained from the regression plots for the mean or average data (Fig. 3). From these data points, which are the averages of 16 values each (15 for B-wave latency), we can calculate actual variances of the regression slopes and coefficients of determination. Note that the B-wave and P100 latency slopes for the average data are very close, 16.2 versus 16.6 msec/log unit. Thus, both the average data and the data from individuals indicate that the VEP P100 latency is increased only to the extent that the PERG B-wave latency is increased. Confidence limits for these slopes are given in Figure 3. The confidence limit range of approximately 3 msec for both B-wave and P100 slopes contrasts with values of about 8–10 msec from the data of Tobi-matsu et al10 and establishes more precisely the near equality of the effect of decreased retinal illumination on VEP/PERG latencies.
Table 2. Least squares latency and amplitude slopes for individual eyes

<table>
<thead>
<tr>
<th>Subject</th>
<th>Lat.*</th>
<th>A†</th>
<th>B‡</th>
<th>Lat.*</th>
<th>A†</th>
<th>B‡</th>
<th>RCT* (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-Wave</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>#1 OD</td>
<td>18.1</td>
<td>-1.64</td>
<td>-0.54</td>
<td>19.0</td>
<td>0.22</td>
<td>0.02</td>
<td>0.85</td>
</tr>
<tr>
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<td>16.5</td>
<td>-1.70</td>
<td>-0.64</td>
<td>21.0</td>
<td>0.25</td>
<td>0.02</td>
<td>3.53</td>
</tr>
<tr>
<td>#2 OD</td>
<td>18.4</td>
<td>-2.04</td>
<td>-0.52</td>
<td>16.5</td>
<td>-1.02</td>
<td>-0.16</td>
<td>-1.95</td>
</tr>
<tr>
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<td>19.1</td>
<td>-1.97</td>
<td>-0.56</td>
<td>14.9</td>
<td>-0.68</td>
<td>-0.10</td>
<td>-4.20</td>
</tr>
<tr>
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<td>-2.16</td>
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</tr>
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<td>14.5</td>
<td>-0.98</td>
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* msec/log Unit luminance reduction.
† μV/log Unit luminance reduction.
‡ Fraction of control amplitude lost/log Unit luminance reduction.
§ Largest RCT found during testing.
¶ Affected eye.

Figure 3 also shows that the B-wave amplitude was reduced by 52% for every log unit illuminance decrease while the PI100 amplitude was almost unaffected. The 98% confidence intervals reported in Figure 3 indicate that these slopes are highly significantly different. Student t-tests show that each mean B-wave amplitude is significantly different (at the P = 0.01 level) from the means at contiguous points. However, there were no significant differences in the RCT or PI100 amplitudes from control (0.0 log unit) values over the entire range of retinal illumination tested.

Figures 4 illustrates that the relative constancy of the RCT with changes in retinal illumination does not depend on a normal optic nerve. This subject was tested within 10 days of the onset of optic neuritis in the right eye. Figure 4 demonstrates the characteristic increased P100 latency OD. With her permission both eyes were tested in the study protocol. The delayed tracings in Figure 4 illustrate the effect of a 1.0 log-unit luminance decrease on each eye. The RCT in each eye was essentially unaffected even though all latencies were longer.

Table 2 also lists regression slopes for the normal and affected eyes of the patients with optic neuritis. Note the similarity between the normal and affected eyes of the two patients with unilateral disease. Sub-
Fig. 3. Mean latencies (a) and amplitudes (b) versus log unit decrease in retinal illumination. Each point is the average of 16 eyes, the one from each subject used for the statistics in Table 2. Vertical bars represent ±1.0 SD. To emphasize relative changes, each amplitude was expressed as a fraction of the appropriate control mean amplitude at 0.0 log unit. Thus, in (b) 1.0 equals 3.55 μV for the B-wave, 9.2 μV for the P100. Regression slopes followed by 98% confidence intervals for these slopes are as follows: Latencies—B-wave: 16.2 msec/log unit (14.5 to 17.9), P100: 16.6 msec/log unit (14.7 to 18.5), RCT: 0.4 msec/log unit (–1.3 to 2.1); Amplitudes—B-wave: –0.52/log unit (–0.43 to –0.61), P100: –0.06/log unit (0.18 to –0.28). Coefficients of determination were greater than 0.96 for each regression line except P100 amplitude, for which the slope was too small. Variances of the control means for B-wave and P100 amplitudes were used in calculating the confidence limits for the amplitude slopes since these were used to normalize the data as described above. One of the subjects used here had zero B-wave amplitude for the PERG at 1.6 log unit. Hence, only 15 eyes contributed to that point for the B-wave latency.

Subject 18 was illustrated in Figure 4. The patient with bilateral optic neuritis also had a constant RCT over the range of luminances tested.

A potential clinical application of these data is illustrated in Figure 5. A 75-yr-old woman with known cataracts in both eyes, left eye (OS) worse than OD, was seen for electrophysiologic evaluation to exclude ONL as the etiology of her decreasing vision OS. Her visual acuity was 20/60 in both eyes. Because of progressive, but vague, ocular symptoms accompanying
the visual loss in an otherwise normal examination, ONL was considered possible by the referring ophthalmologist. Even for her age, her VEP was abnormal OS and borderline OD. However, the simultaneous VEP/PERG showed a normal RCT in both eyes. Together with the much lower B-wave amplitude OS, the normal RCT suggests that her visual loss was not due to ONL. The abnormal VEP might have been due to decreased retinal illumination secondary to her cataracts, particularly OS. Without the PERG, the abnormal VEP would have been misleading if it had led to a diagnosis of ONL.

The results for the other cataract patients were similar to Figure 5. The means are reported in Table 1 with normal values for comparison. Increased VEP latencies accompanied by low amplitude PERGs of increased latency and normal RCT were normal findings for these uncomplicated cataracts. A direct comparison with our normal values (Table 1) was not possible because of the difference in age ranges. Previous work by one of us (D.I.K.) indicates that normal upper limits for B-wave and P100 latencies in 55-75-yr-old subjects are only 2-5 msec longer than those for subjects younger than 50 yr of age. Thus it is clear that the large, abnormal values of B-wave and P100 latencies for our cataract patients resulted in relatively small increases in RCT which may be normal for this age group (55-75 yr). If the PERG amplitude is too small, however, RCT cannot be determined.

### Discussion

Using 50' checks and NDFs, Chiappa\(^1\) reported that each tenfold decrease in retinal illumination increased P100 latency by 10–12 msec. Using 30' checks, we found a comparable result (Fig. 3). In addition we showed that most of the alteration in VEP latency can be accounted for by a nearly equal increase in the B-wave latency of the simultaneously recorded PERG. We also noted a differential effect of reduced retinal illumination on PERG and VEP amplitudes. Moreover, our report established these conclusions more precisely (originally suggested by the study of Tobimatsu et al).\(^10\) Of clinical importance is that these conclusions for the mean data apply to each individual eye tested (Figs. 1,2; Table 2).

These results extend previous ones on the diagnostic significance of the simultaneous VEP/PERG, particularly when ocular factors coexist with possible ONL. In particular, a normal PERG eliminates poor refraction and nonfixation, purposeful or secondary to poor vision, as etiologies for an abnormal VEP.\(^6,9\) Analogously, a prolonged PERG of reduced amplitude can account for the prolonged VEP of early maculopathy.\(^3,4\)

As reported here P100 amplitude and the RCT are relatively unaffected by decreased retinal illumination. As long as there is a certain unspecifiable amount of retinal function, optic nerve and cortical events necessary for these measurable quantities
seem to be unaffected. Even when B-wave amplitude was reduced by 90% with 1.3 or 1.6 log-unit illuminance reductions, little or no effect on P100 amplitude and RCT was seen (Figs. 1–4).

We are not trying to say that only 10% of retinal function is necessary to initiate normal optic nerve function—such an assumption of linearity is unwarranted. However these results do support an earlier suggestion that the retinal events leading to the PERG are more sensitive to disruption by ocular or nonneurologic factors than those neurologic events responsible for the VEP.6,8

A possible reason for the differential effects of decreased retinal illumination on VEP and PERG amplitudes is that different retinal cell populations may be involved. The PERG appears to monitor a retinal area possibly two to four times as large as the foveal or macular area of stimulation required for the VEP.19–21 We can speculate that, being relatively enriched in rods (compared with the macula), this larger area may simply be more affected by decreased illumination. Because of our photopic testing conditions, this particular explanation is probably not true. In any case, our data show that the VEP/PERG and RCT calculated from it are useful in assessing the electrophysiologic effects of decreased retinal illumination.

The interpretation of the VEP/PERG for cataract patients requires a caveat. Cataracts probably do decrease retinal illumination. However they may also cause acuity problems or distort visual information of various spatial frequencies, independent of their luminance effects. Acuity effects on the VEP/PERG are most noted at smaller check sizes;5–7 15' or less, which are useful in detecting subtle ONL when 30' and 60' VEP testing is normal.7

In a pilot study of 11 normal subjects attempting to separate luminance effects from distortion of spatial information in early cataract patients, we used over-refraction by + spherical lenses to cause visual blurring. Having done this for the VEP/PERG to 7.5' checks6 and 15' checks,7 we expected similar results for 30' checks. However, for 30' checks, VEP latencies were increased by less than 2 msec in every normal subject until visual acuity was reduced to at least 20/100. At 20/200 the largest latency increase was still only 5 msec. Contrast detection of smaller spatial frequencies (2–6 cycles/degree) was decreased by an average of 0.3 log units with lenses causing an acuity of 20/100.

Although not proof, the much larger increases in VEP and PERG latencies for the cataract patients studied here, despite minimal visual complaints and good acuity (at least 20/60), suggest that early cataracts do cause luminance effects, which we reproduced using NDFs. Undoubtedly, early cataracts may also cause visual distortion of various spatial frequencies, but apparently these are not enough to alter VEP latencies to 30' checks.

Because the VEP was abnormal for all the cataract patients in this study, the VEP alone could be misleading diagnostically for these patients. Only the VEP/PERG was able to show that ONL was not present (Table 1, Fig. 5). Whether or not early cataracts distort spatial frequency information and decrease retinal illumination, the normalcy of the RCT found in these patients makes it an empirically useful monitor of optic nerve function when there are ocular opacities. The RCT is prolonged when ONL occurs (Table 2) but is normal when conditions exist which prolong the VEP secondary to their measurable effects on the PERG. We conclude that the VEP/PERG and the calculated RCT help resolve the ambiguity surrounding an abnormal VEP in patients with coexisting ocular conditions such as early cataracts which may reduce retinal illumination.

Key words: pattern electroretinography, retinal illumination, retinocortical time, cataracts, visual-evoked potential, PERG

References


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