# The Cone Electroretinogram in Retinopathy of Prematurity

*Anne B. Fulton, Ronald M. Hansen, and Anne Moskowitz*

**Purpose.** To test the hypothesis that retinopathy of prematurity (ROP) affects the cone photoreceptors less than the rod photoreceptors.

**Methods.** Electroretinogram (ERG) responses to a 1.8-log-unit range of red flashes on a white, rod-saturating background were recorded in 42 subjects with a history of preterm birth and ROP (28 untreated; 6 treated) or no ROP ($n = 8$). The sensitivity ($S_{CONE}$) and saturated amplitude ($R_{CONE}$) of the cone photoresponse were calculated by fit of a model of the activation of cone phototransduction to the a-waves. The cone-driven b-wave amplitude was evaluated as a function of stimulus intensity. $S_{CONE}$ and $R_{CONE}$ were compared to the rod response parameters ($S_{ROD}$, $R_{ROD}$) recorded from the same preterm subjects. Responses in the former preterm subjects were compared to those in control subjects.

**Results.** The values of $S_{CONE}$ and $R_{CONE}$ in the preterm subjects overlapped broadly with those in the control subjects. The shapes of the b-wave stimulus–response functions did not differ between preterm and control subjects. The relative value of $S_{CONE}$ was significantly greater than that of $S_{ROD}$.

**Conclusions.** ROP has less effect on the cone than on the rod photoresponses, suggesting that cones are more resistant to the ROP disease process. The similar shape of the b-wave stimulus–response function in preterms and control subjects is evidence that ROP does not alter the balance of ON and OFF signals in the cone pathway. (*Invest Ophthalmol Vis Sci.* 2008; 49:814–819) DOI:10.1167/iovs.07-1226

The sensitivity of rod-mediated vision and of the rod photoresponse is low in infants and children with a history of retinopathy of prematurity (ROP).[1–3] In rat models of ROP, oxygen levels that are too high or too low have adverse effects on the structure and function of the immature rods,[4–8] and early rod dysfunction predicts the abnormal retinal vasculature,[5] which is the hallmark used by clinicians to diagnose ROP. Less is known about the role of cones in ROP. Children's cone-mediated visual functions, including acuity and color vision, are affected by ROP,[9,10] and the cone-driven multifocal ERG responses of the central retina are attenuated in older children with a history of mild ROP.[11] The effects of ROP on cone and cone-driven function in the peripheral retina are unknown.

Cone ERG responses to full-field stimuli are relatively more mature than are rod ERG responses in healthy 4- and 10-week-old infants,[12] in keeping with the earlier anatomic development of the cones than of the rods.[13] Primate cones differentiate earlier than rods, and peripheral cone outer segments mature earlier than rod outer segments.[14–16] We reasoned that the greater maturity of infants' cones, as well as the structure of the cones,[17] would offer relative protection from the adverse events that induce ROP. In the present study, we compared full-field cone and rod ERG responses in the same subjects to test the hypothesis that ROP has less effect on cones than on rods.

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## Methods

### Subjects

Forty-two subjects with a history of preterm birth were studied. All had been monitored in the newborn intensive care nursery by experienced pediatric ophthalmologists who used indirect ophthalmoscopy and schedules for examination similar to those used in the multicenter treatment trials.[10,18,19] Gestational age at birth ranged from 23 to 32 (median 27) weeks and birth weight from 490 to 1850 (median 815) g. The subjects were categorized by ROP history: treated ROP, untreated ROP, or no ROP. None had active ROP at the time of the ERG test. The treated subjects ($n = 6$) had severe ROP that required ablation of the peripheral avascular retina at preterm ages; none had a retinal detachment. In these subjects, the median estimated area of residual retina was 80% (range, 75%–90%) of the total retinal area when tested.[20] In those categorized as untreated ($n = 28$), mild ROP had been documented but resolved spontaneously without treatment. In eight subjects, ROP never developed.

Nineteen subjects were tested as infants at the median age of 10 (range, 7–11) weeks after term, which is 40 weeks' gestation. Twenty-three other subjects were tested at the median age of 13 (range, 5–23) years. In normal subjects, both cone and rod ERG responses to full-field stimuli are completely mature by the age of 1 year.[12,21] Previously reported term-born, 10-week-old ($n = 28$) and mature ($n = 13$) control subjects provided data for comparison.[12] The rod responses of 11 of the 42 preterm subjects have been reported.[2]

This study conformed to the tenets of the Declaration of Helsinki and was approved by the Children's Hospital Committee on Clinical Investigation. Informed consent was obtained from the parents of the infants and children, assent from the older children, and consent from those 18 years of age and older.

### General ERG Procedure

Parents stayed with infants and children throughout the procedure. The pupil was dilated with cyclopentolate 1%, and the subject was dark-adapted for 30 minutes. Then, under dim red light, proparacaine 0.5% was instilled, and a bipolar Burian-Allen electrode was placed on the cornea. A ground electrode was placed on the skin over the ipsilateral mastoid.

Thirty-seven subjects were tested with the Compact 4 system (Nicolet, Madison, WI), and five with the Espion system (Diagnosys, Lowell, MA). Despite differences between the two systems in the spectral bandwidth of the stimuli (described below) and in data acquisition (2564 Hz digitization rate for the Nicolet; 2000 Hz for the Espion), rod and cone photoresponse parameters in adult control subjects obtained using the Espion system ($n = 7$) did not differ



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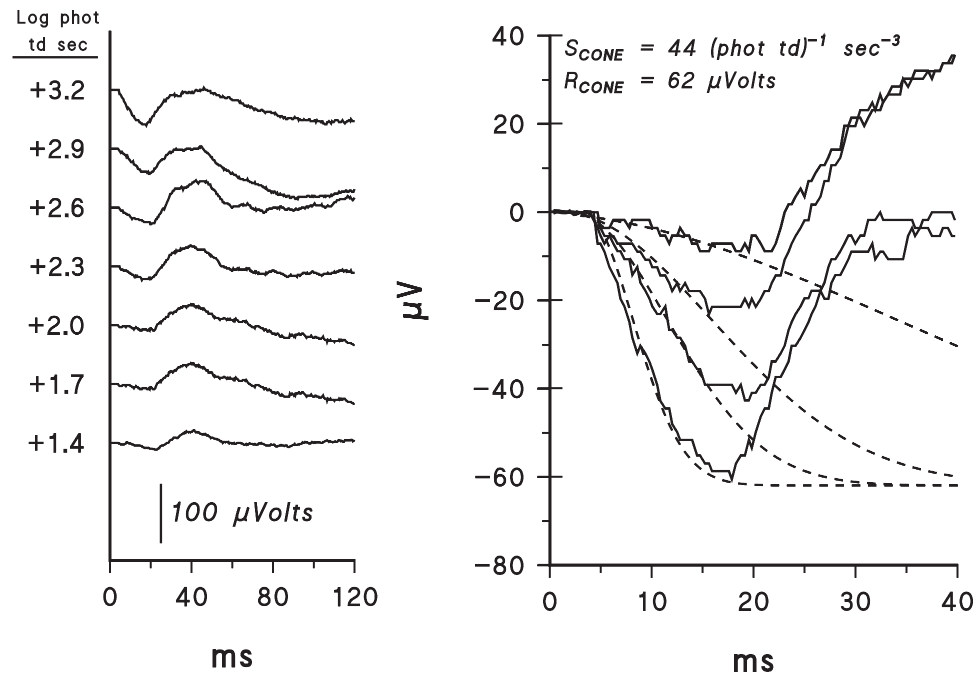


**FIGURE 1.** *Left*: Sample ERG records from a 10-week-old infant with a history of mild, untreated ROP. Responses to a 1.8-log unit range of red flashes on a steady white background are shown. *Right*: The first 40 ms of the records. *Dashed lines*: equation 1 fit to these records; for clarity, responses to only four of the seven intensities are shown. The values of $S_{CONE}$ and $R_{CONE}$ are close to the median values in the 19 preterm infants.

significantly from those obtained previously with the Nicolet system ($n = 13$).[12,21] Therefore, the data obtained with the two systems have been combined.

Responses were differentially amplified (band pass, 1–1000 Hz), displayed, digitized, and stored for analysis. A voltage window was used to reject responses contaminated by artifacts. Two to 16 responses were averaged in each stimulus condition. The inter-stimulus interval ranged from 2 to 60 seconds and was selected so that subsequent b-wave amplitudes were not attenuated.[21]

## Cone ERG

After 3 to 5 minutes of adaptation to a steady, white, rod-saturating background (~ +3 log phot td), responses were recorded to a 1.8-log-unit range (+1.4 to +3.2 log phot td · s) of full-field, brief (<3 ms), red stimuli, incremented in 0.3-log-unit steps. In the Nicolet system, a Wratten 29 filter ($\lambda > 610$ nm) was used; in the Espion system, a 630 nm LED (half bandwidth, 30 nm) was used. Cone photoresponse parameters were derived from the a-wave, as described later. On records such as those shown in Figure 1, the trough-to-peak amplitude and implicit time of the b-wave were measured and examined as a function of log flash intensity.

Fit of a model of the activation of cone phototransduction[22,23] was restricted to the first 11 ms of the response to reduce postreceptor contamination.[12,22,24–27] This model incorporates a low-pass exponential filter to represent the capacitance of the cone membrane[23,28,29] by numerical convolution of the filter output with the delayed Gaussian function used to model the rod response.[30,31] The cone model[23] is

$$R(i,t) = (\{1 - \exp[-0.5I\, S_{CONE}(t - t_d)^2]\}R_{CONE}) * \exp(-t/\tau) \quad (1)$$

where $I$ is the flash in photopic troland-seconds, $S_{CONE}$ is a sensitivity parameter [(phot td)$^{-1}$ · s$^{-3}$], $t_d$ is a brief delay (in milliseconds), $R_{CONE}$ is the saturated response amplitude (in microvolts), and $\tau$ is the time constant of the low-pass filter (in milliseconds). The symbol * represents the convolution operation. In the present study, as in the study of normal infants' cone responses,[12] $\tau$ was fixed at 1.8 ms and $t_d$ at 3 ms. Goodness of fit of the model (equation 1) to the a-wave was evaluated by the RMS errors.

## Rod ERG

Responses to full-field, brief (<3 ms), blue stimuli ranging from those that evoked a small b-wave (<15 μV) to those saturating the a-wave were recorded. In the Nicolet system, a Wratten 47B filter ($\lambda < 510$ nm) was used; in the Espion system, a 470 nm LED (half bandwidth, 30 nm) was used. The rod photoresponse parameters ($S_{ROD}$ and $R_{ROD}$) were calculated by fit of the Hood and Birch[32] formulation of the Lamb and Pugh[30,31] model to the a-waves. The equation is

$$R(i,t) = \{1 - \exp[-0.5IS_{ROD}(t - t_d)^2]\}R_{ROD} \quad (2)$$

where $I$ is the flash in scotopic troland-seconds, $S_{ROD}$ [(scot td)$^{-1}$ · s$^{-3}$] a sensitivity parameter, $R_{ROD}$ the saturated response amplitude (in microvolts), and $t_d$ a brief delay (in milliseconds). All three parameters, ($S_{ROD}$, $R_{ROD}$, and $t_d$) were free to vary.[2]

## Calibrations

Stimuli were measured with a detector and appropriate photopic or scotopic filter (IL 1700; International Light, Newburyport, MA) placed at the position of the subject's cornea. Retinal illuminance varies directly with the area of the pupil and transmissivity of the ocular media and inversely with the square of the posterior nodal distance.[33] We used direct estimation of each subject's dilated pupil and published estimates of ocular media density[34,35] and axial length of infant and mature eyes[36–38] to make this calculation. In summary, equal intensity stimuli produce approximately equal retinal illuminance in 10-week-old infant and mature subjects.[33,39–41] For both the Nicolet and Espion systems, the maximum intensity red stimulus produced a retinal illuminance of approximately +3.2 log phot td · s; the maximum-intensity blue stimulus produced an illuminance of approximately +3.6 log scot td · s.

## Analyses

The values of $S_{CONE}$ and $R_{CONE}$ and the b-wave stimulus–response functions in the former preterm subjects were compared to those of normal, term-born, 10-week-old infants or mature control subjects.[12] Each subject's $S_{CONE}$ and $S_{ROD}$ values were expressed as a proportion of the normal mean for age to facilitate comparison of cone and rod sensitivity.[12,21] Comparisons between groups and between cone and rod response parameters were made by using Student's *t*-test. For both infants and mature subjects, the photopic b-wave amplitude and implicit time were evaluated for variation with stimulus intensity and group (former preterm, control) using analysis of variance. Cone and

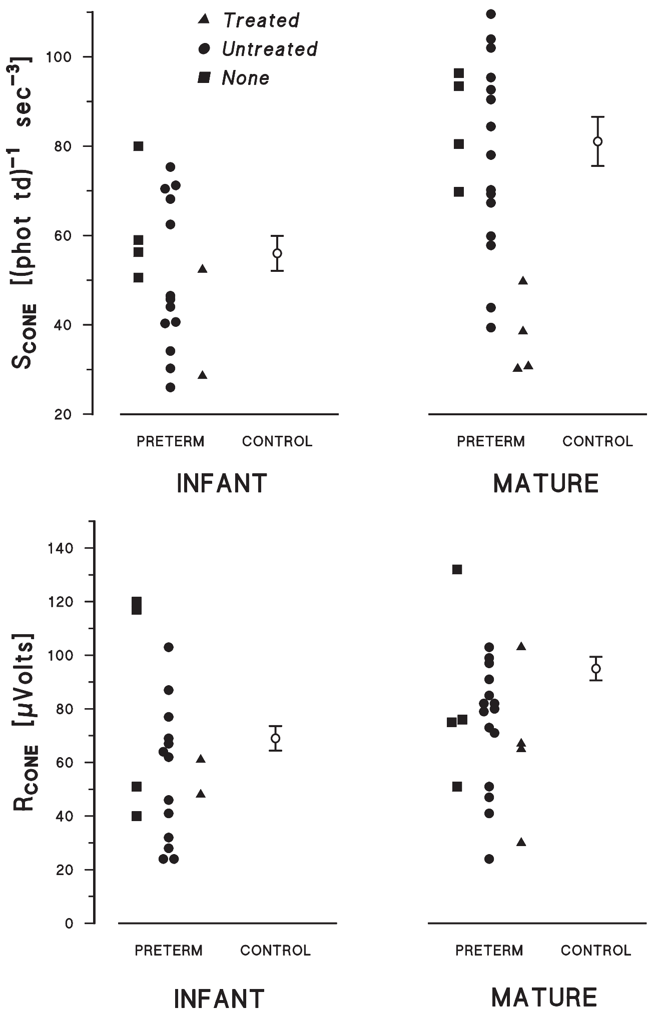


**Figure 2.** $S_{CONE}$ (*top*) and $R_{CONE}$ (*bottom*) in former preterm subjects ($n$ = 42), grouped by age at test. Different symbols indicate each ROP category: treated, untreated, none. In each panel, the mean (±SEM) for the term-born controls[12] is also shown.

rod response parameters were evaluated for significant variation with ROP category (treated, untreated, none) using analysis of variance. For the former preterm subjects with treated ROP, the response parameters were evaluated for possible relation to residual retina by using Spearman rank order correlation. For all statistical tests, the level of significance was set at $P < 0.01$.

## Results

Sample cone ERG records from a former preterm infant with a history of untreated ROP are shown in Figure 1. Also shown is the fit of the model of the cone photoresponse (equation 1) to the a-waves. The model describes reasonably well the leading edge of the a-wave. The RMS errors did not vary significantly with age and did not differ significantly between the former preterm and control subjects.

The values of the cone photoresponse parameters, $S_{CONE}$ and $R_{CONE}$, in all former preterm subjects and the mean values in control subjects are shown in Figure 2. $S_{CONE}$ and $R_{CONE}$ in the former preterm subjects were broadly distributed around the mean control values. The means and standard errors are summarized in Table 1. $S_{CONE}$ and $R_{CONE}$ did not differ significantly between former preterm and control subjects in either age group. All $S_{CONE}$ and $R_{CONE}$ values in those with treated ROP (Fig. 2) were below average, with one exception. Neither parameter correlated with the estimated area of retina remaining after treatment ($S_{CONE}$: Spearman rho = 0.717; $P$ = 0.109; $R_{CONE}$: Spearman rho = 0.717; $P$ = 0.109). Similarly, the rod response parameters (Table 1) in those with treated ROP did not correlate with the estimated area of residual retina ($S_{ROD}$: Spearman rho = −0.359; $P$ = 0.485; $R_{ROD}$: Spearman rho = 0.837; $P$ = 0.038).

The shapes of the b-wave stimulus–response functions in the former preterm subjects were similar to those in the age-appropriate control subjects (Fig. 3). For both groups of infants, there was a monotonic increase in amplitude with stimulus intensity, whereas in the older subjects, whether former preterm or control, a photopic hill[42–46] was seen with the peak at ~ +2.3 log photopic td · s. The absence of a photopic hill in healthy infants has been previously reported.[12] At the +2.3-log photopic td · s stimulus, in both infants and older subjects, the amplitude of the b-wave response in former preterm subjects was about the same proportion of that in control subjects (infants, 0.76; older subjects, 0.87). For the infants, the b-waves were significantly smaller in former preterm than in control subjects ($F$ = 17.1, $df$ = 1, 322, $P < 0.01$), with the greatest difference at stimulus intensities ≥ +2.3 log photopic td · s. Among the mature subjects, b-wave amplitudes did not differ significantly between former preterm and control subjects ($F$ = 2.09; $df$ = 1, 236; $P$ = 0.15). Analysis of variance showed no significant interactions, consistent with the impression that the shapes of the b-wave stimulus–response functions did not differ between former preterm and control subjects in either age group. The implicit times of the b-wave responses (data not shown) did not vary significantly with stimulus intensity (+1.4 to +3.2 log photopic td · s) or group (former preterm subjects, controls) in either age group (infants: $F$ =

**Table 1.** Summary of Activation Parameters

| | Infant* | | | | Mature† | | | |
|---|---|---|---|---|---|---|---|---|
| | Preterm | Control‡ | *t* | *P*§ | Preterm | Control‡ | *t* | *P*§ |
| Cones | | | | | | | | |
| $S_{CONE}$ [(phot td)$^{-1}$ · s$^{-3}$] | 52 (3.8) | 56 (3.9) | −0.76 | 0.45 | 72 (5.2) | 81 (5.5) | −1.19 | 0.24 |
| $R_{CONE}$ (µV) | 62 (6.8) | 69 (4.6) | −0.91 | 0.37 | 76 (5.9) | 96 (4.4) | −2.27 | 0.03 |
| Rods | | | | | | | | |
| $S_{ROD}$ [(scot td)$^{-1}$ · s$^{-3}$] | 31 (3.5) | 41 (3.0) | −2.19 | 0.03 | 71 (5.1) | 90 (2.9) | −2.71 | <0.01 |
| $R_{ROD}$ (µV) | 184 (12.8) | 167 (8.7) | 1.19 | 0.24 | 271 (17.5) | 389 (21.3) | −4.35 | <0.01 |

Data are expressed as the mean ± SEM.
* $df$ = 45 for all tests.
† $df$ = 34 for all tests.
‡ Data from Hansen and Fulton.[12]
§ Level of significance for all tests: $P < 0.01$.

6.10; $df = 1, 322$, $P = 0.02$; mature subjects: $F = 0.54$; $df = 1, 245$; $P = 0.46$).

When expressed as proportion of normal mean for age, the mean relative value of $S_{CONE}$ was significantly larger than $S_{ROD}$ ($t = 2.68$; $df = 41$; $P < 0.01$). The mean relative values of $R_{CONE}$ and $R_{ROD}$ did not differ significantly ($t = -0.246$; $df = 41$; $P = 0.814$). In Figure 4, the sensitivity of the photoreceptor responses, $S_{CONE}$ and $S_{ROD}$, expressed as a percentage of the normal mean for age, is compared for each ROP category. $S_{CONE}$ varied significantly with ROP category ($F = 5.81$; $df = 2, 41$; $P < 0.01$) as did $S_{ROD}$ ($F = 5.81$; $df = 2, 41$; $P < 0.01$).

## Discussion

In subjects with a history of preterm birth, the sensitivity of the cones is higher than that of the rods (Fig. 4). The data show

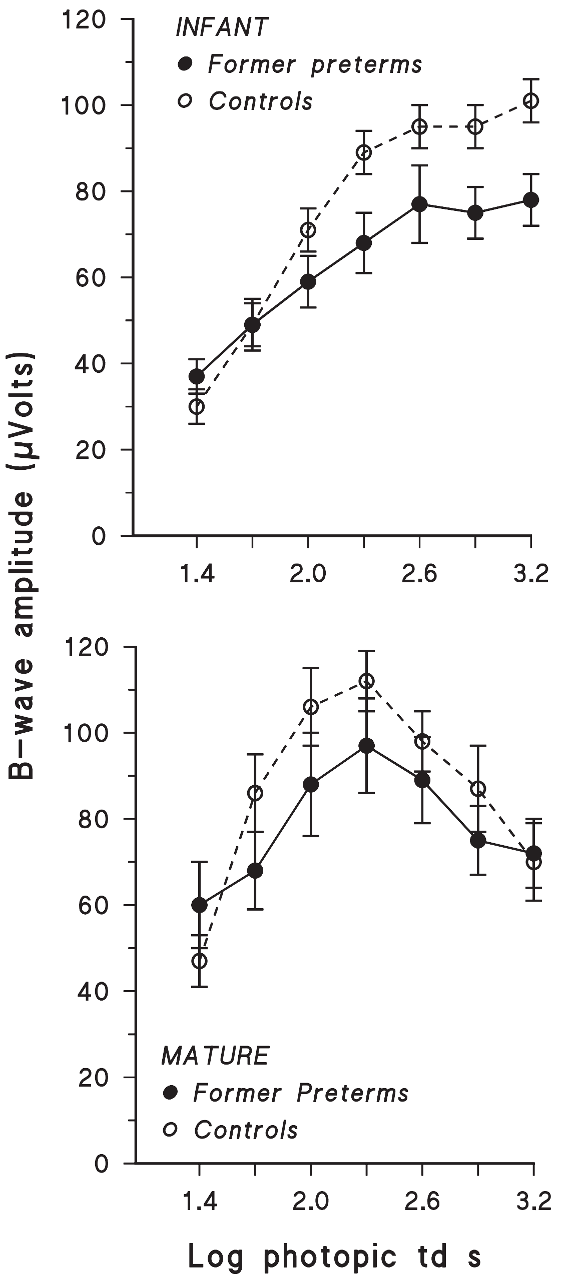


**Figure 3.** b-Wave stimulus–response functions in former preterm subjects compared with those in age-appropriate control subjects.[12] The means ± SEM are shown.

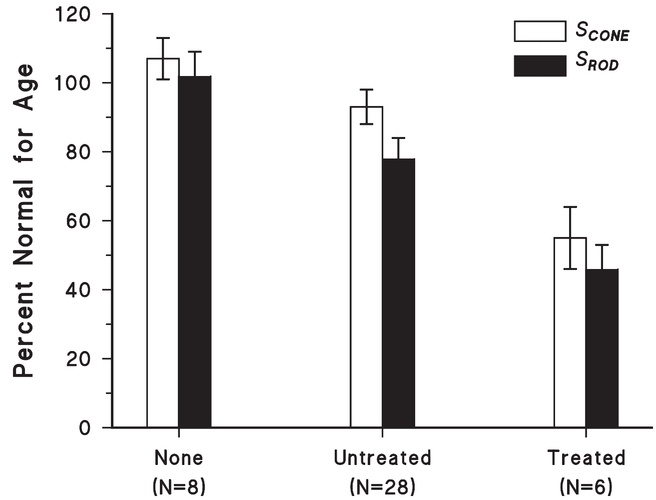


**Figure 4.** Cone ($S_{CONE}$) and rod ($S_{ROD}$) photoresponse sensitivity, expressed as a percentage of normal mean for age, displayed by ROP category: none, untreated, treated. Error bars, ±SEM.

only minimal dysfunction of the cones in those with mild, untreated ROP and somewhat greater dysfunction in those who had more severe ROP that required treatment (Figs. 2, 4). We suspect that cellular dysfunction, rather than loss of cells or area of responsive retina, underlies the deficits in sensitivity because the magnitude of the deficits was not accounted for by loss of retinal area. Similarly, the attenuation of the rod response parameters in these subjects and others[21] did not correlate with area of retina remaining after treatment.

The shapes of the b-wave stimulus–response functions were similar in former preterm and control subjects (Fig. 3). The cone pathways include both ON and OFF bipolar cells, each contributing their relative strengths and timing to determine the shape of the observed b-wave function in the mature[47] and immature[12] retina. Thus, our results suggest that the combining of the ON and OFF signals in the cone pathways is not altered by ROP.

Although the shapes of the functions were similar in the former preterm and control subjects, the amplitudes of the b-wave response to full-field stimuli are mildly attenuated in the former preterm subjects (Fig. 3). Postreceptor responses of the central retina to multifocal stimulation were significantly attenuated,[11] but it could not be determined whether the relative contributions of ON and OFF signals were altered. In view of the b-wave responses to full-field stimuli (Fig. 3), it is unlikely that the relative ON and OFF contributions are differentially affected by ROP. In experimental ROP, neural changes accompany abnormal retinal vascularization,[5,48] and in our own recent high-resolution OCT observations of adolescents and young adults with a history of mild ROP, the abnormal intraretinal capillaries encroached on the neurons in the central retina.[49] Although the neurovascular abnormality does not appear to discriminate between ON and OFF neurons, we suspect it has a role in attenuating the postreceptor activity that is represented in the ERG b-wave.

At least two explanations for the lower vulnerability of cones than rods (Fig. 4) warrant consideration. First, earlier maturation may protect the cones. It is the immature photoreceptors that appear particularly vulnerable to retinal oxygen levels that are too high or too low.[8] Second, cones appear more resistant to pathologic processes. Compared with rods, cones have twice as many mitochondria and approximately three times the surface area of mitochondrial cristae.[17] Thus, the cones are equipped for greater aerobic ATP production, and this, Perkins et al.[17] theorize, protects against metabolic insults and apoptosis. As a corollary, they postulate that therapeutic interventions that support mitochondrial energy production may be beneficial in many photoreceptor diseases.[17] Furthermore, cones, in contrast to rods, have the capability of using endogenous glycogen, affording protection against the adverse effects of hypoxia and attendant hypoglycemia.[50] The data from the subjects represented in Figure 4 and from additional subjects[2] indicate that ROP affects the rods, and it is known that in some patients, ROP has a progressive, degenerative course.[51] Thus, therapies that support mitochondrial energy production may be beneficial in ROP and may even have a role in preventing ROP, because it is rod sensitivity that predicts the vascular abnormalities in rat models of ROP.[5]

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