Supernormal Cone Electroretinograms in Central Retinal Vein Occlusion

P. Gouros and C. J. MacKay

In 12 successive cases of unilateral central retinal vein occlusion (CRVO), the strongly light-adapted cone electroretinogram (both a- and b-wave) was always slower and larger (supernormal) to long-wave stimuli compared with that of the unaffected eye. This supernormality became less as the level of light adaptation decreased; in the dark-adapted state, long-wave stimuli produced subnormal responses from the affected eye in all but two subjects. This supernormality was not caused by ineffectiveness of the adapting light related to a reduced cone quantal catch because it occurred in the dark. At any one state of adaptation, the supernormality increased with the wavelength of stimulation, paralleling the relative absorption ratio of long-middle wavelength-sensitive cones. This suggests that cones, especially long wavelength-sensitive cones, are less able to reduce their responsiveness to light with increasing levels of light adaptation in a retina affected by CRVO. Invest Ophthalmol Vis Sci 33:508–515, 1992

We describe an unusual change in cone electroretinograms (ERG) after central retinal vein occlusion (CRVO). In 12 consecutive cases of CRVO (several repeatedly tested), the amplitude of the cone ERG, both a- and b-wave components, was larger, ie, “supernormal,” in the affected compared with the unaffected eye if (1) the retina was sufficiently light adapted or (2) the test stimuli were long wavelength. The phenomenon appears to involve the long (L) more than the middle (M) wavelength-sensitive cones but not the short (S) wavelength-sensitive cones or rods. Supernormality of the ERG is an unusual phenomenon because most retinal abnormalities reduce rather than increase the amplitude of the ERG. In general, CRVO has been reported to decrease the amplitude of the white-flash cone ERG.1–6 Although there are rare reports of supernormal responses,1–7 Our results suggest that the supernormality we found was the same phenomenon as that described in these occasional reports. This phenomenon is not only important for diagnosing and following this retinal abnormality but also identifies some differences in the physiology of the different classes of human cones.

Materials and Methods

Twelve subjects (age range, 30–85 yr) with unilateral CRVO were studied 2.5 weeks to 3 yr after the initial insult occurred. All subjects had a normal eye, which was compared simultaneously with the affected eye. Informed consent was obtained from all subjects after the nature of the procedure had been explained fully. The methods used for examining the ERG were identical to those we described in recent articles on the light-adapted cone ERG.8–10 The discovery of this phenomenon came from our attempts to understand the behavior of the S cone ERG at high levels of retinal adaptation better.

The ERG was recorded simultaneously from both eyes using bipolar Burian-Allen contact-lens electrodes (Hansen Ophthalmic, Iowa City, IA). The pupils were dilated widely and measured before and after each recording session, lasting approximately 30 min. The ERG was detected with a Nicolet (Madison, WI) CA-1000 signal averager coupled to a Ganzfeld stimulator providing a relatively strong adapting field (17,000 photopic trolands) at maximum brightness. This level can be changed by reducing the current across a 12-V, 80-W halogen projector lamp, the source of the field. The retinal illumination was expressed in photopic trolands, considering the pupillary area as homogeneous although it varies with the cosine of the visual angle to the pupil. Superimposed on this steady white-light field were flashes obtained from a Grass strobe (PS2; Grass Instruments, Quincy, MA), which had been removed from its housing and incorporated into a metal box mounted on the dome of the Ganzfeld above the subject’s head. The strobe
and adapting lights were diffused homogeneously on the matte white inner surface of the Ganzfeld. The flash could be filtered by 7 × 5-cm filters placed in a receptacle in the strobe housing. The following Kodak Wratten filters (Rochester, NY) were used: nos. 98 (450 nm), 48 (471 nm), 75 (488 nm), 61 (534 nm), 21 (593), and 29 (633 nm). The numbers in parentheses indicate the nominal wavelength of maximum transmission of each filter at the approximate color temperature of the strobe.

The recording system's frequency response extended from 5–1500 Hz, and the computer's window discriminator was used to reject large artifacts. At least 100–1000 responses to the same flash were averaged. The flash rate for the cone ERG used was 5.1 Hz; for the rod ERG, it was 1 Hz. We could detect signals as low as 0.1 μV with this technique. A signal detection level of approximately 1 μV would be sufficient to reproduce our results. A function reflecting the relative absorption of the human L and M cones for different wavelengths of stimulation was determined as follows. The relative absorption of the L and M cone types in the tritanopic human eye previously was determined. The absorption of each cone type was tested at five selected wavelengths: 450, 500, 550, 600, and 625 nm. The L–M ratio was determined for each of these wavelengths. This ratio then was compared to the CRVO–normal amplitude ratio for cone ERGs at different wavelengths. The a- and b-wave amplitude and implicit times were measured in the normal way by determining the amplitude of the initial negative (a-wave) and the subsequent positive (b-wave) response. The implicit time therefore represents the time from the flash to the negative peak (a-wave) or positive peak (b-wave) of the response.

**Results**

There were small quantitative differences between the ERGs of different patients and between the ERGs of the same patient studied at different times after the onset of the insult. Qualitatively, however, our results were the same regardless of the time at which the retinopathy was studied from a few weeks to 3 years after the insult. The patients are being followed to determine the significance of these quantitative differences, but this does not alter the results reported here.

Figure 1 illustrates moderately light-adapted (cone) ERGs to white light stimuli from two patients with CRVO. The upper set shows the most typical pattern; the response from the affected eye was reduced in amplitude and delayed in time compared with that in the unaffected eye. Eight of our 12 patients followed this pattern. The lower set shows ERGs in which the response from the affected eye was larger than that in the affected eye; the response from the affected eye also was delayed. Four of our 12 patients followed this pattern. The supernormality involved both the a- and b-wave components of the ERG.

Figure 2 shows the ERGs of one of these four subjects in the dark-adapted state, using two different wavelengths of stimulation. The short-wavelength (blue) stimulus, which strongly stimulates the rods, elicited a smaller response from the affected eye. All 12 patients had subnormal rod responses in their affected eyes. The longer-wavelength (red) stimulus, which strongly stimulates the L and M cones and only weakly stimulates the rods, elicited a larger response from the affected eye. This is an important illustration because it shows that a cone response can be supernormal under the same conditions that a rod response is subnormal in CRVO. Therefore, the supernormality cannot be caused by a change in the resistance of the eye and does not require the retina to be light adapted.

Only two patients had a supernormal cone response in the dark-adapted state. As the retina was light adapted, the cone ERG from the affected eye became larger than that from the normal eye (Fig. 3).
highest level of retinal adaptation (17,000 photopic trolands, upper pair of traces), the response of the eye with CRVO was larger than that of the normal eye; at the lower levels of adaptation, the converse occurred.

Figure 4 shows that increasing light adaptation affects both the a- and b-wave of the cone ERG in 11 of our patients. As light adaptation increased, the amplitude and implicit time of the responses decreased progressively. At low levels of adaptation, the amplitude of the response of the normal eye tended to be larger than that of the affected eye; at high levels of adaptation, the reverse occurred. In the dark-adapted state, the difference between the a-wave amplitude of the affected eyes was not significantly different than that of the normal eyes. However, at 4 log photopic trolands of light adaptation, the a-wave of the affected eyes was significantly larger than that of the normal eyes (P = 0.025, by student t-test). In the dark-adapted state, the b-wave of the eyes with CRVO was significantly smaller than that of the normal eyes (P = 0.005), but at 4 log photopic trolands of light adaptation, the b-wave of the affected eyes was larger than that of the normal eyes (P = 0.05). At all levels of adaptation, however, the implicit times of the cone ERGs were later in affected eyes than in normal eyes.

By comparing the ratio of the cone response of the affected to the unaffected eye at different levels of light adaptation (Fig. 5), the influence of light adaptation on these cone ERGs became more apparent. At low levels of light adaptation, this ratio was less than 1; at high levels of adaptation, it is greater than 1 for both the a- and b-waves. These differences were both significant (P = 0.005). One patient's response was more than threefold as large in the eye with CRVO than in the normal eye at the highest level of retinal adaptation. Light adaptation, therefore, enhances the supernormality of the cone ERG in CRVO.

This supernormality of the cone ERG also depends on the wavelength of stimulation. Long-wavelength stimuli are more effective for producing supernormal responses than short-wavelength stimuli. Figure 6 shows that, at three different levels of retinal adaptation, the ERG elicited by the long-wavelength (red) stimulus was larger in the affected eye than in the normal eye. With short wavelengths (blue), the opposite occurs. This subnormal response to short wavelengths involves all cone responses (L, M, and S).

Figure 7 depicts the ratio of responses of the affected eye to the normal eye for both a- and b-wave responses at high levels of light adaptation, averaged for these 12 patients. The longer the wavelength of stimulation, the greater was the supernormality of the response of the affected eye for both a- and b-wave responses. This difference occurred regardless of the size of the response because the short-wavelength
Fig. 4. The top panel shows the normalized averaged a- and b-wave amplitudes of the cone ERG (above) elicited by long-wavelength (red) stimuli from 11 patients with unilateral CRVO: (○) normal, (●) affected eye at different levels of background retinal illumination in photopic trolands. The responses were normalized for each patient by making the maximum response of either eye equal to 100%; this procedure facilitates the comparison. The corresponding implicit times of these responses are shown in the bottom panel. The vertical lines indicate the standard error.

(Blue) and the long-wavelength (red) stimuli both produce smaller cone ERGs than the two middle-wavelength stimuli. Only the longer-wavelength stimuli produce supernormal ERGs. The continuous line in Figure 7 is the ratio of the relative absorptions of human L versus M cones.11

To illustrate that the phenomenon of supernormality to long-wavelength stimuli was independent of the amplitude of the response, we used neutral-density filters to produce roughly equivalent response amplitudes for six different wavelengths of stimulation in the normal eye (Fig. 8, right top). There was a progressive increase in supernormality with an increasing wavelength of stimulation. The continuous line with black circles shows the relative absorbance of L versus M cones (Fig. 7). The close correspondence between the two ratios suggests that the supernormality reflects the L more than the M cone contribution to the response.

It could be argued that the supernormality of the a-wave might be a result of a delayed b-wave in the eye with CRVO; this would expose more of the a-wave. Figure 9 shows that the supernormality of the a-wave involves, not only the initial a-wave (first arrow), but the later negativity (second arrow) that occurs after the b-wave response is over. Therefore, the supernormality of the cone ERG appears to involve the entire P-III process, of which the initial a-wave is one manifestation. Figure 9 illustrates that this supernormality is independent of the strength of stimulation and, consequently, of the amplitude of the cone response.

One of the questions raised by previous results was whether the supernormal ERGs in patients with CRVO found using red-light stimuli and light adaptation were related to the rare reports of supernormal ERGs to white light in the literature. Figure 10 shows a plot of the ratios of b-wave amplitudes between the affected eye and the normal eye for white and red light.
testing in all 12 patients. The white-light responses were obtained in the presence of a moderate-adapting light; the red-light responses were obtained in the presence of a strong-adapting light. Only 4 of the 12 subjects had supernormal responses to white light; all had supernormal responses to red. There was a tendency for higher ratios to red to be associated with higher ones to white.

Discussion

Our results indicate that CRVO alters both the a- and b-waves of the cone ERG and therefore alters the physiology of the outer and inner retinal layers. It appears to produce different effects on the four photoreceptor systems in the retina. It reduces and delays the amplitudes of the rod and S cone responses. It also delays the responses of the L and M cones, but it changes their responsiveness in an unusual way, especially those of the L cones. These cone responses become larger than normal, especially when the cones are light adapted. This augmentation of amplitude does not require adaptation because two cases were detected in which the cone ERG was supernormal in the dark-adapted state. Therefore, the supernormality does not require light adaptation and consequently is not caused by a reduced quantal catch by the affected cones. This phenomenon would seem to depend on some alteration in the transduction mechanism that delays and augments the electrical response, especially of the L cones. This alteration also appears to influence the ability of these cones to adapt to light normally. It is this latter phenomenon that leads to an exaggeration of the supernormality with light adaptation.

The finding that this insult appears to influence L cones differently from M cones is extraordinary because there is no physiologic evidence that these two cone types differ in anything other than the absorption spectrum of their photopigments. Our results, however, suggest that such a difference exists. The supernormality differs significantly at wavelengths...
Fig. 7. The ratio between the amplitude of the ERG of the CRVO to that of the normal eye for both the a- and b-waves obtained at a high retinal illumination (17,000 photopic trolands) for all 12 subjects at different wavelengths of stimulation. The continuous line represents the ratio of L to M cone absorptions at different wavelengths. The vertical lines indicate the standard error.

where only the L and M cones are contributing to the ERG, ie, wavelengths longer than about 500 nm. This change also parallels the ratio of absorptions of L to M cones. It is conceivable that the abnormality does not alter the transduction mechanism of the cones but perhaps changes some antagonistic neural interactions that release or disinhibit the L cone response. Whatever this effect is, it involves both the a- and the b-waves of the ERG and consequently must occur at the level of the photoreceptors. This hypothesis predicts unique ERG changes in protanopic or deuteranopic subjects with unilateral CRVO.

Supernormality of the ERG in CRVO is a relatively rare event, according to the literature. Using our paradigm of testing, it was found in every patient. It is easy to understand why this phenomenon has not been detected routinely in the past. It requires conditions that favor the L cone response, ie, relatively strong light adaptation and long-wavelength stimuli. All previous studies of CRVO used white-light testing and only moderate or no adapting lights. In our study, white-light testing on a moderate-adapting field detected a supernormal response in only 33% (4 of 12) of the patients. Using red testing lights and stronger-adapting fields, all subjects had supernormal responses.

There are other reports of supernormal responses in the ERG with vascular insufficiency of the retina. It was reported that both the amplitude and implicit time of the b-wave of the ERG increased with ischemia. Supernormal ERGs also have been reported in patients with hypertensive retinopathy, Takayasu's disease, diabetic retinopathy, and venous stasis glaucoma. Supernormal ERGs also occur if there are increased flow rates, oxygenation, and/or pH changes in the retina. They may be seen during...
early stages with metallic foreign bodies in the eye. It would be interesting to investigate these conditions using the method we outlined.

Supernormal, delayed ERGs have been found in the rod system in a unique hereditary retinal degeneration of the retina, where there was a superimposed cone dystrophy. This was thought to be caused by a defect in cyclic guanosine monophosphate, which, when inhibited pharmacologically, will produce supernormal rod responses. In CRVO, the pattern is reversed: the cone response is supernormal, and the rod response is subnormal. In both cases, the supernormality is associated with a prolongation of implicit time. There are other retinal abnormalities, such as retinitis pigmentosa and digitalis toxicity, that also are associated with prolongations of implicit time, especially of the cone ERG. It is possible that these abnormalities also may show some of the unique ERG changes found in CRVO, but these changes would be concealed by the binocular nature of these abnormalities.

It is difficult to know whether these unusual ERG changes contribute to a better understanding of CRVO or to a better detection of future ischemic complications. Therapy for CRVO, consisting of isovolemic dilution of the blood, has been suggested. It is possible that the long-wavelength supernormality of the cone ERG could provide a sensitive indicator of any alteration in the retinal circulation produced by such treatment.

Key words: cone electroretinograms, supernormal ERGs, delayed implicit times, central retinal vein occlusion

References


