Principles and Practice of Clinical Electrophysiology of Vision

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PART XIV

Electrophysiological Evaluation of Vascular Diseases, Inflammatory States, and Tumors

80

Use of Electroretinographic Ratios in Assessment of Vascular Occlusion and Ischemia

Mary A. Johnson

Branch and central retinal vein occlusion are common retinal vascular disorders, second only to diabetic retinopathy in terms of frequency of occurrence. They are both easy disorders to diagnose by using clinical techniques. For this reason, investigations into the value of the electroretinogram (ERG) in these disorders have focused on prognosis and not diagnosis.

CENTRAL RETINAL VEIN OCCLUSION

It is estimated that about 20% of eyes with central retinal vein occlusion (CRVO) are ischemic and are therefore at risk of developing neovascularization of the iris (NVI).[4, 14] The determination of ischemia in this disorder, however, is problematic; fluorescein angiograms (FA) often do not capture peripheral capillary nonperfusion, they may be difficult to read because of intraretinal hemorrhage or other factors, the FA changes associated with ischemia in CRVO may not be completely understood,[18] and eyes with CRVO that have no apparent capillary dropout occasionally develop NVI.[13]

The ERG has been shown to be a sensitive and specific test for identifying eyes with CRVO that are at risk of developing NVI. It has the advantages over angiography of providing an evaluation of the entire retina, including far peripheral areas, and of quantifying the amount of ischemia with regard to the retinal area affected, the extent of the damage within the area affected, and the amount of functional loss in perfused but still ischemic eyes.

There are a number of ways that researchers have categorized the ERG changes that occur in CRVO. Eyes with CRVO often have reduced ERG b/a amplitude ratios, reduced b-wave amplitudes, reduced or enhanced a-wave amplitudes, delays in the implicit times of the a- and b-waves, reductions in oscillatory potential (OP) amplitudes, and changes in the Naka-Rushton parameters derived from intensity-response analysis (discussed below). ERGs recorded from most cases of CRVO will show significant changes in some of these parameters, even if the eye is perfused and has a good prognosis. However, eyes with CRVO that develop NVI demonstrate large ERG changes, and it is generally not difficult to identify eyes at risk for NVI even when the ERG is recorded only once, at the patient's initial visit.[2, 9, 12, 13, 16, 19]

ELECTRORETINOGRAM AMPLITUDES

The recent work of Sabates and colleagues[19] has again focused attention on the dramatic reductions that are often seen in the b/a ratio in ischemic eyes with CRVO. The amplitude of the b-wave is mea-

sured from the a-wave trough to the b-wave peak. The amplitude of the a-wave is measured from the baseline to the trough of the a-wave. Sabates et al. reported that five out of eight eyes in his study that had b-wave reductions that were so large that the b-wave did not extend beyond the prestimulus baseline (the b/a ratio measured less than 1, see Fig 80–1) developed NVI, whereas only one eye that did not have this characteristic developed the complication. Similar results were recently obtained by Kaye and Harding[13] and Breton et al.,[2] thus confirming findings that date to Karpe's original monograph published in 1945.[11] Johnson and McPhee[9] found the b/a ratio to be specific but not sensitive for NVI in a prospective study of 93 eyes with CRVO. They attributed some of the differences among studies to the different stimulus luminances used, given the dependence the b/a ratio has on retinal illuminance (Fig 80–2). A fuller discussion of b/a amplitude ratios can be found in Chapter 66.

Much of the reduction in b/a ratios can be attributed to preferential reductions in the b-wave amplitude. In a prospective study of 30 CRVO eyes, 7 that later developed NVI and 23 that did not, Kaye and Harding[13] reported that b-wave amplitudes were decreased on average by 102 μV in eyes that developed NVI when compared with the normal fellow eyes and by 63 μV when compared with affected eyes that did not develop NVI. Mean a-wave amplitudes were not significantly different for any of the comparisons. This latter result may be due to the fact that in CRVO the a-wave may either increase or decrease with disease severity. Curiously, the b/a ratio was found to be a better predictor of NVI development than was b-wave amplitude. This paradox might be explained by two factors: the large variability of ERG amplitude and the fact that the a-wave amplitude may be either abnormally large or abnormally small in CRVO. Abnormally small a-waves, of course, suggest that more than the middle retina is involved in the disorder.

Other investigators have also demonstrated substantial b-wave reductions in CRVO.[2, 7, 9] These studies will be discussed more fully in the section dealing with intensity-response functions.

OP amplitudes are reduced in CRVO, but while there is a significant difference between the means of distributions of OPs recorded from eyes that develop NVI when compared with eyes that do not develop this complication, there is a substantial overlap between these distributions. This overlap results

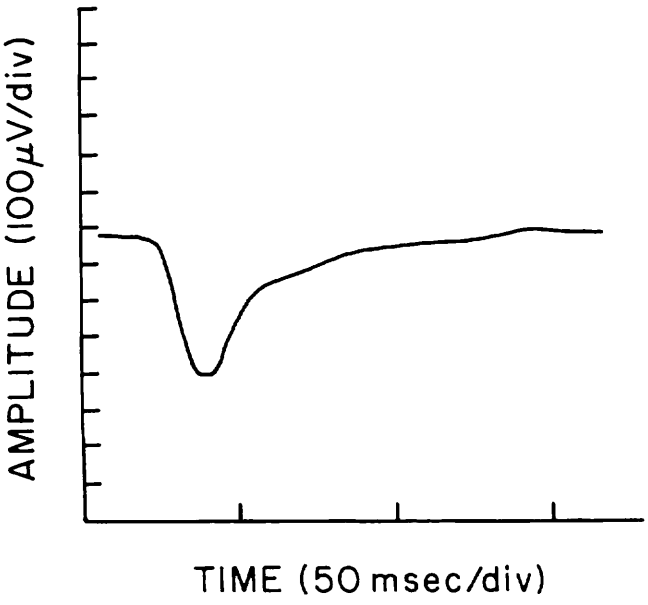

FIG 80–1.
An ERG recorded from an eye with CRVO and NVI. The b/a amplitude ratio measures less than 1.

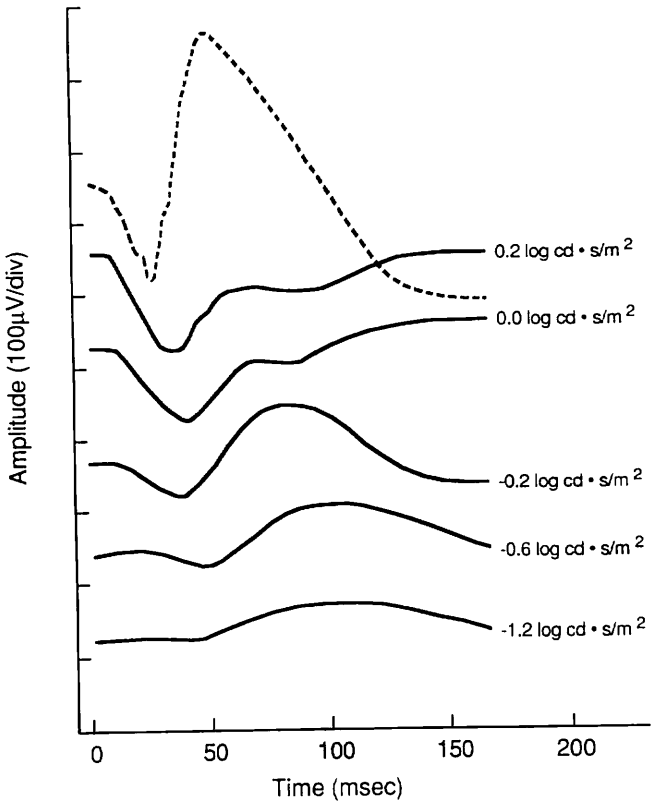

FIG 80–2.
ERGs recorded as a function of stimulus luminance for an eye with CRVO and NVI *(solid lines)*. For comparison, the *dotted line* is a normal ERG recorded at 0.2 log cd · sec/m^2. Note that the b/a ratio is less than 1 here only for the two brightest stimuli.

from the fact that CRVO eyes not at risk for NVI have substantial OP reductions.[10]

TEMPORAL FACTORS

Large delays in ERG implicit times are found in eyes with CRVO that develop NVI. Values for the scotopic single-flash a- and b-waves and the peak of the 30-Hz flicker response have been reported.[2, 7, 9, 13, 16] In a prospective study of 62 patients with CRVO, McPhee et al.[16] showed that both the scotopic b-wave and the 30-Hz response recorded from patients at their first visit identified patients who had or would later develop NVI with high sensitivity and specificity. Their data for scotopic b-wave implicit time, measured from stimulus onset to the peak of the b-wave, are illustrated in Figure 80–3,A. While ERGs from most of the eyes with CRVO showed delays in b-wave timing, eyes that had or would develop NVI showed much larger changes than did the eyes that did not develop NVI. A risk factor criterion of 58 ms, which was 8 ms longer than the upper limit of the range of normal values for b-wave implicit time, yielded a sensitivity of 94% and a specificity of 64% for this data set. Figure 80–3,B, which pictures the normal and affected eyes of a patient with CRVO and NVI, illustrates the size of the effect that is often seen.

Delays in the implicit time of the b-wave were the most discriminant feature of the ERGs recorded by Kaye and Harding in CRVO.[13] In agreement with the data of McPhee et al.,[16] they found that the difference between the means of the ERGs recorded from eyes that developed NVI vs. the eyes that did not develop NVI was 7.4 ms, a difference that was significant at the $P < .001$ level. Furthermore, there was no overlap between these two distributions at the 99% confidence level. They also found significant intereye differences for both groups. These differences measured 9.6 ms for the NVI group and 2 ms for the comparison between the ERGs recorded from the eyes with nonproliferative CRVO and their fellow eyes.

A similar picture is seen for the 30-Hz flicker ERG.[2, 7, 9, 16] McPhee et al.[16] showed that when using a criterion of 40 ms or greater, a value that is 7 ms greater than the upper limit of the normal range, the 30-Hz flicker ERG shows equivalent performance to the scotopic b-wave in identifying eyes that had or would develop NVI (Fig 80–4,A). At this criterion value, the sensitivity for this data was 100%, and the specificity was 68%. Figure 80–4,B illustrates a 30-Hz flicker ERG recorded from the normal and affected eyes of a patient with CRVO. Implicit time is measured from the stimulus trace to the center of the first corneal-positive waveform, and in cases where the waveform peaks shortly after the stimulus

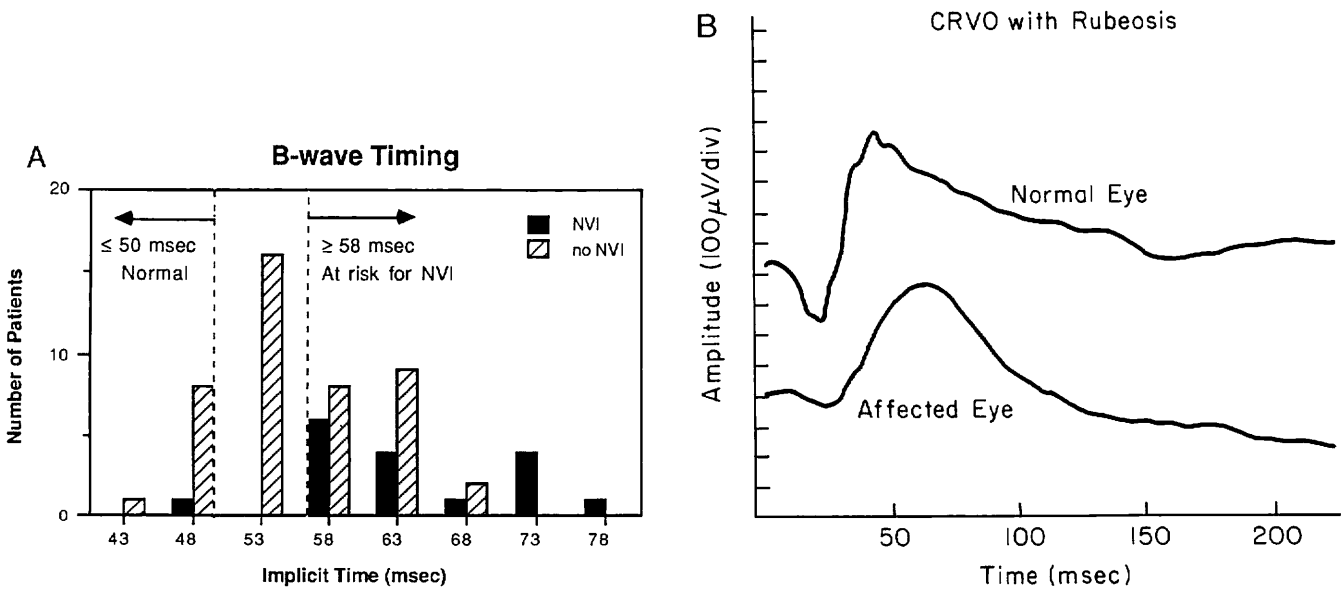

FIG 80–3.

A, b-wave implicit time for CRVO eyes with NVI *(solid bars)* and without NVI *(hatched bars)*. **B**, ERGs recorded from the normal and affected eyes of a patient with CRVO and NVI. The ERG recorded from the affected eye shows reduced a- and b-wave amplitudes and delays in implicit times when compared with the normal, fellow eye.

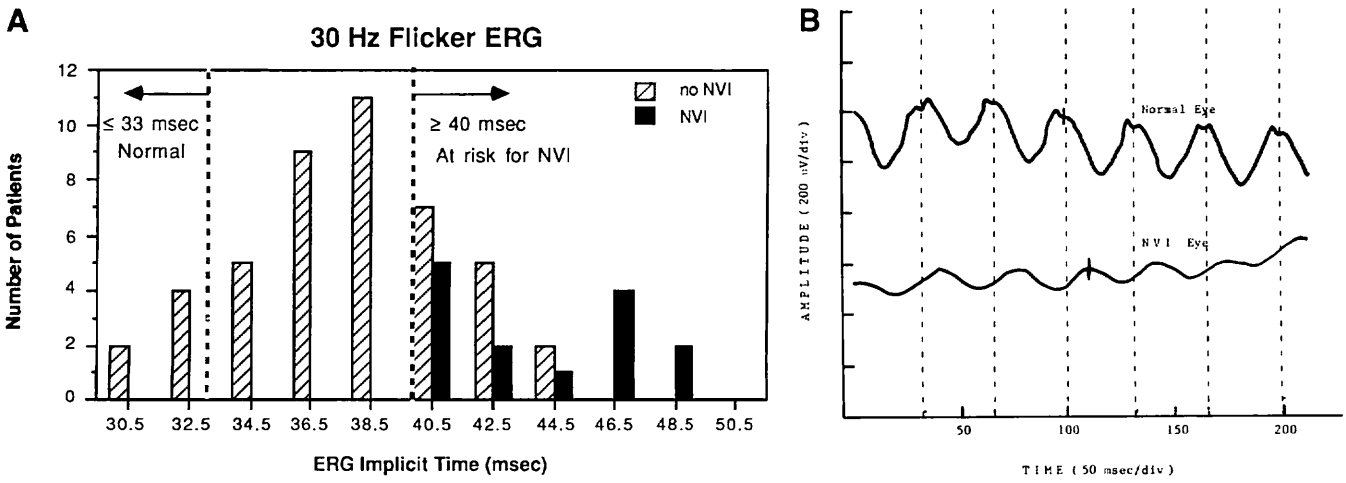

FIG 80–4.

A, 30-Hz ERG implicit time for CRVO eyes with NVI *(solid bars)* and without NVI *(hatched bars)*. **B**, ERGs recorded from the normal and affected eyes of a patient with CRVO and NVI. The ERG recorded from the affected eye shows a reduced amplitude and a delay in implicit time when compared with the normal, fellow eye. *Cursors* mark the midpoint of two waveforms.

trace, a period of one epoch (33 ms) is added to the implicit time measurement. This is done because additional ERG data, collected at frequencies ranging from 5 to 30 Hz, showed that the occurrence of the waveform shortly after the trace indicates a phase lag and not a lead in these eyes. McPhee et al.[16] measured implicit time as the time from stimulus onset to the center of the waveform and not to the peak of the waveform because high-frequency components, which usually occur in healthy eyes at the leading edge of the flicker ERG, often disappear in eyes with CRVO. In these cases, measuring implicit time as the time to peak will accentuate the actual shift in time in waveforms recorded between normal eyes and affected but nonproliferative eyes, thus reducing the ability to identify the individuals who have real time shifts and who are at risk for NVI.[20]

Even though the 30-Hz flicker ERG time delay is a sensitive measure for NVI, large delays in the flicker ERG are occasionally observed in CRVO[2] and diabetic[1] eyes that are not at risk for neovascularization and that have otherwise relatively healthy ERGs. However, in the one study published that directly compared FA and ERG data,[7] 30-Hz flicker data still outperformed routine fundus FA in the ability to discriminate between eyes with proliferative and nonproliferative CRVO.

INTENSITY-RESPONSE ANALYSIS

As discussed in more detail in Chapter 31, ERG b-wave amplitude increases monotonically with stimulus intensity up to moderately high levels of luminance. These intensity-response data are typically analyzed by fitting them with a saturating, nonlinear function of a form first used by Naka and Rushton in 1966 in their work on the S potential in fish.[17] This so-called Naka-Rushton function has the form:

$$R = \frac{R_{max} I^n}{I^n + K^n} \quad (1)$$

where R is the response amplitude at intensity I; R_{max} is the asymptotic amplitude; K is the semisaturation constant, i.e., the intensity at which R_{max} reaches half of its asymptotic value; and n is related to the slope at I = K. The value of performing this analysis is that the parameters derived from Equation 1 can be evaluated in terms of putative pathophysiological mechanisms of disease.

Eyes with CRVO often show reductions in R_{max} and n and elevations in K. An elevation in K indicates that more light is required to produce normal-amplitude ERGs, e.g., retinal sensitivity is reduced. Retinal heterogeneity is reflected in the slope parameter. By using Monte Carlo simulations, it has been formally demonstrated that heterogeneity in either R_{max} or K will decrease n.[15]

As with the other ERG parameters that we have examined, eyes that develop NVI have large elevations in K and often have large reductions in R_{max}. Using ROC (receiver operating characteristic, from signal detection theory) analysis, which is a method

of comparing entire distributions of data and which reflects the amount of overlap between distributions, Johnson and McPhee[9] have shown that the probability of detection (P_d) for K is .84 and that the P_d for R_{max} is .65. These numbers indicate the probability of detecting an eye that will progress to NVI when using only the parameter and no additional patient information. A linear discriminant analysis performed on the data showed that virtually all of the information present in the Naka-Rushton parameters was contained in K.

Breton and colleagues[2] have also shown, by discriminant analysis, that R_{max} and K are sensitive and specific tests for identifying CRVO eyes at risk for NVI. However, in contrast to Johnson and McPhee,[9] Breton et al. showed that R_{max} performed better than K in discriminating between CRVO eyes that would later develop NVI and those not at risk for this complication. A major difference between this study and the study of Johnson and McPhee[9] was the algorithm used for fitting the data.

Eyes with CRVO and elevations in K act as

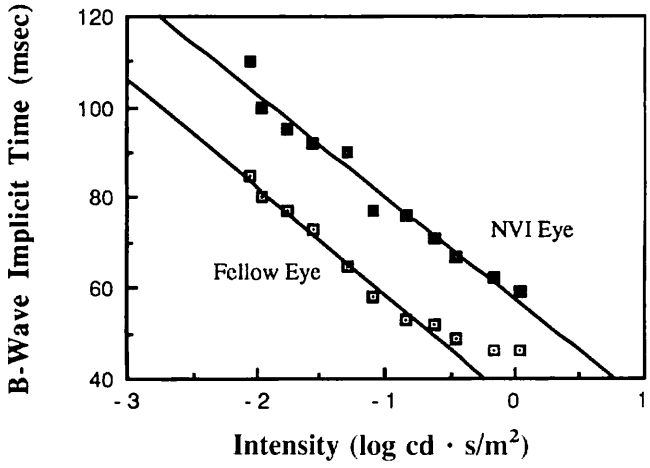

FIG 80–5.
Implicit times of scotopic single-flash b-waves as a function of stimulus luminance for the affected and normal eyes of a patient with CRVO who later developed NVI. Both functions were fit by linear regression after eliminating the last three data points from the asymptote of the normal function (r^2 = 0.98 for the normal eye and 0.97 for the affected eye). The slopes of the upper sections of these biphasic functions are not significantly different. The function from the normal eye cannot be fit to the data from the affected eye by pure vertical translation, which indicates that at least some of the implicit time delay must be due to reduced retinal sensitivity. Because the data from the NVI eye have not yet asymptoted, it is not possible to determine the amount of vertical and horizontal shift that is necessary to superimpose the functions.

though they are seeing less light, and this is a major cause of the delays in ERG timing which occur in this disease. Examination of the scotopic b-wave implicit time vs. stimulus luminance functions pictured in Figure 80–5 for the normal and affected eyes of a patient with CRVO and NVI illustrates two facts: (1) that a dimmer stimulus produces a response occurring later in time and (2) that, for this patient, the implicit time vs. luminance function recorded from the normal eye requires at least some horizontal translation (i.e., along the log intensity axis) to fit the data recorded from the affected eye. The highly significant correlation between the logarithm of K and the scotopic b-wave is 0.81, and between log K and the 30-Hz flicker response it is 0.74.[9]

BRANCH RETINAL VEIN OCCLUSION

The same types of effects observed in CRVO also occur in branch retinal vein occlusion (BRVO), but on a much smaller scale. In fact, for the most part, the changes observed cannot be used to manage patients on an individual basis, undoubtedly because a much smaller area of the retina is affected.[11] Johnson et al.[5] showed that ERGs recorded from eyes with BRVO and retinal neovascularization showed reductions in R_{max}, elevations in K, and delays in the scotopic b-wave and 30-Hz flicker implicit times, but the overlap in the distributions of these parameters for the proliferative and affected but nonproliferative eyes was substantial. Thus, while this result is scientifically interesting, it is not clinically useful.

RETINAL ARTERY OCCLUSION

The ERG in retinal artery occlusion is discussed more fully in the section of Chapter 6 on b/a ratios. In cases of complete and long-standing central retinal artery occlusion (CRAO), the ERG consists of a supernormal a-wave and a very reduced if not absent b-wave. The highly negative ERG is present soon after the onset of the occlusion. The reduced b-wave and supernormal a-wave is presumably due to the damage to the inner retinal generators of Granit's[3] PII component. Less severe occlusion produces the intermediate ERG findings of partially increased a-wave and decreased b-wave amplitudes.

Complete occlusions of the ophthalmic artery result in an extinguished ERG. The ophthalmic artery provides circulation to both the central retinal artery

and the choroid plexus, and thus the lack of recordable retinal potentials is presumed to be due to infarction of both outer and inner retinal layers.

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