Principles and Practice of Clinical Electrophysiology of Vision

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b/a-Wave Amplitude Ratios in Retinal Vascular Disease

Mary A. Johnson

The electroretinogram (ERG) is an epipotential that represents the average graded electrical activity of several different retinal cell types. According to the classic analysis of Granit,[2] the ERG can be divided into subcomponents that represent the processes of these cellular mechanisms (Fig 66–1). Distal P_{III}, the photoreceptor response, is a corneal-negative potential and has the shortest latency of Granit's three processes. P_{II}, which probably results from Müller cell–reflected bipolar cell activity, is a corneal-positive potential. These processes combine to produce the ERG a- and b-waves, respectively. Because of their opposite polarities, P_{II} and P_{III} interfere destructively, and consequently the observed a- and b-waves recorded from a normal eye are much smaller than their underlying processes.

Granit's component analysis was based in part on the effect of interrupting the flow of blood to the retina by occluding the carotid arteries or by altering respiration. The effect of these perturbations was dramatic. P_{II} (the b-wave) was the first component affected. Initially, the b-wave paradoxically grew larger but, with time, became reduced in amplitude and finally disappeared. P_{III} was very resistant to the deleterious effects of ocular hypoxia, which suggests that the photoreceptors continue to function well in conditions of low oxygen tension, that a residual supply of oxygen is available to the photoreceptors, or that the generation of the a-wave is a process that is not very oxygen sensitive. With increasing hypoxia, the amplitude of the a-wave increased to several times its normal size, presumably as a consequence of the reduction in interference between a much reduced P_{II} and a normal P_{III}. The magnitude of this effect was not lost on the clinical ERG researchers of the 1940s, and some of the earliest investigations into the clinical utility of the ERG were performed on patients having retinal vein or artery obstructions.

An ERG classification scheme that segregated the differential effects of retinal vascular obstruction on a- and b-wave amplitudes was described by Henkes in a 1953[4] study. In an attempt to identify clinically meaningful differences in ERGs recorded from patients with vascular obstructions, Henkes distinguished between ERGs having larger-than-normal a-waves in the presence of reduced b-waves (the negative [−] form) and ERGs having larger-than-normal a-waves and normal or supernormal b-waves (the negative [+] form) (Fig 66–2). Today, this terminology is infrequently used, but the concept of the negative (−) ERG, a reduction in the b-wave amplitude (measured from the a-wave trough to the b-wave peak) relative to the a-wave amplitude (measured from the baseline to the a-wave trough), is still considered to be an important sign of severe inner retinal dysfunction in vascular disease.

The remainder of this chapter will discuss the contribution of the reduced ERG b-wave/a-wave (b/a) ratio to our understanding of prognosis in a

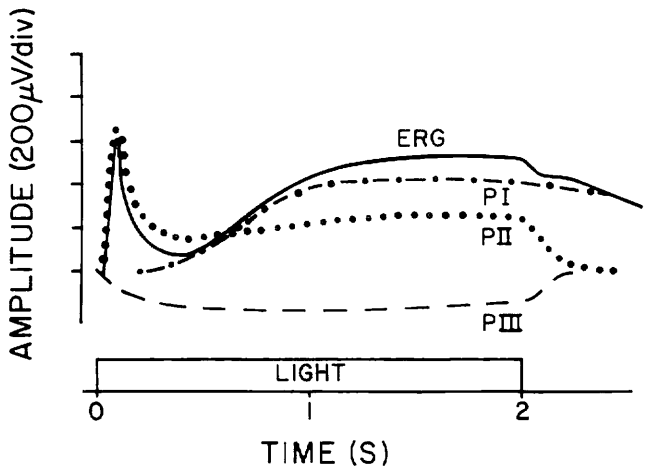

FIG 66–1.
The ERG and its putative underlying components. (Adapted from Granit R: *J Physiol* 1933; 77:207–238.)

number of ischemic retinal vascular diseases. A crucial point to keep in mind while reading this overview is that most investigators allude to the b/a ratio as though it were an invariant characteristic of the ERG. In fact, the b/a ratio depends strongly upon stimulus intensity, as is illustrated in Figure 66–3,A–C. Thus, in order to compare the results of different studies, it is essential to know the retinal illuminance of the stimuli used. This requirement generally necessitates Ganzfeld stimulation and calibration of the individual instrument, requirements that have not been met by many of the studies that are described here. These omissions notwithstanding, the effect of a clinically meaningful vascular obstruction on the ERG is generally so large that the observations reported below deserve consideration.

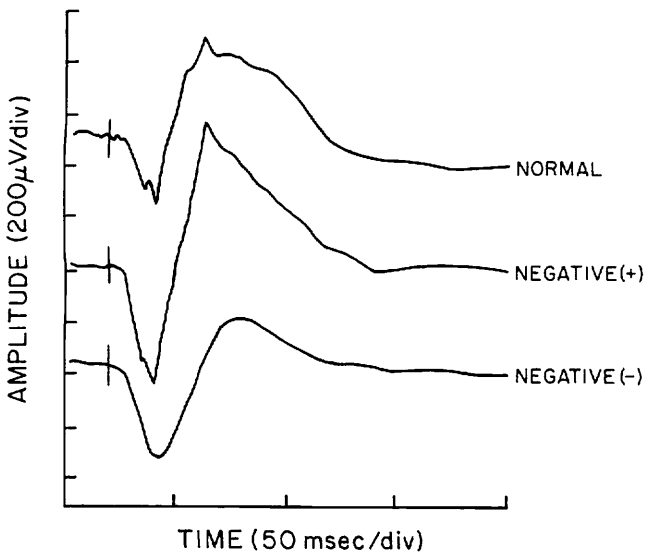

FIG 66–2.
A normal ERG drawn with negative (+) and negative (−) ERGs. Henkes[4] described a negative (+) ERG as having a supernormal a-wave and normal or supernormal b-wave, and a negative (−) ERG as having a supernormal a-wave and reduced b-wave.

RETINAL ARTERY OCCLUSION

The destructive interference of P_{II} and P_{III} is probably best appreciated by examining the ERG in eyes suffering from wholesale inner retinal destruction. Such is often the case in eyes with central retinal artery occlusion (CRAO). In cases of complete and long-standing CRAO in which the circulation to the inner retina is blocked for periods of about 1½ hours or longer, the ERG consists of a supernormal a-wave (Fig 66–4). The highly negative ERG is present soon after onset of the occlusion. No or little b-wave is observable in these cases, presumably because the inner retinal generators of P_{II} are not functioning due to a lack of perfusion by the central retinal artery. The a-wave has a larger-than-normal amplitude, presumably because P_{II} is no longer generated and hence does not interfere with P_{III}. P_{III} is believed to be unaffected by the occlusion because the choroidal circulation, which fuels the photoreceptors, is supposedly unaffected, but the assumption that the photoreceptor response is completely normal in this condition has not been tested. Less severe artery occlusions or situations in which circulation is provided by the cilioretinal artery produce the intermediate ERG findings of partially increased a-wave and decreased b-wave amplitudes.

Karpe and Uchermann[11] described ERG findings in a study of 16 CRAO eyes (13 patients). Fifteen of these eyes had a negative (−) ERG in which the b-wave potential did not approach the potential of the prestimulus baseline. The other eye had an extinguished ERG but also had concomitant diabetic retinopathy not evaluable because of cataract. The visual acuities in the group were very poor, except in one case where the cilioretinal artery provided blood flow to the macula. In one instance, administration of a vasodilator increased the b-wave from 0 or less (measured from prestimulus baseline) to 120 μV. Occlusion of a branch of the retinal artery, described by the authors in seven cases, resulted in a subnormal or negative (−) ERG, presumably because of the smaller retinal area affected.

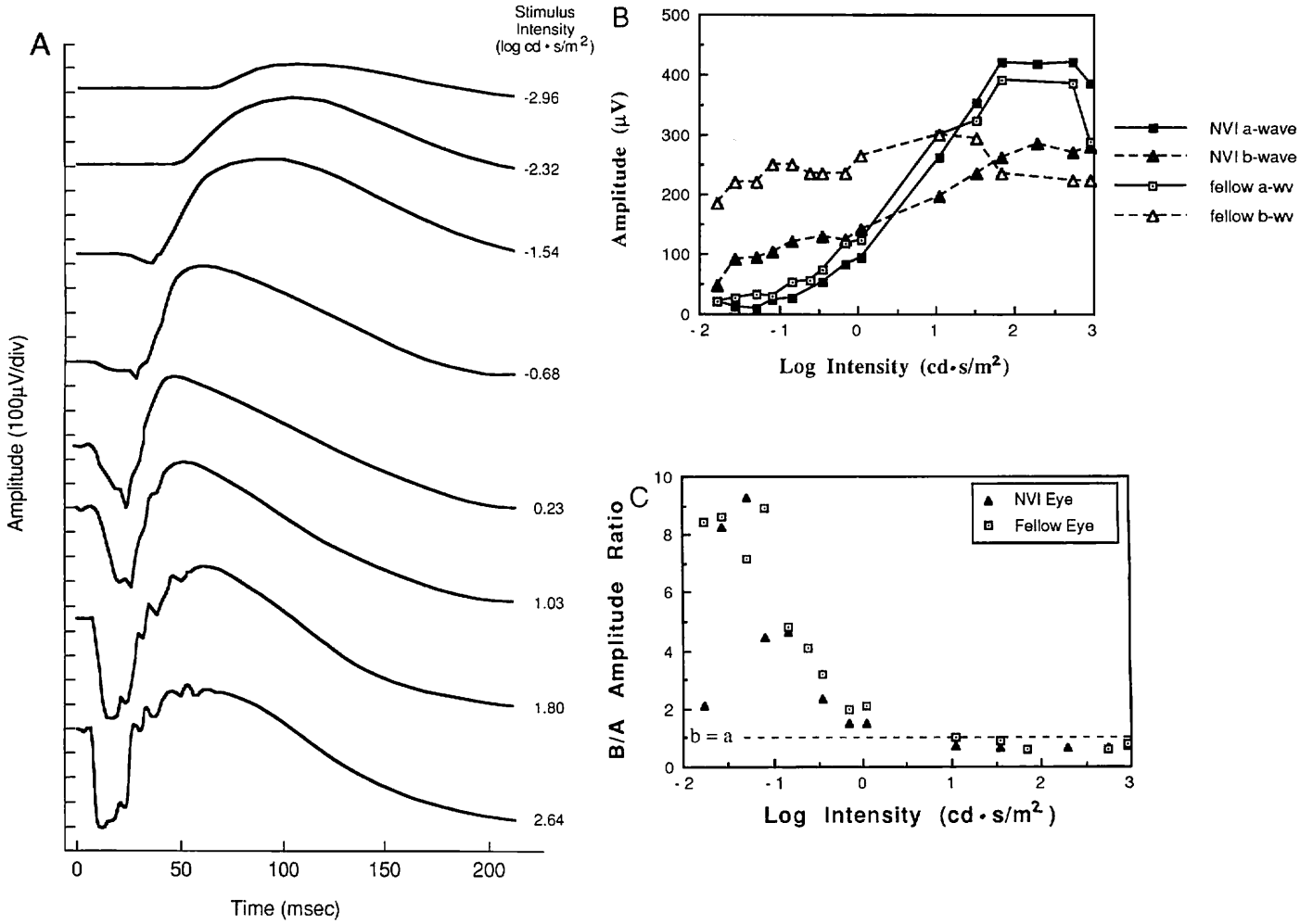

FIG 66–3.

A, ERGs recorded as a function of stimulus luminance for a normal observer. Note that as stimulus luminance increases, the a-wave amplitude grows at a faster rate than does the b-wave amplitude, and this results in smaller b/a ratios. This relationship is plotted in **B** for the normal and affected eyes of a patient with central retinal vein occlusion and iris neovascularization *(NVI)*. For this patient, the greatest recorded difference between eyes occurs at the 0.03 log cd · sec/m^2 intensity. Here, the difference in b/a ratio between eyes of 2.13 (fellow eye) vs. 1.50 (affected eye) is due largely to a reduction in b-wave amplitude. **C,** extreme differences between eyes in the b/a ratios were rarely seen for this patient, although sizable reductions in b-wave amplitudes were observed for all but the highest intensities.

Delays in the implicit time of the a-wave also are observed in CRAO (Fig 66–4). However, these delays are found only in the presence of substantial b-wave amplitude reductions and are predicted from the reduced degree of interference from P_{II}.

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 the outer and inner retinal layers.

RETINAL VEIN OCCLUSION

ERG changes produced by branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) were first documented by Karpe in 1945.[9] While only minor changes can be observed in the ERG in eyes with BRVO, ERG changes are often considerably more dramatic when the central vein is occluded. Karpe described selected cases of CRVO in which the ERG showed marked diminution of the b-wave and supernormal a-waves (e.g., a reduced

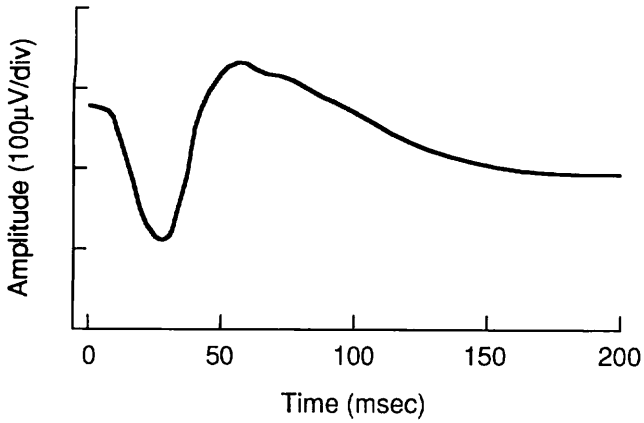

FIG 66–4.
The large a-wave and extremely reduced b-wave indicate extensive inner retinal damage in this eye with CRAO.

b/a ratio or a negative (−) ERG) and suggested that the extent of a-wave domination is best appreciated by a comparison to the fellow eye. He stated that the determination of b-wave amplitude loss was important for prognosis: a normal or positive (+) ERG indicated good prognosis while a subnormal or negative (−) ERG indicated poor prognosis.[8, 9*]

An important point that Karpe emphasized in his 1945 monograph is that there is a tremendous amount of variation in the relative amplitudes of b-waves and a-waves among normal individuals. As will be seen from subsequent discussions, most cases of CRVO do not produce the extreme reduction in the b-wave that is associated with total obstruction of the central retinal artery. The diminution of the b-wave relative to the a-wave in CRVO may be quite small. In addition, several studies[5, 14, 15] have shown that the ERG recorded from the normal, fellow eyes of patients with CRVO are not always normal, which makes a comparison of ERGs between eyes problematic. However, the extreme reductions in the b-wave relative to the a-wave seen in some eyes with CRVO almost always portend a poor outcome for the eye, a result explored in more detail later.

Henkes[4] followed on Karpe's observations with a study of 62 patients with CRVO. Twenty-five of the patients had a total occlusion† of the central retinal vein, and of these, 11 had negative (−) ERGs in which the b-wave was reduced and the a-wave was supernormal. In 6 of the 11 eyes, the b-wave measured between 200 and 290 μV, and the a-wave amplitude was not specified. Nine other individuals in this sample had ERGs that showed only reductions in b-wave amplitude. One patient in this sample later developed neovascular glaucoma (NVG); his ERG had a reduced b-wave measuring 200 μV. Henkes suggested that the finding of a reduced or negative (−) ERG in CRVO was sufficiently robust that it should be used in the classification of nonperfused vs. perfused CRVO.

Karpe and Uchermann[11] performed a prospective study of 39 eyes with CRVO that had ERGs performed at presentation and repeated at a later date. At presentation, 15 of these eyes had negative (−) ERGs, and 7 of the 15 later developed NVG. Although there was a wide distribution of b-wave amplitudes represented in this group of 15 (amplitudes varied between 0 and 440 μV), there was almost no overlap between distributions of amplitudes from eyes that developed vs. eyes that did not develop NVG. Furthermore, none of the eyes that developed NVG had b-wave amplitudes greater than 120 μV. The time between onset of the occlusion and the patient's first ERG varied between 3 days and 6 months, so even though the authors showed that the ERG changed in some individuals over the course of the disease, these convincing results were all based on the one ERG recorded at presentation.

Karpe and Germanis[10] further explored the prognostic value of the ERG recorded at the patient's first visit in a prospective study on 87 eyes of 86 patients. Twenty-nine eyes had a negative (−) ERG, and 7 of the 29 developed NVG and were enucleated. Although data on only 57 of the patients were provided, the average b-wave amplitudes of the eyes in the group that developed glaucoma were significantly reduced when compared with the b-wave amplitudes of the eyes that did not develop glaucoma. The overlap between groups was greater in this study than in the study of Karpe and Uchermann.[11] Pupil sizes in the study of Karpe and Germanis varied widely because some patients received homatropine, others were not dilated, and still others were receiving miotics for the treatment of chronic open-angle glaucoma. The differences in pupil sizes may have resulted in a range of retinal illuminances that varied by 0.6 log units or more among subjects. As demonstrated in Figure 66–3, the b/a ratio depends to a large extent on retinal illuminance.

Recent studies have also shown that negative (−) ERGs (reduced b/a amplitude ratios) presage a poor outcome for eyes with CRVO. However, there are

**By "poor prognosis," Karpe and other researchers of the time were referring to either poor visual acuity or to the development of neovascular glaucoma (NVG).*

†By "total occlusion," Henkes is probably referring to ischemic or nonperfused CRVO as opposed to perfused CRVO.

two major differences between the current and the classic studies. In the classic studies, the presence of a negative (−) ERG was a risk factor for NVG, but typically fewer than 50% of the eyes with this characteristic developed NVG. In contrast, current studies suggest that the presence of a negative (−) ERG is a highly specific sign for the development of neovascular complications but not a highly sensitive sign; patients with normal b/a ratios also develop proliferative disease. The important difference between the current and classic studies, and a possible explanation for some of the discrepancies between the two sets of results, is that the end points are not the same. In the days before panretinal photocoagulation (PRP), no treatment was effective in preventing ischemic CRVO eyes from developing NVG, and thus the end point of the earlier studies was typically NVG. Today, eyes that develop angle neovascularization are usually treated before NVG results. Eyes that develop neovascularization around the pupillary margins but not involving the angle are often treated, as are eyes that look ischemic but have no neovascularization. If the data of Hayreh et al.[3] on the natural history of CRVO, which shows that only about half of the eyes that develop neovascularization of the iris (NVI) proceed to NVG, can be applied to the earlier populations, almost an equal number of eyes in the older studies must have developed NVI without progressing to NVG, and these eyes may have shown subtler ERG changes. This argument suggests that most eyes today that would go on to develop NVG if left untreated are the ones with the worst b/a ratios. Eyes with less severe ERG changes and NVI may not, in many cases, progress to NVG.

A study by Sabates and his colleagues[13] illustrates the effect of different end points on interpretation. By using a hand-held strobe light (which at the distances used typically produces a much brighter stimulus than do most current Ganzfeld stimulators), Sabates et al. recorded ERGs in 45 perfused, indeterminate, or nonperfused CRVO patients. Eight indeterminate or nonperfused patients had ERG b/a ratios measuring <1, i.e., the b-wave was so reduced that it did not extend beyond the prestimulus baseline in these individuals. Five of the 8 eyes developed NVI, while only 2 of these 5 progressed to NVG. In addition, 1 eye having an ERG "uncharacteristic of either severely ischemic or nonischemic CRVO" but not otherwise described developed neovascularization. The authors also demonstrated a case where the ERG of a patient with an initially normal b/a ratio deteriorated until the ratio became less than 1 and suggested that patients who do not show this finding initially may develop it later in the course of the disease.

Similarly, Breton et al.[1] showed that a reduced b/a ratio is very specific for the development of NVI. In accordance with clinical judgment, however, the authors did not follow these patients but instead chose to treat them with PRP. Thus, as with most current studies, they did not test the relationship between a reduced b/a ratio and NVG. Six out of 18 patients in the study of Breton et al.[1] developed NVI, and of these 6, 5 had b/a ratios ≤1. Kaye and Harding[12] obtained similar findings in the 7 out of 27 patients in their sample who developed NVI. However, they found more overlap in the distributions of b/a ratios in the intrasubject comparisons and in the outcome comparisons.

In agreement with Kaye and Harding,[12] Johnson and colleagues[6, 7] found the b/a ratio reduction to be a very specific indicator of NVI, but they described a substantial amount of overlap in the distributions of b/a ratios in individuals who developed NVI and those who did not. In a 1988 study, they reported a significantly reduced b/a ratio in only one out of nine proliferative CRVO patients, seven who had NVI and two who later developed this complication. One patient who had NVG at the time of testing had a b/a ratio of 4.53, with a b-wave that measured 400 μV. Johnson and colleagues[7] further defined the distribution of b/a ratios in a prospective study of 93 CRVO patients. Thirty-five patients in this study developed NVI, 9 of whom had the complication at the time of testing. Fifty-eight patients did not develop NVI over a follow-up time that varied between 9 months and 5 years (median, 22 months). The b/a ratios of the affected eyes of patients who developed NVI were significantly smaller than the ratios measured in the fellow eyes ($p < .0004$, 31 paired observations) and smaller than the ratios measured in the affected eyes of individuals who did not develop NVI ($p = .024$). However, there was a substantial amount of overlap in the distributions, which suggests that management of the individual patient would be difficult if only this parameter were used. Figure 66–5 illustrates this finding for the latter comparison.

There are several reasons why these three latter studies may show the b/a ratio to be less of a sensitive indicator of severe ischemia in CRVO than the studies of Sabates and Breton. The differences may be due to differences in sample sizes, differences in stimulus luminances, or the possibility that there are several etiologies of CRVO that manifest themselves

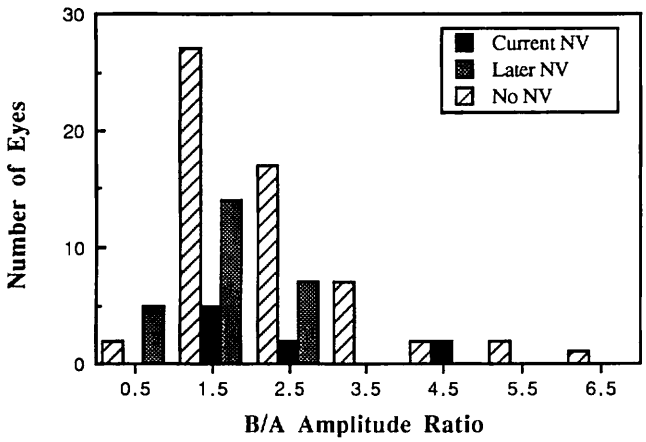

FIG 66–5.
b/a Amplitude ratios in 93 eyes with CRVO. The mean of the distribution of ratios from eyes that did not develop NVI is only 0.53 higher than the mean of the total sample of eyes that developed NVI, and eyes that had NVI at the time of testing did not have lower b/a ratios than did eyes that developed NVI at a later time.

as functionally different. Heterogeneities in the disease, caused by the presence of contributing conditions that affect the risk for complications or by differences in etiology, are probably best appreciated in studies having large sample sizes. In this regard, the results of the ERG ancillary study of the multicenter Central Vein Occlusion Study should help us to better understand the value of the b/a ratio in the prognosis of CRVO.

CONCLUDING REMARKS

What place does the ERG b/a measurement have in the management of patients with retinal vascular occlusion? In cases of CRAO, a reduced b/a ratio can help affirm the diagnosis and can quantify the severity of the occlusion. In CRVO, the b/a ratio predicts the development of NVI with high specificity but not high sensitivity, but it is less specific for the development of NVG than for NVI. Other measures of visual function, e.g., visual acuity, relative afferent pupillary defect, etc., are severely affected in eyes that also show a reduced b/a ratio, and thus a severely reduced b/a ratio portends a poor visual outcome for the eye, even in the absence of neovascular complications.

Other parameters of the ERG are reported to be more sensitive in identifying eyes with CRVO that are at risk for the development of NVI. These parameters are discussed in Chapter 80.

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