Electroretinogram b/a wave ratio improvement in central retinal vein obstruction

Yoshie Matsui, Osamu Katsumi, Hiroshi Sakaue, Tatsuo Hirose

Abstract
The electroretinogram (ERG), especially the b/a wave ratio, is considered a good indicator of retinal ischaemia in central retinal vein obstruction (CRVO). Seven CRVO patients who showed b/a wave ratio improvement from <1-0 [negative type (-) ERG] to ≥1-0 and one from 1-07 to 1-53 were studied. Three mechanisms of change were observed: firstly, the b-wave amplitude increased without an a-wave amplitude decrease (group A, n=2); secondly, the b-wave amplitude increased with an a-wave amplitude decrease (group B, n=4); and, thirdly, both decreased, but the a-wave amplitude decreased more markedly (group C, n=2). In group A, the visual acuities improved markedly. In group B, the visual acuities improved in two cases in which the b-wave amplitude reached the normal range; the visual acuities did not improve in two cases in which the b-wave amplitude did not reach the normal range. In group C, the visual acuities remained poor. The negative (-) ERG or significantly reduced b/a wave ratio is associated with ischaemic CRVO and did not occur because of the filtering effect of the haemorrhage, which may reduce the stimulus light for the ERG. Improvement of the reduced b/a wave ratio with an increased b-wave amplitude was accompanied by improvements in fundus appearance and visual acuity in CRVO. The results suggest that the retinal ischaemia in CRVO, as revealed by the ERG and fluorescein angiogram, may be reversible in some cases.

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The prognosis of central retinal vein obstruction (CRVO) is believed to depend on the severity of the circulatory disturbance of the retina: the more severe the disturbance, the poorer the prognosis.12 Ablating the non-perfused retina by laser coagulation in ischaemic CRVO has been a topic of discussion.14 Therefore, when a diagnosis of CRVO is made, besides finding the possible cause of the disease, the next step is evaluating the degree of retinal ischaemia. When the central retinal artery is completely obstructed, causing severe generalised retinal ischaemia, the electroretinogram (ERG) b-wave, which is generated in the neural retinal layers, is selectively depressed, and the a-wave, which originates in the receptors, remains normal or becomes larger than normal.14 On the other hand, in CRVO, the ERG b-wave, both amplitude and implicit time, and the b/a wave ratio vary, and the variation is believed to depend upon the degree of retinal ischaemia.2-15 If the ERG b-wave ratio becomes very small in the eye with CRVO, similar to that observed in central retinal artery obstruction, one can conclude that the overall retinal ischaemia is very severe. Thus, the ERG b/a wave ratio can be used as a measure of the degree of retinal ischaemia at the time of initial evaluation as well as during follow up in patients with CRVO. Johnson et al14'15 reported that the log K value of the Naka-Rushion function of the b-wave amplitude is well correlated with retinal ischaemia. Aside from the ERG b-wave, 30 Hz flicker implicit time is also reported to be a sensitive indicator of retinal ischaemia.14'15 It had been reported that 5–7% of eyes with non-ischaemic CRVO progress to the ischaemic type14'15; meanwhile, it had not been reported that ischaemic CRVO can become non-ischaemic.

We report herein the clinical findings in eight cases of CRVO in which the ERG b/a wave ratio improved during the course of observation.

Patients and methods
We studied eight patients (six men, two women; 35 to 76 years old) with unilateral CRVO who were referred to the Retina Associates, Boston. Of 15 patients who showed negative (-) type ERGs at the initial visit and had ERGs recorded more than once, these eight showed improved ERG b/a wave ratios during follow up. Two patients with diabetes mellitus and three patients with systemic hypertension with no change in the retina specific to each disease were included in this study.

The ERG was recorded in cases 1 and 3–7 by a method described previously.18 A Jacobson-type contact lens electrode (Dunker Laboratories Inc, Sarasota, FL, USA) was used as an active electrode. The reference electrode was placed on the ipsilateral cheek, and the ground electrodes were placed on both earlobes. The patients' pupils were fully dilated with 1% cyclopentolate hydrochloride and 2-5% phenylephrine hydrochloride. Thirty minutes of dark adaptation preceded the ERG recording. The light source was stroboscopic light (Model PS-22, Grass Instrument Co, Quincy, MA, USA). The photopic b-wave was determined with a red light, and the scotopic b-wave was obtained with a dim blue light. Photopic flicker responses were obtained with a relatively bright white flickering light (intensity 8 at 32 Hz). Single white flash responses were recorded with an actual light intensity of 48-5 lux seconds. Responses were amplified using a filter with passband 0-66–3000 Hz (Model 7D, Grass Instrument Co).

In cases 2 and 8, the ERG was recorded with the LKC System UTAS E 2000 (LKC Technologies, Inc, Gaithersberg, MD, USA). A Burian-Allen monopolar type contact lens
electrode was used as the active electrode. The reference electrode was placed on the forehead, and the ground electrodes were placed on both carotids. The patients' pupils were fully dilated with 1% cyclopentolate hydrochloride and 2.5% phenylephrine hydrochloride. After 45 minutes of dark adaptation, responses to single white flash stimuli with a Ganzfeld stimulator bowl were recorded, the intensity of which was 2.8 log cd/m². The responses were amplified using a filter with bandpass 0.3–500 Hz.

Initial ERGs were recorded between 1 and 6 months after CRVO onset, and the last ERGs were recorded between 6 and 75 months after CRVO onset. Panretinal photocoagulation (PRP) was performed in cases 1 and 7 at 11 and 3 months, respectively, after CRVO onset.

A standard sequence was used in the fluorescein angiography (FA) examination as reported previously. The early frames concentrated on the disc and macula, the intermediate frames on the midperipheral area in each quadrant, and the late frames on the disc and macula again. These studies were performed using Kodak Tri-X 400 ASA film (Kodak, Rochester, NY, USA), and measurements were made on an Agfa F0711P positive print transparency.

The clinical work in this study was performed in conformity with the tenets of the Declaration of Helsinki. Before the ERG testing and FA, the procedures were explained fully to patients, and informed consent was obtained in all cases.

**Results**

**OVERALL ANALYSIS**

Table 1 shows the results of ERG with bright white flash in each patient. In all cases (except case 3 whose b/a wave ratio was 1.07), the ERG b/a wave amplitude ratio increased during follow-up from <1.0 to ≥1.0. After analysing the change of the a-wave and b-wave amplitudes, we found three variations that affect the ERG b/a wave ratio: group A is comprised of those in which the b/a wave ratio increased because of an increased b-wave amplitude only; group B, those in which the a-wave amplitude decreased and the b-wave amplitude increased; and group C, those in which both the a-wave and b-wave amplitudes decreased, but the a-wave amplitude did so more markedly.

**Group A**

**Cases 2 and 3.** The b/a wave amplitude ratio increased mainly due to an increase of the b-wave amplitude from 457 to 510 μV and 319 to 450 μV in cases 2 (Fig 1, top) and 3 (Fig 1, bottom) and Fig 2, top), respectively. The a-wave amplitudes remained at approximately the same level. The visual acuities improved from 20/500 to 20/100 and counting fingers at 6–8 feet to 20/200 in cases 2 and 3, respectively. Regarding the other ERG components, the a-wave peak time shortened in both cases (Fig 2, top, Table 2).

In case 2, capillary dropout and fluorescein leakage initially were prominent on FA in the midperipheral retina with severe intraretinal haemorrhage and retinal oedema. At the time of the second ERG recording, capillary dropout and fluorescein leakage were not observed. Retinal haemorrhage diminished markedly.

In case 3, exudates in the posterior pole and extensive intraretinal haemorrhage were prominent (Fig 2, middle left). On FA, the veins were markedly dilated, while the presence of capillary dropout was undetermined because of extensive retinal haemorrhage (Fig 2, middle right). Exudates disappeared during follow-up with the decrease of retinal haemorrhage (Fig 2, bottom left). On FA, venous dilatation and leakage were diminished (Fig 2, bottom right).
Figure 2 (Top) The electroretinogram (ERG) recordings with bright white flash in case 3 (group A) at 1 and 5-5 months after the onset of central retinal vein obstruction (CRVO). Arrows indicate the start of flash stimulus. The b-wave amplitude increased, while the a-wave amplitude remained at the same level of the ERG recording 5-5 months after CRVO onset. (Middle left and middle right) The fundus photograph and fluorescein angiogram (FA) at 1 month. (Bottom left and bottom right) Fundus photograph and FA at 5-5 months after CRVO onset. (Middle left) Exudates in the posterior pole and extensive intraretinal haemorrhage were prominent. The optic nerve head is congested. (Middle right) On FA, the scots were markedly dilated, while the presence of capillary dropout was seen but partly covered by the extensive retinal haemorrhage. (Bottom left) Exudates disappeared during follow up with the decrease of retinal haemorrhage. The optic nerve head is less congested. (Bottom right) On FA, venous dilatation diminished.

Group B
Cases 1 and 4-6. In case 1, the ERG results were compared from recordings done 4-5 and 75 months after CRVO onset. In this group, the b-wave amplitudes increased, while the a-wave amplitudes decreased. These four cases were subdivided further into two types according to the b-wave amplitude at the last ERG recordings (Fig 3).

In Group B1 (cases 1 (Fig 3, top left and Fig 4, top) and 4 (Fig 3, bottom left)), the b-wave amplitudes improved to the level of our age-matched normal controls in both cases: 278 to 405 μV (normal range for the age: 361–498 μV) and 363 to 420 μV (normal range for the age: 353–444 μV), respectively. The a-wave amplitudes decreased from supernormal to the normal level of our age-matched controls, 220 μV in case 1 and 298 μV in case 4, respectively. The visual acuities improved in these two cases from counting fingers at 2–3 feet to 20/100 and from 20/25 to 20/20, respectively. All other ERG components improved in case 1 and improved or remained at the same level except for the scotopic b-wave amplitude in case 4 (Table 2).

In group B2 (cases 5 and 6), the b-wave amplitudes increased from 344 to 385 μV in case 5 (Fig 3, top right) and 100 to 158 μV in case 6 (Fig 3, bottom right), but did not reach the level of the age-matched normal controls. The a-wave amplitudes decreased from 422 to 319 μV in case 5 and from 192 to 150 μV in case 6. The visual acuities remained at counting fingers in both cases.

In case 1, extensive capillary dropout with microaneurysms and multiple cotton wool spots initially were observed (Fig 4, middle left). Intraretinal leakage assumed a cystoid pattern in the fovea (Fig 4, middle right). After follow up, multiple photocoagulation scars were present.
Table 2 Changes of electroretinogram results

<table>
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<th>Case No</th>
<th>Duration from onset (months)</th>
<th>Photopic b-wave amplitude (µV)</th>
<th>Scotopic b-wave amplitude (µV)</th>
<th>Flicker amplitude</th>
<th>a-Wave peak time with white flash (ms)</th>
<th>Photopic b-wave peak time (ms)</th>
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<td>84-3</td>
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Age-matched normal controls:
Photopic b-wave amplitude: 57-0-83-0, 56-5-78-5, 50-0-73-0, and 45-5-64-5 µV at ages 26-35, 46-55, 56-65, and >66 years.
a-Wave peak time with white flash: 9-3-11-5, 12-1-12-8, 11-3-15-8, and 12-2-17-2 ms at ages 26-35, 46-55, 56-65, and >66.

outside and partly inside the vascular arcade (Fig 4, bottom left). On FA, capillary dropout and vein leakage disappeared (Fig 4, bottom right).

In case 4, multiple intraretinal haemorrhage, which was present initially, cleared during follow up. Capillary dropout was not observed on FA at the initial visit, while leakage from the optic disc and dilatation of the retinal veins were prominent. FA was not repeated.

In case 5, exudates in the posterior pole and extensive retinal haemorrhage observed initially disappeared during follow up. A pigmented scar in the macula appeared during follow up. Extensive capillary dropout and micro-
Electroretinogram b/a wave ratio improvement in central retinal vein obstruction

An electroretinogram (ERG) was recorded with bright white flash in case 1 (group B) at 4-5 and 75 months after the onset of central retinal vein obstruction (CRVO). Arrows indicate the start of the flash stimulus. The b-wave amplitude increased, and the a-wave amplitude decreased at the ERG recording 75 months after CRVO onset. (Middle left and middle right) Fundus photograph and fluorescein angiogram (FA) at 1 month. (Bottom left and bottom right) Fundus photograph and FA at 5-5 months after CRVO onset. (Middle left and middle right) Initially, extensive capillary dropout with microaneurysms and multiple cotton wool spots were present and intraretinal leakage assumed a cystoid pattern in the fovea. (Bottom left) After follow up, multiple photocoagulation scars were present outside and partly inside the vascular arcade. (Middle right) Chorioretinal atrophy was observed in the macula. (Bottom right) On FA, capillary dropout and vein leakage disappeared.

Aneurysms were observed in the posterior pole on FA at the time of the initial ERG recording. However, FA was not repeated in this patient.

In case 6, exudate in the posterior pole disappeared, and retinal haemorrhage decreased during follow up. FA was not performed because of patient allergy to fluorescein.

Group C
Cases 7 and 8. The a-wave and b-wave amplitudes with bright white flash both decreased in these cases, with the decrease of the a-wave amplitude larger than that of the b-wave amplitude: 224 to 133 μV in case 7 (Fig 5, top and Fig 6, top), and 426 to 298 μV in case 8 (Fig 5, bottom). As a result, the b/a wave amplitude ratio increased. The a-wave peak time shortened in both cases (Table 2). The visual acuities remained hand movement in case 7 and counting fingers in case 8.

In case 7, exudate was extensive around the disc. The retina in the macular area was oedematous initially (Fig 6, top left). Extensive capillary dropout was observed on FA at the time of the initial ERG recording (Fig 6, bottom right). The intraretinal haemorrhage decreased, the exudate disappeared, and macular degeneration developed during follow up (Fig 6, bottom left). However, FA was not repeated.
Figure S

Figure 5 The results of the electrotretinogram (ERG) with bright white flash in group C patients. The visual acuities at the time of each ERG recording are shown beside the b/a wave amplitude ratio. PRP = panretinal photoocoagulation; HM = hand movement; CF = counting fingers.

In case 8, the retina in the macular area was oedematous initially, and macular degeneration appeared during follow up. Capillary dropout was not observed in either the first or second FA.

The amount of retinal haemorrhage decreased but was still extensive at the time of the second ERG recording.

Case report
A 65-year-old female patient (case 1) (Fig 7) noticed a decrease of vision in her right eye, and 1 month later, she was diagnosed with CRVO and treated with systemic steroids. She was re-examined by us 2 months after CRVO onset. She had been suffering from diabetes mellitus, but had no diabetic retinopathy in either eye. At the first ERG recording, 2 months after the onset of CRVO, both the a-wave and b-wave amplitudes were supernormal, and the b/a wave amplitude ratio was 1.62. The vein was markedly engorged and tortuous. Multiple intraretinal haemorrhages and cotton wool exudates were observed. Visual acuity was counting fingers at 4–5 feet.

At the time of her second ERG recording 2½ months later, both the a-wave and b-wave amplitudes, but especially the latter, decreased, and the b/a wave amplitude ratio decreased to 0.76. Retinal haemorrhage and exudates were marked. However, at the third ERG recording 8 months after onset, the b-wave amplitude increased from 278 to 446 μV, a more marked change than the increase in the a-wave amplitude (363 to 367 μV). Accordingly, the b/a wave amplitude ratio increased to 1.22. Visual acuity remained counting fingers at 6–8 feet. The amount of retinal haemorrhage and exudates decreased.

Figure 6 (Top right) The electrotretinogram (ERG) recordings with bright white flash in case 7 (group C) at 2 and 7 months after the onset of central retinal vein obstruction (CRVO). Arrows indicate the start of flash stimulus. Both the a-wave and b-wave amplitudes decreased as the ERG recording 7 months after CRVO onset. (Top left and bottom right) The fundus photograph and fluorescein angiogram (FA) at 2 months. (Bottom left) The fundus photograph at 7 months after CRVO onset. (Top left) The retina in the macular area was oedematous initially. (Bottom right) Extensive capillary dropout was observed on FA at the time of the initial ERG recording. However, FA was not repeated. (Bottom left) The intraretinal haemorrhage decreased, the exudate disappeared, and macular degeneration developed during follow up.
At the fourth ERG recording 10 months after CRVO onset, the b/a wave ratio increased to 1.44, and her visual acuity improved to 20/300. Barrage photocoagulation was performed with green laser 11 months after onset because of the presence of marked and widespread capillary dropout in the posterior pole on FA (Fig 4, middle right). The fifth ERG recording, after laser treatment showed a decrease in both the a-wave and b-wave amplitudes temporally. The visual acuity increased to 20/200. Retinal haemorrhage diminished and exudates were absorbed, while vascular anastomosis was observed on the disc. At the sixth ERG recording 14 months after laser treatment (30 months after CRVO onset), both the a-waves and the b-waves increased (217 to 311 μV and 396 to 513 μV, respectively). Retinal haemorrhage and the vascular anastomosis on the disc disappeared.

During the 4 year follow up, three additional ERGs were recorded, with similar findings. Finally, 75 months after onset, the b/a wave amplitude ratio increased to 1.84. The b-wave amplitude increased and the a-wave amplitude decreased compared with the ERG results at 4-5 months from onset when the b/a wave amplitude ratio was <1.0. On FA, capillary dropout, which was observed until 42 months after CRVO onset, could not be observed at 62 months (Fig 4, bottom right). The visual acuity improved to the 20/100–20/70 range. All other ERG components increased in amplitude but remained below normal (Table 2).

**Discussion**

After analysing the ERG recordings of the eight cases in which the b/a wave amplitude ratio was below 1.0, then increased during the follow up period, we observed three patterns of change in the ERG b/a wave ratio: firstly, an increased b-wave amplitude (group A); secondly, an increased b-wave amplitude associated with a decreased a-wave amplitude (group B); and thirdly, decreased a-wave and b-wave amplitudes, the former more marked, resulting in an increased b/a wave ratio (group C). The a-wave amplitude remained at almost the same level in group A and decreased in groups B and C.

Considering the improvement of the ERG, FA, fundus appearance, and visual acuity, we speculate that the degree of retinal ischaemia actually decreased and the retinal function showed significant improvement in two group A patients and two group B1 patients in which the b-wave amplitude improved to the level of the normal controls. These cases suggest that ischaemic CRVO may improve to less ischaemic CRVO. On the other hand, in the two patients in group B2, the b-wave amplitude increased but did not reach the level of the normal controls. The visual acuities remained poor, although retinal haemorrhage and exudates decreased in both cases. In this group, the b-wave amplitude seemed to be an important factor: the greater the improvement of the b-wave amplitude to the level of the normal age-matched controls the more active the compensation against ischaemia (the recovery of retinal blood flow). In group C, the retinal function was not thought to be improved, because both the a-wave and b-wave amplitudes decreased. The visual acuities remained poor in these cases. Although the ERG b-wave amplitude, which reflects the overall retinal function, is not a direct predictor of visual acuity, we reported recently that when the b-wave amplitudes or the b/a wave ratios were decreased on the initial ERG recordings soon after the onset of CRVO, the visual acuities were poor (worse than 20/200) in all cases after follow up of more than 1 year. Therefore, the patients should be followed carefully, because the follow up periods of five of the eight cases (60%) in this study were less than 1 year.

According to the classification of Hayreh, the visual prognosis of ischaemic CRVO is poor; however, that of non-ischaemic CRVO is favourable. According to our results, we believe that an improvement of retinal function and a change in the degree of retinal ischaemia from ischaemic CRVO to less ischaemic CRVO can occur. To our knowledge, such an occurrence in CRVO has not been reported, with the exception of an improvement in b-wave amplitude from a negative (−) type ERG reported in metallosis bulb. In experimental research using monkeys, Hayreh et al. reported that haemorrhagic CRVO (ischaemic CRVO) occurred when the central retinal vein occlusion is accompanied by transient (6–7 hours) central retinal artery occlusion. When both the central retinal vein and artery are occluded completely, retinal capillary obliteration occurred without development of haemorrhagic or venostatic (non-ischaemic) CRVO. Kurachi and coauthors reported that temporal retinal circulatory disturbance in Takayasu’s disease caused a transient decrease of b-wave amplitude: temporal negative (−) type ERG instead of a permanent change. Hayreh et al. reported that retinal damage after transient central retinal artery occlusion was reversible if the retinal ischaemia was less than 97 minutes and the ERG b-wave was reversible for up to 135 minutes of ischaemia. Therefore, under certain conditions, retinal impairment caused by transient ischaemia might be reversible – for
example, when the period of ischaemia is short, when the degree of ischaemia is moderate, or a combination of these.

The ERG b-wave is generated in the middle retinal layer in which the blood supply is provided mainly by the retinal circulation. Accordingly, the b-wave amplitude is believed to be a good indicator of the retinal circulation. Among our eight cases, the b-wave amplitude returned to normal in four (groups A and B1); the visual acuities improved in all of them. The b-wave amplitudes improved but did not reach the level of the normal age-matched control in two cases (group B2) and decreased in two cases (group C). In these four cases, the visual acuities remained poor.

We report here that improvement of retinal function in ischaemic CRVO accompanied with visual acuity improvement can occur, and is correlated with the recovery of the b-wave amplitude recorded with bright white flash. A nationwide CRVO study is under way that will provide information about how the ERG would be helpful to manage this disease.

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