Multifocal Electroretinographic Features of Central Retinal Vein Occlusion

Fiona M. Dolan,1 Stuart Parks,2 David Keating,2 Gordon N. Dutton,1 and Aled L. Evans3

PURPOSE. To determine the features of wide-field multifocal electroretinography (WF-mfERG) recorded in patients with central retinal vein occlusion (CRVO) and to compare WF-mfERG responses of the affected and fellow eyes. In addition, WF-mfERG responses were also compared by using standard electroretinography (ERG).

METHODS. WF-mfERG and ERG responses were recorded from both eyes of 56 patients with CRVO. The WF-mfERG responses, obtained using a custom-built system were grouped into central and peripheral rings. The P1 amplitudes, and P1 and N1 implicit times were grouped and averaged within both rings. Nonparametric statistical analysis was used to compare the ERG results from the affected and fellow eyes. The results were also compared with normative data (5% to 95% confidence limits).

RESULTS. CRVO markedly affected all the parameters of the WF-mfERG. In the affected eyes, 98% of the central and 91% of the peripheral P1 implicit times fell outside the normal range, as opposed to 35% of the 30-Hz flicker implicit times. The WF-mfERG responses obtained from eyes with CRVO were significantly different (P < 0.01) from those derived from the fellow eye. The central and peripheral P1 implicit times were also abnormal in 59.2% and 46.9% of the fellow eyes, respectively.

CONCLUSIONS. WF-mfERG is more susceptible than the standard ERG to changes in the nonlinear dynamics of the eye due to the multiple frequencies of stimulation used to record WF-mfERG responses. WF-mfERG could be a sensitive indicator of the underlying disease affecting the retina in eyes with CRVO and may have a role in the clinical setting. (Invest Ophthalmol Vis Sci. 2003;44:4954–4959) DOI:10.1167/iovs.03-0083

Central retinal vein occlusion (CRVO) is a common ocular problem, which in 20% of affected patients, if left untreated can result in a painful blind eye, due to development of neovascular glaucoma.1 In the early stages of the disease, it is prudent to monitor patients carefully and apply timely argon laser photocoagulation to those eyes at risk of neovascular complications.2 Electroretinography (ERG) provides an objective measure of the loss of retinal function in affected eyes,3–16 but controversy exists regarding which parameter of the ERG is most useful for monitoring patients with CRVO.7,9

In recent years, the introduction of a new electrophysiology technique called multifocal electroretinography (mfERG), first described by Sutter and Tran,17 has been useful for objective assessment of retinal function in many retinal disorders.18–20 Simultaneous recordings of retinal function are obtained from numerous locations. Wide-field (WF)-mfERG performed using a custom-built system,21 enables identification of focal areas of retinal dysfunction out to a 90° retinal field.

The purpose of the present study was to determine the features of the WF-mfERG recorded in patients with CRVO. We set out to establish whether there were differences in the WF-mfERG first-order responses between the eyes affected with CRVO and the fellow eyes, comparing the responses obtained with normative data derived from a group of 60 age-matched control subjects. In addition, we compared the percentages of abnormal WF-mfERG parameters to the percentages of abnormal ERG responses in both the affected and unaffected eyes.

METHODS

WF-mfERG responses were recorded simultaneously from both eyes of 56 patients diagnosed with CRVO. The first-order WF-mfERG responses, namely the P1 amplitude, P1 latency, and N1 latency were analyzed. The P1 amplitude is measured from the most negative trough of the waveform to the most positive peak of the WF-mfERG waveform. The P1 latency is defined as the time taken from the onset of the stimulus to the most positive peak of the waveform, and the N1 latency is the time taken from the onset of the stimulus to the first negative trough of the waveform. A custom-built WF-mfERG system was used,21 and the recordings were made using filter bandwidths of 3 to 100 Hz to minimize signal distortion found with negative P1 waveforms, as described previously.22 Disposable skin electrodes were attached lateral to the lateral canthi and a reference electrode was attached to the glabellar region (impedance values of <2.5 kΩ were achieved). Gold leaf scleral electrodes were placed in the lower fornix of each eye. The patient was seated 30 cm in front of a 61-hexagon array and maintained fixation on a central target. The sizes of the hexagons were scaled empirically to account for photoreceptor topography, adaptation variation across the field and the projection luminance gradient. The hexagonal array was displayed on a custom screen impregnated with microlight diffusing optic lenses, with a screen luminance of 1500 cd/m2. An appropriate pseudorandom binary m-sequence of length 215 – 1 was used to control the 61 hexagonal elements. The chosen m-sequence was checked to ensure that cross-contamination did not occur between the first three orders of the response.25 Total WF-mfERG recording time was 8 minutes broken into 30-second segments to facilitate good fixation, and the patient’s fixation on the central target was observed throughout the test. The raw waveform was visible throughout the recording and segments were rejected if there was saturation due to excessive blinking or evidence of poor fixation. An amplifier gain of 100,000 with an analog-to-digital converter (ADC) digitalization rate of 1,200 Hz was used.

To analyze the 61 WF-mfERG responses from each eye, the results were grouped into two rings: a central ring, comprising the inner 19 mfERG responses and a peripheral ring, comprising the remaining 42 responses, as shown in Figure 1. The P1 amplitudes, P1 latency, and the N1 implicit times were grouped and averaged within both rings.

From the 1Department of Ophthalmology, and the 2ElectroDiagnostic Imaging Unit, Tennent Institute of Ophthalmology, Gartnavel Hospital, Glasgow, Scotland, United Kingdom; and the 3Department of Clinical Physics and Bio-engineering, Southern General Hospital, Glasgow, Scotland, United Kingdom.

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Corresponding author: Stuart Parks, ElectroDiagnostic Imaging Unit, Gartnavel General Hospital, 1053 Great Western Road, Glasgow G12 0YN, UK; s.w.parks@clinmed.gla.ac.uk.
A full-field standard ERG was also performed on both eyes simultaneously, according to International Society for Clinical Electrophysiology of Vision (ISCEV) standards, using a standard flash strength of 2.5 cd·s·m$^{-2}$. All electrophysiology tests were performed on pupils dilated to the maximum with tropicamide 1% and phenylephrine 2.5%.

CRVO was defined by the clinical picture of typical hemorrhages in all four quadrants of the retina associated with dilatation and tortuosity of the venules. Patients were excluded if there was clinical evidence of any other retinal disease in the affected eye. Because of the differences in severity of symptoms and the methods of referral to the retinal vein thrombosis clinic, there was a variation in the time from onset of symptoms and presentation for electrophysiology assessment. All patients were assessed within 24 weeks of the onset of symptoms (mean time from onset of symptoms 8.43 weeks), 30 (65.2%) patients were assessed within the first 8 weeks of the acute event.

The study was conducted according to the tenets of the Declaration of Helsinki, and after a detailed explanation of the procedure; all patients gave informed consent before inclusion in the study. All patients underwent a full ophthalmic and medical assessment at presentation, including logarithm of the minimum angle of resolution (LogMAR) acuity, pupil assessment, Goldmann tonometry, gonioscopy, dilated fundus examination, digital photography, and fundus fluorescein angiography.

**RESULTS**

Fifty-six patients were examined, 33 men and 23 women aged 29 to 89 years (mean, 66 ± 11.5 [SD]). WF-mfERG and standard ERG were recorded and analyzed from both eyes of each patient, except in seven cases (four men and three women), in which the results from the fellow eye were excluded because of preexisting retinal disease. (Two patients had previous retinal detachments, four had previous CRVO, and one had a previous central retinal artery occlusion.)

**WF-mfERG**

Table 1 shows the results from the two rings of WF-mfERG recordings of the affected and the fellow eyes. A typical example of WF-mfERG trace arrays from a patient’s affected eye and the fellow eye is shown in Figure 2. Because a normal distribution of WF-mfERG responses could not be assumed, non-parametric statistical analysis (Wilcoxon), comparing the WF-mfERG responses from the affected and the fellow eyes was performed. The differences in all the WF-mfERG parameters assessed reached statistical significance ($P < 0.01$) between the affected and unaffected eyes, as shown in Table 1. The central and peripheral P1 amplitudes and P1 implicit times of both the affected and the fellow eyes are shown graphically in Figures 3 and 4, respectively, alongside the normal range ($n = 60$, aged 18–81 years, mean 45 ± 18). Not surprisingly, the central and peripheral P1 implicit time was abnormal in almost all the affected eyes, 98.2% and 91.1% respectively; however, the central and peripheral P1 implicit times were also abnormal in a considerable proportion of the normal fellow eyes, 59.2% and 46.9%, respectively. For comparison the variations

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*Figure 1. WF-mfERG stimulus showing central and peripheral rings and approximate corresponding retinal field stimulation dimensions.*

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*Figure 2. Example of WF-mfERG trace arrays from a patient’s affected eye and the fellow eye.*
in normal peripheral WF-mfERG latency and amplitude responses, as a function of age, are shown graphically in Figure 5.

In addition, the amplitudes of the central and peripheral WF-mfERG P1 responses of the affected eyes are abnormal in 53.6% and 50% respectively. Analysis of the WF-mfERG responses of the fellow eye, show the central and peripheral P1 amplitude responses to fall outside the normal range in 8.2% and 28.6% of the eyes, respectively.

**Standard ERG**

The scotopic and photopic recordings of the ERG responses from the affected and unaffected eyes are summarized in Table 2. Nonparametric statistical analysis (Wilcoxon) showed a significant difference \( P < 0.01 \) between the scotopic rod b-wave amplitudes and implicit times and also a significant difference

<table>
<thead>
<tr>
<th>WF-mfERG Parameter (normal range)</th>
<th>Range of Responses</th>
<th>Mean (±SD)</th>
<th>% Outside Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central P1 amplitude (nV) (74–122 nV)</td>
<td>14–168 48–153</td>
<td>72.6 (34.91) 98.6 (21.17)</td>
<td>&lt;0.001 53.6 8.2</td>
</tr>
<tr>
<td>Peripheral P1 amplitude (nV) (61–108 nV)</td>
<td>17–196 42–131</td>
<td>60.96 (29.36) 74.55 (18.40)</td>
<td>0.04 50.0 28.6</td>
</tr>
<tr>
<td>Central P1 implicit time (ms) (36–40 ms)</td>
<td>39–71 37–52</td>
<td>49.09 (7.06) 41.81 (2.71)</td>
<td>&lt;0.001 98.2 59.2</td>
</tr>
<tr>
<td>Peripheral P1 implicit time (ms) (37–42 ms)</td>
<td>40–65 39–54</td>
<td>48.48 (5.97) 42.49 (2.71)</td>
<td>&lt;0.001 91.1 46.9</td>
</tr>
<tr>
<td>Central N1 implicit time (ms) (22–24 ms)</td>
<td>23–39 23–30</td>
<td>29.65 (3.33) 25.4 (1.90)</td>
<td>&lt;0.001 94.6 67.3</td>
</tr>
<tr>
<td>Peripheral N1 implicit time (ms) (23–26 ms)</td>
<td>25–38 24–31</td>
<td>29.92 (3.07) 26.59 (1.79)</td>
<td>&lt;0.001 92.9 40.8</td>
</tr>
</tbody>
</table>

* Statistical significance between affected and fellow eyes (Wilcoxon).

![Figure 2](http://iovs.arvojournals.org/pdfaccess.ashx?url=data/journals/iovs/933433/) **Figure 2.** WF-mfERG trace array from a patient’s left eye with CRVO (A) and the fellow unaffected eye (B).

![Figure 3](http://iovs.arvojournals.org/pdfaccess.ashx?url=data/journals/iovs/933433/) **Figure 3.** (A) The WF-mfERG P1 amplitude responses from the central rings (normal range, 74–122 nV) and the (B) peripheral rings (normal range, 61–108 nV) of the affected and the fellow eyes. Dashed lines: 5% to 95% confidence limits of the normal range, derived from 60 age-matched control subjects.
(P < 0.01) between the maximal b-wave amplitudes and maximum b-wave implicit time, when comparing the affected eyes with the fellow eyes. Analysis of the photopic responses (Wilcoxon) showed a significant difference (P < 0.01) between the cone b-wave amplitudes and implicit times and the flicker implicit times, when comparing the two eyes.

The percentages of ERG responses that fell outside the 5% to 95% confidence limits are shown in Table 2. The most adversely affected ERG parameter was the photopic flicker implicit time, which was abnormal in 35.7% of affected eyes, and the least-affected ERG parameter in the eyes with CRVO was the scotopic maximum implicit time, with only 3.6% of affected eyes having an abnormal result.

Comparison of WF-mfERG and ERG Responses in the Eyes with CRVO

More of the affected eyes had abnormal WF-mfERG responses, compared with ERG responses. Because mfERG is thought predominantly to reflect cone function,18 we correlated all the photopic ERG amplitude responses and all the photopic ERG implicit time responses from the affected eye with all the WF-mfERG amplitude and implicit time responses, respectively. A significant correlation (Pearson, <0.05) was found between the central P1 WF-mfERG and the photopic flicker amplitude and latency responses. The correlation of the central P1 WF-mfERG amplitude and latency responses against the flicker amplitudes and latencies in the affected eye is presented in Figure 6.

FIGURE 4. The WF-mfERG P1 implicit time responses from the (A) central rings (normal range, 36–40 ms) and the (B) peripheral rings (normal range, 37–42 ms) of the affected and the fellow eyes. Dashed lines: 5% to 95% confidence limits of the normal range, derived from 60 age-matched control subjects.

FIGURE 5. Peripheral P1 (A) amplitude and (B) latencies for patients and control subjects as a function of age.

**DISCUSSION**

This was a preliminary study, designed to determine the effects of CRVO on WF-mfERG parameters. The results showed that (1) CRVO markedly affected both the P1 and N1 parameters of the WF-mfERG, (2) all the WF-mfERG first-order responses obtained from an eye with CRVO were significantly different (P < 0.01) from those derived from the fellow unaffected eye, (3) the P1 implicit times were delayed and P1 amplitudes were reduced in a large percentage of the fellow eyes, (4) the WF-mfERG responses were more likely to be subnormal and fall outside the 5% to 95% confidence limits in the affected and unaffected eyes than were the ERG responses, and finally, (5) there was a significant correlation between the central WF-mfERG P1 amplitudes and latencies and the 30-Hz flicker amplitude and latencies in the affected eyes.

We first observed subnormal P1 amplitudes and P1 implicit time delays in eyes with CRVO. This observation is in keeping with a previous report of mfERG responses in a subgroup of five patients with CRVO,25 in whom the P1 amplitudes and implicit times were reduced and delayed in the affected eyes. Significant differences between the ERG responses of the affected and unaffected eyes have been reported.4,5,7,9

The WF-mfERG abnormalities noted in the fellow eyes probably reflect abnormal retinal function in a patient population with underlying systemic disease, including hypertension (42%), diabetes mellitus (12%), high cholesterol (26%), and myeloproliferative disorders (3.6%), and supports previous ERG studies of patients with CRVO, which found 36% of fellow eyes to have abnormal ERG responses.26
Table 2. Standard ERG Responses from the Affected and Fellow Eyes

<table>
<thead>
<tr>
<th>Standard ERG Parameters (normal range)</th>
<th>Range of Responses</th>
<th>Mean ± SD of Responses</th>
<th>% Outside 5–95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Affected Eye</td>
<td>Fellow Eye</td>
<td></td>
</tr>
<tr>
<td>Rod amplitude (µV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(72–367 µV)</td>
<td>0–481</td>
<td>70–525</td>
<td>160.75 (112.1)</td>
</tr>
<tr>
<td>Rod implicit time (ms)</td>
<td>75–130</td>
<td>66–102</td>
<td>98.60 (13.66)</td>
</tr>
<tr>
<td>Max A amplitude (µV)</td>
<td>55–379</td>
<td>91–572</td>
<td>214.8 (78.30)</td>
</tr>
<tr>
<td>Max B amplitude (µV)</td>
<td>40–713</td>
<td>140–724</td>
<td>331.4 (148.7)</td>
</tr>
<tr>
<td>Max B implicit time (ms)</td>
<td>31–65</td>
<td>30–59</td>
<td>45.54 (8.28)</td>
</tr>
<tr>
<td>Cone A amplitude (µV)</td>
<td>10–50</td>
<td>9–45</td>
<td>27.52 (9.4)</td>
</tr>
<tr>
<td>Cone B amplitude (µV)</td>
<td>6–237</td>
<td>66–207</td>
<td>101.27 (48.0)</td>
</tr>
<tr>
<td>Cone latency (ms)</td>
<td>20–49</td>
<td>20–33</td>
<td>29.84 (6.5)</td>
</tr>
<tr>
<td>Flicker amplitude (µV)</td>
<td>9–220</td>
<td>32–250</td>
<td>63.64 (49.3)</td>
</tr>
<tr>
<td>Flicker latency (ms)</td>
<td>21–35</td>
<td>20–30</td>
<td>26.48 (3.53)</td>
</tr>
</tbody>
</table>

* Statistical significance between the fellow and affected eyes (Wilcoxon).

This study showed that more of the WF-mfERG responses from both the affected and the fellow eyes fell outside the normal range (5%-95% confidence limits) than did the ERG responses. In the affected eye, 98% of the central P1 implicit times and 91% of the peripheral implicit times fell outside the normal range compared with 35% of the 30-Hz flicker implicit time in the same eyes. The reason for this finding is unclear; the normal range of our standard ERG responses is in keeping with previously reported normative data. The WF-mfERG response is a result of multiple frequencies of stimulation as opposed to the ERG waveform, which is a response to a single frequency of stimulation. Therefore, it is likely that the WF-mfERG reflects more of the nonlinear processes in the retina, processes potentially affected by retinal ischemia due to changes in the adaptive mechanisms of the retina secondary to the underlying disease caused by the vein occlusion. Palmowski et al. also reported mfERG results suggestive of changes in the nonlinear dynamics of the retina, when analyzing eyes with diabetic retinopathy, a disease process that also affects the retinal vasculature.

ERG has been used in the management of patients with CRVO since 1946. To date, most studies agree that CRVO causes ERG abnormalities and that a highly abnormal ERG is associated with a poorer prognosis. However, there is controversy in the literature regarding the most useful ERG parameters to monitor patients with CRVO, as reviewed by Hayreh et al. and more recently Williamson et al. The standard ERG results obtained in this study are typical of those described in the literature.

More current studies on the use of ERG in CRVO have shown that both the timing and amplitude of the 30-Hz flicker, reflecting predominantly cone photoreceptor function, are good predictors of neovascular complications. mfERG is gaining recognition as an investigative tool for assessing diseases of the retina under photopic conditions and as such may be comparable to the photopic ERG. In the present study, there was a significant correlation between the flicker amplitude response and the WF-mfERG central P1 amplitude response. Severns and Johnson showed that the 30-Hz amplitude was a good predictor of neovascular complications, and the results from this current study open the possibility for using the WF-mfERG as a prognostic indicator of ischemic complications in eyes with CRVO.
The origins of the waveforms recorded with mfERG are still poorly understood. However, a recent animal study suggested that the mfERG has large contribution from the ON- and OFF-bipolar cells, in addition to a smaller contribution from the inner retinal components and the photoreceptors. In our study, both the P1 and N1 amplitudes and implicit times were affected by CRVO, and by extrapolating the animal mfERG model to the human eye, then the WF-mfERG abnormalities noted in this study of eyes with CRVO (i.e., P1 amplitude reduction and P1 and N1 implicit time delay) may reflect primarily bipolar cell dysfunction in this common vascular disease. Further microelectrode studies and histopathological analysis of CRVO are needed to investigate this hypothesis.

CONCLUSION

These data suggest that the WF-mfERG may have a role in the assessment of patients with CRVO. In the affected eye, 98% of the central P1 implicit times and 91% of the peripheral P1 implicit times fell outside the normal range as opposed to 35% of the 30-Hz flicker implicit times in the same eyes. The reason for the discrepancy between the two tests may be that the WF-mfERG is more susceptible than the standard ERG to changes in the nonlinear dynamics of the eye because of the multiple frequencies of stimulation used to obtain WF-mfERG responses. Therefore, the WF-mfERG could be a more sensitive indicator of the underlying disease affecting the layers of the retina in eyes with vein occlusion. WF-mfERG also has the advantage of taking 8 minutes to perform once the pupils have been dilated, as opposed to the 40 minutes required to obtain a full standard ERG, possibly making the WF-mfERG a more efficient and better-tolerated investigative tool than standard ERG in a busy clinical setting.

We observed that the more severely affected eyes tended to have poorer WF-mfERG responses. The sensitivity of WF-mfERG at differentiating ischemic from nonischemic CRVO in the acute phase, and importantly, clarification of the role of WF-mfERG in predicting neovascular complications in patients with CRVO will be the subjects of further investigation.

References