Multifocal electroretinogram in retinal vein occlusion

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Abstract

Purpose: To determine the effects of retinal vein occlusion (RVO) on multifocal electroretinogram (MF-ERG) parameters, to correlate MF-ERG and standard electroretinogram (ERG) and to correlate MF-ERG with findings of optical coherence tomography (OCT) in cases of RVO.

Methods: Both eyes of 50 patients with RVO and 50 eyes of 25 normal subjects were examined using MF-ERG, standard ERG, fluorescein angiography and OCT. The latency in millisecond (ms) and response density in nanovolt (nv/degenerations) were measured for each of four quadrant areas and central area. OCT was used to measure the foveal retinal thickness. Fluorescein angiography was used to measure retinal ischemia.

Results: Central retinal vein occlusion (CRVO) markedly affected all parameters of MF-ERG. In pathological quadrants in branch retinal vein occlusion, the response densities of MF-ERG were decreased and latencies of p-wave were prolonged. The MF-ERG responses obtained from eyes with RVO were significantly different (P > 0.05) from derived from the fellow eyes. The amplitude of MF-ERG were abnormal in 40 eyes and implicit times were delayed in 48 eyes compared with normal subjects. While 30 Hz flicker implicit were abnormal in only 24 eyes with RVO. Implicit times were prolonged in eyes with macular ischemia than in eyes without ischemia.

There were significant correlation between foveal retinal thickness measured by OCT and P response density MF-ERG in cases of retinal vein occlusion.

Conclusion: MF-ERG is more susceptible than standard ERG to eye changes of RVO due to the multiple frequencies of stimulation used to record MF-ERG response. MF-ERG could be sensitive indicator of underlying disease affecting the retina in eyes with RVO. MF-ERG is useful for detecting local retinal dysfunction in patients with RVO and sensitive to morphological changes and functional disorders induced by RVO.

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1. Introduction

Retinal vein occlusion preferentially affect the inner retinal layers and are frequently associated with a break down of blood-retinal barrier and consecutive retinal edema (Silva et al., 1995; Hood, 2000). Variable degree of ischemia can be present due to non-perfusion after capillary damage in the affected area.
The clinical picture may vary widely in RVO from few dot hemorrhages and full visual acuity to severe ischemia, extensive retinal hemorrhage, edema and severe reduction of visual acuity. The potential for effective treatment and the visual prognosis are very different in these different cases.

Central retinal vein occlusion (CRVO) is a common ocular problem which if left untreated can result in a painful blind eye, due to development of neovascular glaucoma in 20% of affected patients (Hayreh, 1983).

So, 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 complication (The Central Vein Occlusion Study Group, 1995).

Electro-retinogram (ERG) provides an objective measure of the loss of retinal function in affected eye with RVO (Karp, 1946; Larsson and Andreasson, 2001). But, controversy exists regarding which parameter of the ERG is most useful for monitoring patients with RVO (Hayreh et al., 1989; Williamson et al., 1997).

Multifocal electro-retinogram (MF-ERG) is a relative new diagnostic method that was first introduced by Sutter and Tran (1992). This method has been used for objective assessment of retinal function in many retinal disorders (Fortune et al., 1999; Palmowski et al., 1997). A close relationship of signal generation and shape between the first-order kernel response of MF-ERG, and that of full field cone ERG has been demonstrated (Hood et al., 1997). Previous studies have also clearly demonstrated that the inner retina contributes to the MF-ERG (Hood et al., 2002; Chahal et al., 1985).

The purposes of the present study are to describe the response from MF-ERG in RVO, to establish whether there were difference in MF-ERG first-order responses between affected eyes and fellow eye, to correlate MF-ERG and full field ERG parameters and to investigate the MF-ERG responses in the macular area in correlation to ischaemia defined by fluorescein angiography and retinal edema as measured by OCT.

2. Subjects and methods

This study was carried out on patients attending the out patient’s clinic of Mansoura Ophthalmic Center during period from January 2009 to October 2009. Fifty patients with RVO were included in this study; 18 eyes had central retinal vein occlusion, 22 eyes had branch retinal vein occlusion and 10 eyes had hemi retinal vein occlusion. The study included 25 normal subjects. Informed consents were obtained from all subjects. The mean duration ± SD of symptoms at the time of ERG was 6 ± 5 months (range, 1–18 months) (50% of patient had RVO of 6 months duration at beginning of investigation, 26% had RVO of 3 months duration).

All subjects underwent full ophthalmic and medical assessment including Best corrected visual acuity measurement using Snellen chart, pupil assessment, Goldmann tonometry, gonioscopy, dilated fundus examination, photography, fundus fluorescein angiography, optical coherence tomography, full field ERG and multifocal ERG.

RVO was defined by the clinical picture of typical haemorrhage in affected quadrant in BRVO and in all four quadrants of retina in CRVO associated with dilation and tortuosity of the venules. Patients were excluded if there were clinical evidence of any other retinal disease in the affected eye.

All control subjects had normal finding in ophthalmic examination, normal full field ERG, normal MF-ERG, normal fluorescein angiography and normal OCT features.

2.1. Fluorescein angiography (FA)

Topcon TRC 50 IX fundus camera was used to perform fluorescein angiography. Before injection of fluorescein, colour fundus and red-free photographs were taken. Fluorescein was injected rapidly as single bolus dose within approximately 5 s. Immediately after injection, the timer was started then photography began 8–10 s after injection (arm-retinal time) so as not miss early phases of the angiogram (six photographs were taken at intervals of 1–2 s then photographs were taken at 1, 5 and 15 min to assess the late phase).

2.2. Optical coherence tomography (OCT)

A commercially available OCT unit (Topcon, 3 Dimensional OCT-1000, USA) was used to perform OCT. Examination with six radial lines with a length of 6 mm each centered at the fovea and with 30° displacement from each other was performed. Internal fixation was used and the scanning and video images were displayed simultaneously to verify fixation. The OCT software for retinal mapping calculated the mean retinal thickness. Only the most central area (that was 1 mm in diameter with fovea in the center) was used for calculation.

2.3. Electro-retinogram (ERG)

Roland consult, Brandenbrug, Germany instrument was used to record ERG. MF-ERG response were recorded simultaneously from both eyes. The first-order MF-ERG response namely the P1 amplitude, P1 latency were analyzed. The P1 amplitude is measured from the most negative trough of the wave form to the most positive peak of MF-ERG wave form. The P1 latency is defined as the time taken from the onset of the stimulus to reach the most positive peak of the wave form.

Disposable skin electrodes were attached lateral to temporal canthi and a reference electrode was attached to glabellar region. Dawson Trick Litzwork (DTL) electrodes were placed in the lower fornix of each eye. The patient was seated 30 cm in front of 61 hexagon array and maintained fixation on a central target with screen luminance of 1500 cd/m². Total MF-ERG recording time was 8 min broken into 30-s segments to facilitate good fixation and the patient’s fixation on the central target was observed throughout the test. The raw wave form was visible throughout the recording and segments were rejected if there was saturation due to excessive blinking or evidence of poor fixation. An appropriate pseudorandom binary m-sequence was used to control the 61 hexagonal elements. To analyze the 61-MF-ERG responses from each eye, the results were grouped into rings and quadrants. The P1 amplitude and P1 latency were grouped and averaged over central ring and four quadrants (Fig. 1).

Full field standard ERG was performed on both eyes simultaneously according to International Society for Clinical Electrophysiology of Vision (ISCEV). Five steps were done, scotopic rod response was done after dark adaptation for 20 min then scotopic maximal response then oscillatory potential response then light adaptation for 10 min then photopic cone response and 30 Hz flicker response is obtained.
All electrophysiology tests were performed on pupils dilated to the maximum with tropicamide 1% and phenylephrine 2.5%.

Data were analyzed using statistical package for social science (SPSS). Chi square ($x^2$) test of significance was used for comparison between groups. Spearman’s correlation coefficient was used to calculate correlation between variables ($P < 0.01$ considered statistical significant. $R \geq 0.5$ indicated good correlation).

3. Results

The study included 75 subjects: 25 were normal and 50 had retinal vein occlusion. Age and sex include in Table 1. There was no statistical difference in age sex between patients and control subjects ($P = 0.8$). There were 20 patients suffered with diabetes and 22 patients treated with antihypertensive drugs while normal control subjects were free from any systemic diseases.

Fluorescein angiography, optical coherence tomography, full field electro retinogram and multifocal electro retinogram were recorded and analyzed from both eyes of each subjects.

Fluorescein angiography revealed that 30 patients had macular ischaemia and 20 patients had well preserved perifoveal circulation.

3.1. MF-ERG

The results from central area and four quadrants of MF-ERG recordings of affected and fellow eyes in Tables 2–4.

The central implicit times of $P_1$ wave was abnormal in almost all affected eyes (48 eyes of 50 eyes) (96%). However, the central $P_1$ implicit times were also abnormal in a considerable proportion of normal fellow eyes (34 eyes of 50) (68%). In addition, the amplitudes of the central $P_1$ response of the affected eyes were abnormal in 40 eyes of 50 eyes (80%). An example of MF-ERG trace array in CRVO of affected and fellow eye in Figs. 2–4.

The MF-ERG response showed prolonged implicit times in ischaemic maculae (50 ± 5 ms) compared with non-ischaemic maculae (45 ± 7 ms) ($P = 0.01$). The amplitudes were reduced in ischaemic maculae (5 ± 10) compared with non-ischaemic maculae (10 ± 4 nv/degeneration) ($P = 0.001$).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic features among groups.</th>
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<tbody>
<tr>
<td>Diagnosis</td>
<td>Number</td>
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<tr>
<td></td>
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</tr>
<tr>
<td>CRVO</td>
<td>18</td>
</tr>
<tr>
<td>Upper temporal BVO</td>
<td>14</td>
</tr>
<tr>
<td>Lower temporal BVO</td>
<td>8</td>
</tr>
<tr>
<td>Hemicentric RVO</td>
<td>10</td>
</tr>
<tr>
<td>Normal</td>
<td>50</td>
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<table>
<thead>
<tr>
<th>Table 2</th>
<th>MF-ERG in affected and fellow eyes in CRVO.</th>
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</thead>
<tbody>
<tr>
<td>MF-ERG parameter</td>
<td>Normal range</td>
</tr>
<tr>
<td>Central $P$ amplitude (nv)</td>
<td>50–100 (70 ± 10)</td>
</tr>
<tr>
<td>Central $P$ implicit time (ms)</td>
<td>22–30 (28 ± 3)</td>
</tr>
<tr>
<td>Average $P$ amplitude over four quadrants</td>
<td>40–70 (45 ± 5)</td>
</tr>
<tr>
<td>Average $P$ implicit times over four quadrants</td>
<td>20–29 (25 ± 2)</td>
</tr>
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<tr>
<th>Table 3</th>
<th>MF-ERG in BRVO.</th>
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<tbody>
<tr>
<td>MF-ERG parameters</td>
<td>Affected quadrant</td>
</tr>
<tr>
<td>$P$ amplitude (nv)</td>
<td>4–15 (10 ± 3)</td>
</tr>
<tr>
<td>$P$ implicit time (ms)</td>
<td>42–55 (45 ± 5)</td>
</tr>
</tbody>
</table>

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<tr>
<th>Table 4</th>
<th>MF-ERG in hemicentric retinal vein occlusion (HRVO).</th>
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<tbody>
<tr>
<td>MF-ERG parameters</td>
<td>Affected half</td>
</tr>
<tr>
<td>$P$ amplitude (nv)</td>
<td>2–18 (5 ± 5)</td>
</tr>
<tr>
<td>$P$ implicit time (ms)</td>
<td>46–60 (50 ± 7)</td>
</tr>
</tbody>
</table>
MF-ERG $P_1$ implicit times were greater for the affected hemi retina in HRVO than for unaffected hemi retina ($P = 0.05$). The $P_1$ implicit time were prolonged ($P = 0.01$) for affected eye when compared with fellow eyes (Table 4).

In pathological quadrants, in BRVO although the response densities were abnormal in only 10 eyes, latency of $P_1$ wave was prolonged in 20 eyes. The latencies were significantly prolonged compared with normal eyes ($P = 0.03$). On other hand, in central area, the latency was prolonged and amplitude was reduced in 20 eyes. The response densities were significantly reduced compared with those of normal eyes Fig. 5.

### 3.2. Standard ERG

Scotopic and photopic recordings of ERG responses from the affected and unaffected eyes were summarized in Table 5.

There was significant difference between scotopic rod $b$-wave amplitudes and implicit times and also significant difference between maximal $b$-wave amplitude and implicit time when comparing affected eyes with fellow eyes. The most affected ERG parameter was the photopic flicker implicit time which was abnormal in 24 eyes (78%) and the least affected parameter was the scotopic implicit time with only six eyes (12%) had an abnormal result.

### 3.3. Correlation of MF-ERG and standard ERG in affected eyes

More of affected eyes had abnormal MF-ERG response compared with ERG response. Because MF-ERG is thought predominantly to reflect cone function (Chahal et al., 1985). In this study, photopic ERG response from affected eyes was correlated with MF-ERG responses (central area).

A significant correlation was found between central MF-ERG and photopic flicker amplitude and latency response (Table 6).

### 3.4. Correlation between MF-ERG and OCT in affected eyes

The mean retinal thickness in the central 1 mm diameter of macula correlated significantly to amplitude of central MF-ERG. There was trend toward reduced amplitudes in eyes with central retinal thickness ($R = 0.55$, $P = 0.003$). While the implicit times did not correlate to central retinal thickness ($R = 0.2$, $P = 0.05$).
4. Discussion

The present study analyzed different techniques for interpretation of retinal injury in patients with retinal vein occlusion. Whereas OCT measures thickening and morphologic changes of the retina. Fluorescein angiography mainly gives information about the vascular status, making it possible to distinguish ischaemic from non-ischaemic retina as well as providing a non-quantitative measure of the retinal leakage. MF-ERG, on other hand, is a functional method that reflects the actual function of the retinal neurons.

This study designed to determine the effects of RVO on MF-ERG parameters. The MF-ERG first-order responses obtained from an eye with RVO were significant different from those derived from fellow unaffected eye. Also, the $P$ amplitudes were reduced in a large percentage of the fellow eyes to lesser extent. There was significant correlation between MF-ERG $P_1$ amplitudes and latencies and 30 Hz flicker amplitude and latencies in the affected eyes and there was good correlation between central retinal thickness measured by OCT and MF-ERG $P$ wave amplitudes in the central area.

In this study, the results showed that CRVO markedly affected MF-ERG parameters, there was subnormal $P$ amplitudes and $P$ implicit time delay in eyes with CRVO Table 2. This finding is in keeping with a previous report of MF-ERG response in subgroup of patients with CRVO Table 2.

In cases of BRVO, there was delay in implicit time of $P$ with subnormal amplitude in affected quadrant in this study.

The same as, in Ikeda et al. who observed abnormal response densities in the pathological quadrants and in the central area with delay in implicit times (Ikeda et al., 2004).

In cases of hemi centric retinal vein occlusion, there was prolongation of implicit time of $P$ wave of MF-ERG for affected hemi retinae than of MF-ERG for unaffected hemi retina.

Also, Dolan et al. found that MF-ERG $P$ implicit time was greater for the affected hemi retina than for the unaffected hemi retina. MF-ERG $P$ implicit time was prolonged ($P < 0.05$) and MF-ERG reduced ($P < 0.05$) for affected eyes when compared with fellow eyes (Dolan et al., 2006).

Significant difference between the ERG response of affected and unaffected eyes with RVO have been reported (Hvarfner).
et al., 2003; Johnson et al., 1988; Morrell et al., 1991; Dolan et al., 2006).

MF-ERG abnormalities noted in the fellow eyes probably reflect abnormal retinal function in a patient population with underlying systemic disease, including hypertension (22 cases 44%) and diabetes mellitus (20 cases 40%) and supports previous ERG studies of patients with RVO which found 36% of fellow eyes to have abnormal response (Sakaue et al., 1989).

This study showed that more of MF-ERG responses from both the affected and fellow eyes differ significantly from control than did full field ERG responses. The reason for this finding is unclear, but may be explained that: the MF-ERG response, is a result of multiple frequencies of stimulation as opposed to standard ERG wave form, which is a response to single frequency of stimulation (Larkin et al., 1979). Therefore, it is likely that MF-ERG reflects more of non-linear processes in the retina, processes potentially affected by retinal ischaemic due to changes in adaptive mechanisms of the retina secondary to the underlying disease caused by the vein occlusion.

Most studies agree that RVO causes ERG abnormalities and that highly abnormal ERG is associated with a poorer prognosis (Larsson and Andreasson, 2001; Williamson et al., 1997).

In this study, there was reduction scotopic and photopic amplitude and reduction in 30 Hz flicker amplitude, and prolonged implicit time of 30 Hz flicker in RVO. There was significant correlation between the flicker amplitude and MF-ERG central $P_1$ amplitude. Also, Dolan et al. found good correlation between MF-ERG amplitude in central region and flicker amplitude (Dolan et al., 2003). As flicker reflect predominantly cone photoreceptor function and MF-ERG was recognizing as investigating tool for assessing diseases of the retina under photopic conditions (Hood et al., 1997).

In this study, there were significant correlation between central retinal thickness measured by OCT and MF-ERG amplitude in the central region. There was decrease in central MF-ERG amplitude with increase central retinal thickness. Also, Ikeda et al. found significant correlation between foveal retinal thickness and MF-ERG $P_1$ response density (Ikeda et al., 2005).

In contrast, Hvarner et al. reported that no significant correlation between MF-ERG and OCT finding. Also, Hvarner et al. reported that macular ischaemia as measured by

![MF-ERG of ischaemic CRVO over quadrants](image1)

![MF-ERG of over rings in ischaemic RVO](image2)

**Figure 4** MF-ERG in case of ischaemic CRVO. Shows marked decrease in $P_1$ and marked delayed in $P_1$ over rings and quadrants and the form of curve were marked abnormal (the peak and trough were absent only just irregular line).
fluorescin angiography correlated well with prolonged implicit time of MF-ERG (Hvarfner et al., 2006).

Also, in this study there was increase in implicit time with presence of macular ischaemia.

In summary, RVO affected MF-ERG amplitude and implicit time. The site of amplitude reduction and implicit time delay vary according to site of RVO. The degree of amplitude reduction and implicit time delay increase as the severity of RVO increase. OCT and ERG provide functional and anatamical assessment of retina in RVO.

Table 5  Standard ERG responses.

<table>
<thead>
<tr>
<th>Standard ERG parameters (normal range)</th>
<th>Normal values</th>
<th>Affected eye</th>
<th>Fellow eye</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rod amplitude (nv)</td>
<td>(60–105) (90 ± 15)</td>
<td>20–50 (30 ± 10)</td>
<td>40–55 (45 ± 5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Rod implicit time (ms)</td>
<td>(15–19) (16 ± 1)</td>
<td>20–35 (25 ± 5)</td>
<td>17–30 (20 ± 3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Maximal B amplitude (nv)</td>
<td>(200–250) (230 ± 20)</td>
<td>70–120 (90 ± 20)</td>
<td>150–180 (160 ± 7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Maximal B implicit time (ms)</td>
<td>(30–40) (33 ± 3)</td>
<td>50–70 (60 ± 5)</td>
<td>43–48 (45 ± 2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Con B amplitude (ms)</td>
<td>(45–60) (50 ± 10)</td>
<td>40–50 (45 ± 4)</td>
<td>43–52 (49 ± 2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Cone B latency</td>
<td>(12–17) (15 ± 2)</td>
<td>20–33 (25 ± 3)</td>
<td>15–25 (20 ± 5)</td>
<td>0.8</td>
</tr>
<tr>
<td>Flicker amplitude (nv)</td>
<td>(50–70) (60 ± 5)</td>
<td>10–30 (15 ± 5)</td>
<td>45–65 (50 ± 6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Flicker implicit times (ms)</td>
<td>(30–50) (45 ± 3)</td>
<td>50–80 (65 ± 5)</td>
<td>40–60 (45 ± 2)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Table 6  Correlation between MF-ERG and standard ERG.

<table>
<thead>
<tr>
<th>MF-ERG</th>
<th>ERG flicker amplitude</th>
<th>Flicker implicit times</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
</tr>
<tr>
<td>Central MF-ERG amplitude</td>
<td>0.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Central MF-ERG implicit</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Figure 5  A case of upper temporal branch retinal vein occlusion. Shows: upper temporal quadrant of MF-ERG trace appeared abnormal marked reduction in $P_1$ amplitude as compared with the other quadrants.
Conflict of interest

None declared.

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Acknowledgement

This study was approved by the Human Subjects Committee of the University of Mansoura and adhered to the Declaration of Helsinki. A written informed consent was obtained from all participants.

References


