

# DIAGNOSTIC AND SURGICAL TECHNIQUES

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## The Clinical Applications of Multifocal Electroretinography: A Systematic Review

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**Abstract.** Multifocal electroretinography (mfERG) is an investigation that can simultaneously measure multiple electroretinographic responses at different retinal locations by cross-correlation techniques. mfERG therefore allows topographic mapping of retinal function in the central 40–50° of the retina. The strength of mfERG lies in its ability to provide objective assessment of the central retinal function at different retinal areas within a short duration of time. Since the introduction of mfERG in 1992, mfERG has been applied in a large variety of clinical settings. This article reviews the clinical applications of mfERG based on the currently available evidence. mfERG has been found to be useful in the assessment of localized retinal dysfunction caused by various acquired or hereditary retinal disorders. The use of mfERG also enabled clinicians to objectively monitor the treatment outcomes as the changes in visual functions might not be reflected by subjective methods of assessment. By changing the stimulus, recording, and analysis parameters, investigation of specific retinal electrophysiological components can be performed topographically. Further developments and consolidations of these parameters will likely broaden the use of mfERG in the clinical setting. (*Surv Ophthalmol* 52:61–96, 2007. © 2007 Elsevier Inc. All rights reserved.)

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Multifocal electroretinography (mfERG) was developed by Sutter and Tran in 1992 and has revolutionized the objective functional assessment of retinal diseases.<sup>290</sup> In contrast with full-field electroretinography (ERG), which measures the electrical activity of the entire retina, mfERG allows simultaneous measurements of multiple retinal responses at different locations. The use of mfERG

therefore enables topographic mapping of retinal function in the central 40–50° of the retina. Since the introduction of mfERG in the clinical setting, there have been many reports in the literature to evaluate the use of mfERG in the assessment of various ophthalmic conditions. This review aims to summarize the clinical applications of mfERG based on the currently available evidence.

## Basics of the Multifocal Electroretinography

Before looking at the clinical applications of mfERG, this section will provide a brief overview on some of the basic concepts of the mfERG. Several review articles have been published on the fundamental and technical aspects of the mfERG and readers can refer to these publications for further references.<sup>99,105,126,148</sup>

### RECORDING OF mfERG

mfERG recordings can be performed using commercially available systems such as the VERIS system (Electro-Diagnostic Imaging, San Mateo, CA), the RETiscan system (Roland Consult, Wiesbaden, Germany), and the Metrovision system (Metrovision, Pérenchies, France). Clinicians should be aware of the default parameter settings in each system as these will influence the mfERG recordings and interpretations.<sup>20</sup> A guideline has been issued by the International Society for Clinical Electrophysiology of Vision (ISCEV) of which various researchers have found the settings to be useful in most situations.<sup>185</sup> Prior to recording, the subject is usually light-adapted for at least 15 minutes with room lights maintained on during the recording for constant light adaptation. This is important because alteration of the light adaptation state and the extent of local bleaching prior or during mfERG recording can affect the results.<sup>34,143,155</sup> Pre-recording light adaptation may also help to prevent the circadian rhythm of retinal responses.<sup>90</sup> Patients' pupils should be fully dilated to maximize the retinal illumination as changes in pupil size may result in significant alterations in mfERG amplitude and latency.<sup>74</sup>

During mfERG recording, the subject fixates onto the center of a stimulating monitor, which is most commonly a cathode ray tube (CRT) monitor. A liquid crystal display (LCD) monitor or a scanning laser ophthalmoscope (SLO) can also be used. The SLO allows direct retinal stimulation and fixation monitoring simultaneously, although it does not allow for eye tracking or for moving the stimulus to compensate for eye movement.<sup>24,126,237,238,251,252</sup> Each type of stimulus has its own advantages and disadvantages in the recordings of offset and non-linear responses.<sup>128</sup> The stimulus is composed of an array of alternating bright and dark hexagonal flashes which stimulate the central 40–50° of the retina. The sizes of the hexagons are scaled according to the density of retinal response and therefore the sizes of the hexagons get larger as they extend peripherally. The number of hexagons used in the stimulus depends on the spatial resolution

required, in which 241 hexagons will provide greater resolution compared with 61 or 103 hexagons (Fig. 1). With the use of artificial scotomas, studies have shown that mfERG was able to detect small retinal lesions if the defect was at least half the area of a stimulating hexagon.<sup>173,184,323</sup> It has been recommended that the 241-hexagon stimulus should be used for detecting scotomas of 5° or smaller<sup>184</sup> (Fig. 2). Increasing the number of hexagons, however, will lengthen the recording duration and may decrease the signal-to-noise ratio.<sup>91,123</sup> In most clinical settings, 61 or 103 hexagons can provide a good balance between spatial resolution and length of recording as well as better signal-to-noise ratio.<sup>91</sup> The ISCEV guideline recommended the bright and dark hexagons should have luminance of 100–200 cd/m<sup>2</sup> and <1 cd/m<sup>2</sup>, respectively, in order to provide adequate contrast.<sup>185</sup> This will result in a mean screen luminance of 50–100 cd/m<sup>2</sup> during testing. The amplifier setting is usually set at a gain of 100,000 to 200,000 with a bandpass filter range of 3–300 Hz or 10–300 Hz. Proper filter bandwidth setting is essential to remove excessive electrical noise caused by high amplification and to avoid waveform distortion, which is particularly important in the analysis of second-order kernel responses.<sup>21,127</sup>

Recordings can be carried out monocularly or binocularly using contact lens or fiber electrodes. We prefer using a bipolar contact lens electrode (Burian-Allen electrode, Hansen Laboratories, Coralville, IA) because larger responses can be obtained with lower variability and better signal-to-noise ratio compared with other types of electrodes.<sup>126,199</sup> Monocular recording offers the advantage of preventing abnormal recordings due to alternating fixation in patients with intermittent exotropia.<sup>16</sup> Monocular recording also facilitates better fixation monitoring which is essential because poor fixation can result in abnormal mfERG responses, especially when higher number of stimulus elements are used.<sup>44,249</sup> Fixation monitoring can be performed using direct observation or by various monitoring instruments such as a refractor/camera system, a fundus camera or a SLO.<sup>24,139,249,252,275</sup> Although

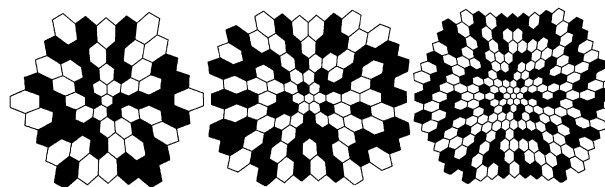


Fig. 1. The mfERG recording stimulus pattern with different number of hexagonal elements. *Left:* 61 hexagons; *Center:* 103 hexagons; *Right:* 241 hexagons.

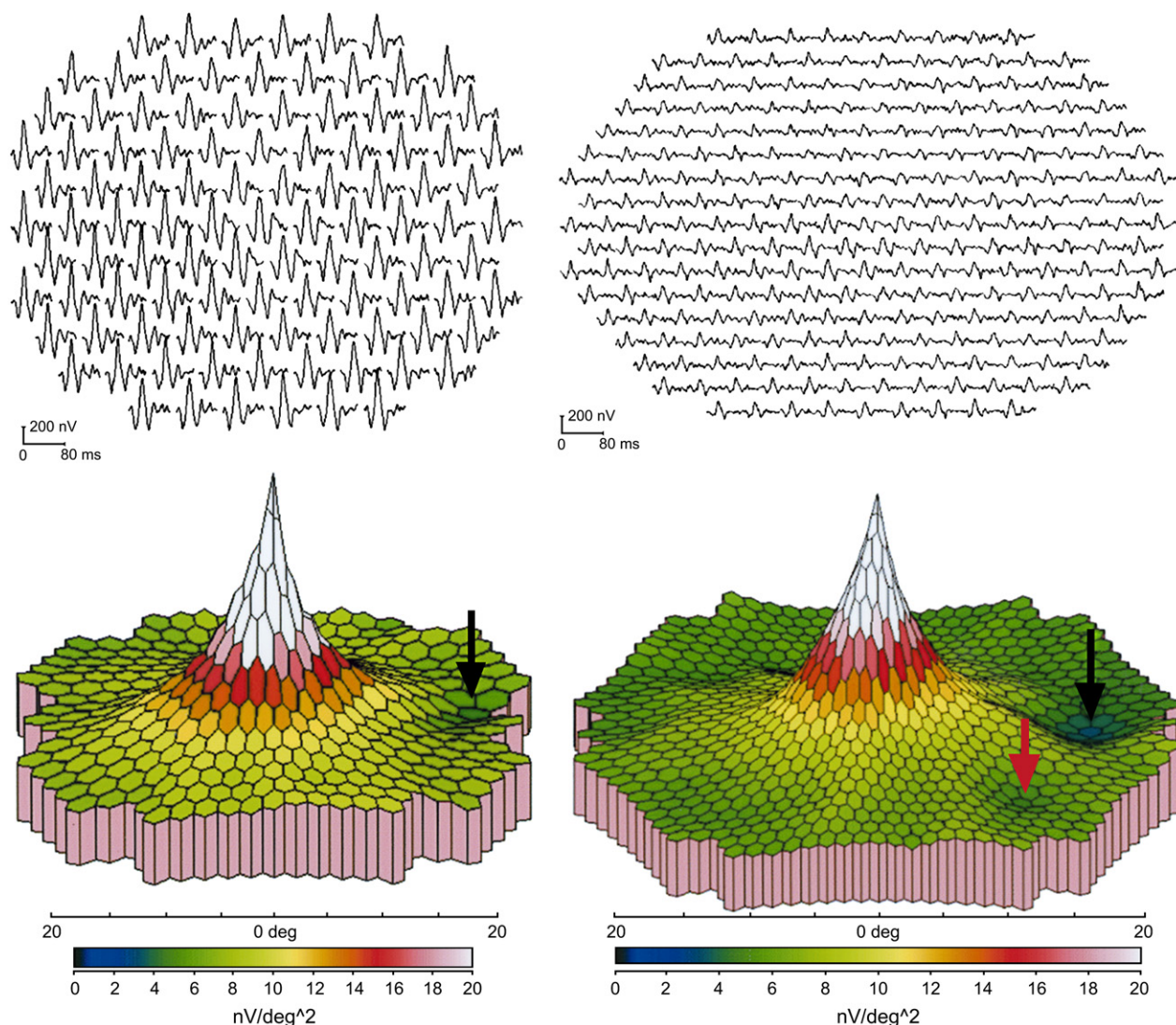


Fig. 2. Different resolutions of mfERG recordings. *Left:* Trace array (top) and three-dimensional topography (bottom) of mfERG responses obtained using a 103-hexagon stimulus which showed regular mfERG responses with the normal blind spot (black arrow). *Right:* Trace array (top) and three-dimensional topography (bottom) of mfERG responses of the same patient obtained using a 241-hexagon. The higher number of hexagonal elements improved the resolution of the mfERG recording. This allowed demonstration of a weaker response at the blind spot (black arrow). A small localized area of retinal dysfunction (red arrow) corresponding to an area of retinal pigment epithelial atrophy due to previous intraocular inflammation could also be detected which was not seen with the 103-hexagon stimulus.

these monitoring devices may detect any unwanted eye movements, it might be difficult to determine the exact fixating location in patients with central scotoma. Therefore, eccentric fixation and fixation instability might account for some of the mfERG abnormalities. One way to improve the fixation in patients with central scotoma is by displacing the fixation cross away from the center of the stimulus in order to place the non-fixating fovea in the center of the pattern. This method also allows better sequential monitoring of macular function and is particularly useful with the SLO system. With good fixation monitoring, so as to reject recordings when

a patient is not placing the fovea at the center of the mfERG pattern or when there is excessive eye movement, mfERG recordings can provide good reproducibility especially for the central retinal responses.<sup>6,195,</sup>

<sup>231,232</sup> Patients' refractive errors should be corrected using corrective lens or a refractor/fixation camera system to provide the optimal image quality. Although it has been suggested that mild refractive blurring in normal subjects do not affect the recordings,<sup>225</sup> several studies have demonstrated that refractive blurring can result in significant mfERG abnormalities.<sup>32,308</sup> This is particularly

important when using mfERG in the assessment of functional visual loss because the subject may deliberately cause refractive blur, which can significantly alter the mfERG responses.<sup>308</sup>

### ORIGIN OF mfERG

The recording technique used in mfERG is known as the *pseudorandom m-sequence* and it allows the extraction of a series of responses from individual retinal locations by cross-correlation. The response components are called *kernels* which are caused by non-linear dynamics of the responses; readers can refer to review articles by Sutter on the details of kernel analyses.<sup>288,291</sup> The standard mfERG mainly measures the cone function and the most commonly analyzed responses are the first-order and the second-order kernel components; they will be briefly discussed in this section.

### FIRST-ORDER KERNEL COMPONENT OF mfERG

The first-order kernel component of the mfERG is the largest mfERG response derived and the waveform is a biphasic wave characterized by an initial negative deflection followed by a positive peak. There may also be a second negative deflection after the positive peak and these peaks are labeled as N1, P1, and N2, respectively (Fig. 3). The first-order kernel component is obtained by adding all the records following a bright flash and subtracting all the records following a dark flash. Because the first-order kernel component is the most common response analyzed in most clinical settings,

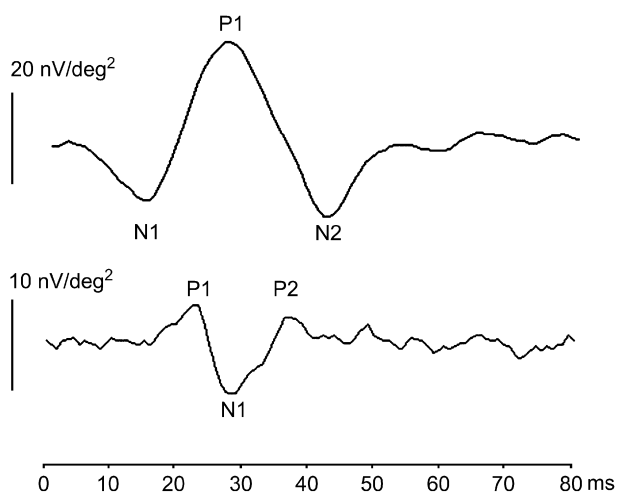


Fig. 3. Waveforms of mfERG responses. *Top*: The waveform of first-order kernel mfERG response with the first negative trough N1, followed by a positive peak P1 and a second negative trough N2. *Bottom*: The waveform of second-order kernel mfERG response with the first positive peak P1, followed by a negative trough N1 and a second positive peak P2.

it is the mfERG response referred to in this review unless otherwise specified.

Although the first-order kernel mfERG response appears as a biphasic waveform similar to the full-field ERG waveform, the origins of the waveforms are rather different. Hood et al compared the components of mfERG with full-field ERG waveforms in normal subjects by altering the background level, and the interval and intensity of the incremental flash.<sup>101</sup> It was shown that there was good correspondence in the waveform shapes between the first-order mfERG response and full-field ERG when the m-sequence stimulus was slowed down by insertion of seven frames at the background intensity. Slowing of the multifocal stimulus removed the non-linear components in the mfERG response. When the frame rate was increased to the standard flicker rate, the initial N1 component of the mfERG remained similar to the a-wave of the full-field ERG, whereas the P1 waveform changed considerably due to non-linear effects. Therefore, it is likely that both the N1 wave of the mfERG and the a-wave of the full-field ERG had the same origin, whereas the P1 mfERG component has some of the origins of the full-field ERG b-wave together with other non-linear effects. Hood et al further investigated the effects of pharmacological suppression of monkey mfERG responses to determine the components of mfERG in human.<sup>94</sup> It was found that after administration of tetrodotoxin (TTX) and N-methyl-D-aspartic acid (NMDA), which blocked most of the inner retinal contributions from the ganglion cells, the waveform of monkey mfERG resembled that of human mfERG. The results suggested that human first-order mfERG response is dominated by cells of the outer retina such as the photoreceptors and the on and off-bipolar cells.

### SECOND-ORDER KERNEL COMPONENT OF mfERG

The waveform of the second-order kernel mfERG is smaller compared with the first-order kernel and is therefore more difficult to measure due to poorer signal-to-noise ratio. It has an initial positive peak followed by a negative trough and these are labeled as P1 and N1, respectively (Fig. 3). This second-order kernel component was proposed to reflect the inner retinal activity from the retinal ganglion cells. However, it has been shown that there was poor correlation between the spatial distributions of second-order kernel responses and retinal ganglion cells.<sup>325</sup> Therefore, in contrast with the first-order kernel response, the second-order kernel component is not a response generated by specific retinal cells. It is a measure of how the mfERG response is



affected by a preceding flash due to non-linear adaptive mechanisms of the retina.

### ANALYSIS AND DISPLAY OF mfERG RESPONSES

mfERG responses can be analyzed and displayed in three commonly used options: trace arrays, group averages, and three-dimensional response density topography. The trace arrays (Fig. 2, top) are composed of the individual mfERG responses which originate from discrete retinal locations and these basic waveforms should be included in all recording printouts. The individual mfERG responses can be selected and grouped for comparisons and commonly performed group averaging methods include ring and quadrant analysis (Fig. 4). Peak implicit times and response amplitudes are the main parameters measured during analysis of mfERG. For the first-order mfERG response, the N1 amplitude is measured from the baseline to the N1 trough and the P1 amplitude is measured from the N1 trough to the P1 peak. Implicit times are measured from the onset of the stimulus to the peak of the waveform. Averaging procedures may be employed during analysis to eliminate artifacts and to smooth out the waveforms. However, these procedures may

artificially distort the mfERG responses and should be applied cautiously.<sup>324</sup> The three-dimensional response density topography (Fig. 2, bottom) plots the response density of the N1 and P1 components per unit area and provides a graphical overview of responses at different retinal locations for ease of visualization.

### Factors Affecting mfERG in Normal Subjects

As with all other investigations, there is a range of normative values of mfERG parameters due to individual variation. In normal subjects without any retinal pathology, several factors can affect the mfERG responses. Important factors that should be considered in the analysis of mfERG include age, severity of cataract, and the refractive error and axial length status.

### INFLUENCE OF AGE ON mfERG

Several studies have investigated the effects of age on mfERG recordings.<sup>5,65,71,73,117,198,208–210,277,298,302</sup> In general, most studies found reductions in mfERG

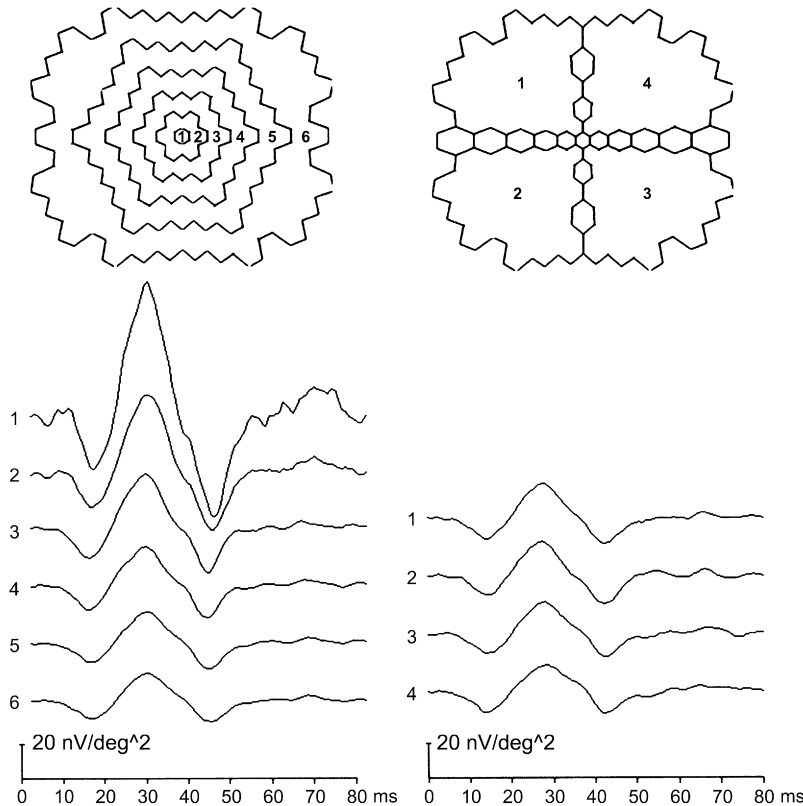


Fig. 4. Common group averaging methods used in mfERG analysis. *Left:* Ring averaging of mfERG responses according to retinal eccentricity from ring 1 (fovea) to ring 6 (peripheral macula). *Right:* Quadrant averaging of mfERG responses according to the retinal quadrant, from quadrants 1 to 4.

response amplitudes and delays in implicit times with increasing age. Seiple et al found that the P1 amplitude decreases by appropriately 10.5% per decade.<sup>277</sup> The effects of age on implicit times are less and were found to increase by about 1% per decade.<sup>277</sup> Tzekov et al also showed that there is about 5% per decade reduction in P1 response amplitude, with 1.2% per decade increase in P1 implicit time associated with aging.<sup>302</sup> The effect of age on mfERG is more marked in the central retina compared with more peripheral retina.<sup>5,65,71,117,198,277,302</sup> These results highlighted the importance for each laboratory to develop an age-matched normative data for mfERG analysis or for corrections for age be published and disseminated to mfERG users.

The cause for the age-related changes in mfERG response is controversial. Fortune and Johnson suggested that the diminished mfERG response was mostly accounted by preretinal optical factors such as higher lens density and smaller pupil size in older subjects.<sup>65</sup> However, Seiple et al showed that smaller pupil diameters would reduce both the levels of adaptation and stimulus luminance and these changes would not result in the age-related reduction in mfERG amplitude.<sup>277</sup> Tam et al also demonstrated that by removing optical factor due to the crystalline lens, no significant differences in N1 and P1 amplitudes and P1 implicit time were found between patients aged 18–25 years and pseudophakic patients aged 70 years or older.<sup>298</sup> There was, however, a significant difference in N1 implicit time between young phakic and older pseudophakic subjects, suggesting a neural factor may be responsible for the mfERG changes in older subjects. Based on these studies, it is therefore likely that the age-related mfERG changes are due to both preretinal optical factors and neural factors such as loss of photoreceptors and inefficient synaptic transmission in older patients.<sup>71,277,298</sup>

#### INFLUENCE OF CATARACT ON mfERG

As discussed in the last section, preretinal optical factor such as cataract may influence mfERG recordings due to light scattering and studies have therefore evaluated the effects of cataract on mfERG.<sup>228,297,299,315,326</sup> Tam et al studied the effects of different cataract severity on mfERG recordings.<sup>299</sup> It was shown that N1 and P1 response amplitudes from the central macula were significantly reduced in subjects with mild or moderate cataract compared with subjects with very mild cataract. Tam et al and Palmowski et al also demonstrated increases in mfERG responses in eyes which had undergone cataract surgery.<sup>228,297</sup> In

another study conducted by Wördehoff et al, it was shown that there were significant increases in P1 response amplitudes in the central macula after cataract surgery, while no significant changes in N1 and P1 implicit times were observed.<sup>315</sup>

Besides assessing the mfERG changes in cataract patients, studies using artificial light scattering have also been performed to mimic the effects of cataract on mfERG.<sup>8,31,296</sup> Similar to the findings in cataract patients, experimental light scattering resulted in reduction in mfERG responses particularly in the central retina.<sup>8,31,296</sup> Chan et al showed that the peripheral mfERG response amplitude densities may also increase due to light scattering.<sup>31</sup> Because lens opacifications are relatively common in older subjects, it is important that the severity of cataract be considered during analysis of mfERG recordings.

#### INFLUENCE OF REFRACTIVE ERROR AND AXIAL LENGTH ON mfERG

Changes in refractive error and axial length in normal subjects may also affect the mfERG recordings. Kawabata and Adachi-Usami studied the effects of refractive error on mfERG in normal young subjects.<sup>125</sup> In order to minimize the differences in retinal image caused by the corrective lens, the test distance was adjusted according to the subject's refractive error. It was shown that amplitudes were reduced and implicit times were delayed as refractive errors increased. Chan and Mohidin also showed that increase in axial length is associated with reductions in both the first- and second-order kernel response amplitudes.<sup>30</sup> Because high myopia is associated with longer axial length, the mfERG changes in myopia may be related to the morphological changes associated with increased axial length. One of the postulated causes of the reduced mfERG response is the loss of cone function associated with myopia and longer axial length much as the full-field ERG may be reduced in these patients.<sup>125</sup> In another study by Chen et al, myopic patients were found to have significantly longer P1 implicit time compared with emmetropes.<sup>41</sup> Analysis showed that refractive error contributed to a greater proportion of variance in the implicit time changes compared with axial length.<sup>41</sup> This suggested that the mfERG alterations in myopia might not be due to anatomical changes alone. Based on these studies, the subject's refractive error and axial length status should therefore be accounted for when analyzing mfERG.

## Clinical Applications of mfERG in Acquired Retinal Diseases

### AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration (AMD) is a common cause of visual impairment in the older population and mfERG has been used to evaluate the extent of retinal dysfunction in AMD patients.<sup>14,54,56,57,72,91,110,122,151,152,167,172,228,248,258</sup> Patients with early AMD were found to have significant reduction in the foveal P1 amplitude and delay in N1 implicit time compared with normal age-matched controls.<sup>167</sup> The extent of mfERG changes is influenced by the severity of AMD as patients with neovascular AMD had more severe reductions in mfERG response amplitudes and delays in implicit times compared with patients with dry AMD.<sup>110,152</sup> Palmowski et al reported that the functional changes demonstrated by mfERG corresponded well with the anatomical changes detected on fluorescein angiography.<sup>228</sup> However, this was only based on the results from three AMD patients and subsequent studies have demonstrated that the mfERG abnormality tends to be more diffuse compared with the morphological changes.<sup>72,91</sup> Gerth et al evaluated all the first-order mfERG responses individually in AMD patients and compared them with the changes on fundus photography and fluorescein angiography.<sup>72</sup> Only 23% of eyes showed significant correlation between various mfERG abnormalities and morphological changes. Implicit times were found to be more sensitive in detecting abnormal retinal responses compared with response density.

Although mfERG appears to be useful in documenting functional changes in AMD patients, it was unclear how it compares with subjective measures of visual function. Feigl et al compared the use of mfERG and various subjective visual function measures such as color vision and contrast sensitivity in assessing patients with early AMD.<sup>57</sup> It was found that mfERG failed to discriminate between control and early AMD subjects, whereas it was possible to use subjective measures to discriminate the two groups. By using a special protocol for recording rod-mediated mfERG instead of the conventional cone-mediated mfERG, Feigl et al also showed that rod-mediated mfERG may be more sensitive in detecting retinal dysfunction in early AMD compared with light-adapted cone-mediated mfERG.<sup>55,56</sup> These results suggest the rod system might be affected earlier than the light-adapted cone system in early AMD. Feigl et al further demonstrated that the use of a global-flash mfERG stimulus by inserting a global bright flash between two dark frames may also detect deficits in

early AMD before the conventional mfERG stimulus.<sup>54</sup> Further studies to optimize the mfERG parameters for the assessment of retinal function in AMD should be conducted.

### DIABETIC RETINOPATHY

Diabetic retinopathy is a major complication of diabetes mellitus and may lead to significant visual impairment. mfERG has been used in a number of studies to evaluate the retinal function in diabetic patients and most studies have demonstrated that implicit time measures are more sensitive compared with amplitude changes in detecting retinal dysfunction.<sup>66,79,81,82,230,301,327</sup> Palmowski et al assessed the retinal function in diabetic patients with or without diabetic retinopathy by analyzing both the first- and second-order mfERG responses.<sup>230</sup> Patients with diabetic retinopathy had significantly lower response amplitudes and longer implicit times for both the first- and second-order components compared with control. In diabetic patients without retinopathy, only the amplitude of the second-order component was reduced. Because the second-order component reflects the dynamics of adaptive mechanisms that are mainly influenced by the inner retinal activity from the retinal ganglion cells, the findings suggested that diabetic patients may develop inner retinal impairment prior to outer retinal dysfunction. Tyrberg et al demonstrated that diabetic patients with retinopathy had significantly longer second-order mfERG implicit times compared with patients without any retinopathy.<sup>301</sup> Fortune et al performed mfERG in diabetic patients with or without diabetic retinopathy to evaluate the local retinal abnormalities.<sup>66</sup> Results showed that mfERG implicit times from locations with clinically visible retinopathy were markedly delayed compared with normal control. Implicit times of responses from areas adjacent to locations with visible retinopathy were also delayed and mfERG is therefore sensitive in detecting local retinal dysfunction before retinopathy develops. In another study, Mita-Harris found that the first- and second-order response amplitudes were significantly higher in diabetic patients without retinopathy compared with control.<sup>197</sup> Klemp et al also showed that transient hyperglycemic state in diabetic patients without retinopathy was associated with shortenings of implicit times for the P1 and N2 components of the first-order kernel response and all components of the second-order kernel response.<sup>133,134</sup> During acute normoglycemia, diabetic patients without retinopathy were found to have prolonged mfERG implicit times compared with healthy controls and the delay was proportional to the patients' level of

chronic hyperglycemia.<sup>134</sup> These results support the hypothesis that hyperglycemia may accelerate retinal metabolism with increase in retinal blood flow in early diabetes. The application of mfERG has thus enhanced the understanding of early retinal functional changes in diabetes.

Several studies have also used mfERG to evaluate the retinal function in diabetic patients with clinically significant macular edema (CSME).<sup>79,107,178,179,319</sup> Foveal thickness as measured on optical coherence tomography (OCT) was found to be significantly correlated with mfERG amplitudes and implicit times.<sup>178,319</sup> Retinal locations with CSME had significant delays in mfERG implicit times with reduction in response amplitude.<sup>79</sup> The changes in implicit times were found to be more diffuse compared with amplitude changes and extended to areas without clinically manifesting macular edema.

Besides analyzing the first- and second-order mfERG responses, analysis of multifocal oscillatory potentials (OP) has also been shown to be useful in the assessment of retinal dysfunction in diabetic patients.<sup>12,79,157,219</sup> Onozu and Yamamoto recorded multifocal OP using a bandpass filter of 100–300 Hz and demonstrated that patients with diabetic retinopathy had reduced multifocal OP amplitude and delayed implicit times.<sup>219</sup> Another technique more commonly used to evaluate multifocal OP is with the use of a slow flash mfERG (sf-mfERG) by inserting three dark frames in between the multifocal stimuli.<sup>317</sup> Because higher order effects are frequently superimposed on the waveform of standard first-order mfERG response, this may cause difficulty in the measurement and interpretation of the later mfERG components.<sup>11</sup> The insertion of dark frames to increase the multifocal flashes interval enabled retinal responses to develop and decay more completely and allowed clearer assessment of first-order kernel responses including OP. Using the sf-mfERG, Bearse et al demonstrated retinal functional abnormalities can occur in diabetic patients without retinopathy.<sup>11</sup> Greenstein et al also showed that there was an absence of macular OP in diabetic patients with CSME.<sup>79</sup> In another study by Kurtenbach et al, it was shown that there were delays in both the first- and second-order multifocal OP implicit times in diabetic patients without retinopathy, suggesting the presence of early retinal dysfunction in diabetic patients.<sup>157</sup> Bearse et al also investigated the local multifocal OP in diabetic patients.<sup>12</sup> In order to increase the signal-to-noise ratio, the first- and second-order sf-mfERG kernels were combined to form a summed second-order kernel OP by digital filtering before isolation of multifocal OP.<sup>12</sup> It was demonstrated that both the

summed second-order kernel OP and the first-order kernel OP were frequently abnormal in diabetic eyes. However, some differences exist between the first- and second-order OP as the summed second-order kernel OP were significantly associated with the local retinal sites of clinical retinopathy, whereas the first-order kernel OP were not. These findings suggest that the effects of fast adaptive mechanisms are more likely to be impaired in locations with diabetic retinopathy.

As the early effects of diabetic retinopathy appear to cause more changes in second-order response compared with first-order response due to alterations in the fast adaptive mechanisms, Shimada et al used a special stimulus to evaluate the fast adaptive effects caused by interactions of flashes in diabetic patients.<sup>281</sup> A periodic global flash is inserted in between the multifocal stimuli and this flash will only contribute to the focal response if it was preceded by a multifocal stimulus.<sup>279</sup> This stimulus results in a direct response due to focal flash and an induced response due to interaction of focal and global flash and was proposed to enhance responses from the ganglion cell and the optic nerve head component (ONHC).<sup>63,222,282</sup> It was shown that diabetic patients without retinopathy had significantly lower amplitude in the induced component, whereas the direct response was similar compared with controls without diabetes.<sup>281</sup> The application of this multifocal stimulus with periodic global flash may enable early detection of retinal dysfunction in diabetic patients.

The technical and analysis settings of mfERG should be considered when using implicit times to assess retinal function in diabetic retinopathy. Schneek et al compared two different methods for measuring the first-order mfERG implicit times known as template stretching and template sliding.<sup>268</sup> The template stretching method scales the entire waveform by multiplying a scaling factor for best fit to a template based on normal data. This will therefore cause more prolongation in implicit times for the later portions of the mfERG response. For the template sliding technique, the difference between the waveform and template is added by a fixed amount. Diabetic patients were found to have more implicit time abnormalities with the template stretching method compared with template sliding. This is because template-stretching method caused less variability in implicit time measures and should therefore be used in assessing diabetic retinopathy. Han et al also proposed using the amplification filter cutoffs of 10–100 Hz instead of 10–300 Hz to improve the signal-to-noise ratio and to lower the inter-subject variability.<sup>82</sup> It was shown that recordings using the lower high



frequency cut-off of 100Hz enabled identification of more implicit time abnormalities in diabetic patients without retinopathy.

Apart from using mfERG to evaluate and monitor retinal function in diabetic patients, longitudinal studies have also studied the use of mfERG in predicting future development of diabetic retinopathy. Han et al assessed the local first-order mfERG implicit times in patients with nonproliferative diabetic retinopathy to determine the association with areas of new retinopathy 1 year later.<sup>83</sup> It was shown that 70% of areas with new retinopathy had delayed implicit time at baseline, whereas only 24% of regions without new retinopathy had abnormal baseline implicit time. Amplitude changes were not found to be useful in predicting subsequent diabetic retinopathy. It was concluded that localized retinal dysfunction as reflected by mfERG implicit time delays often precedes the onset of new signs of diabetic retinopathy. Han et al further improved the prediction of diabetic retinopathy by developing a model which included mfERG implicit times and risk factors of diabetic retinopathy.<sup>84</sup> By using mfERG implicit time, duration of diabetes, presence or absence of diabetic retinopathy at baseline, and blood glucose level at the initial visit, this model had an expected sensitivity of 86% and specificity of 84% in predicting sites of future diabetic retinopathy in 12 months.

### CENTRAL SEROUS CHORIORETINOPATHY

Central serous chorioretinopathy (CSC) is a disease characterized by the spontaneous development of serous retinal detachment at the macula. mfERG has been shown to be useful in assessing the retinal functional impairments in patients with CSC.<sup>35,48,111,149,151,172,187,229,232,292-294,305,329</sup> During acute CSC, retinal dysfunction is reflected by reduction in mfERG response amplitudes and delay in implicit times.<sup>35,111,187,305</sup> Marmor and Tan demonstrated that mfERG response amplitudes were not only depressed in areas of serous retinal detachment but also extended beyond the area of detachment.<sup>187</sup> This suggests a more widespread area of retinal dysfunction occurs as compared with the localized subretinal fluid seen clinically. With the use of mfERG, it has also been demonstrated that the fellow eye of patients with CSC may have abnormal mfERG responses.<sup>35,48,187</sup> These findings suggest that CSC is a bilateral disorder and may be caused by a diffuse pathologic process affecting the choroid and/or the retinal pigment epithelium (RPE). However, this remains controversial since another study by Vajaranant et al failed to demonstrate significant changes in mfERG responses in the

clinically normal fellow eye of patients with CSC.<sup>305</sup> This might be due to a larger range of normal value in the control group or as a result of variation of the disease process so that not all patients with CSC will have bilateral involvement. Further research to clarify these findings will be useful.

Another application of mfERG in CSC is in the monitoring of the clinical course of the disease (Fig. 5). It has been shown that mfERG abnormalities may persist even after resolution of the subretinal fluid clinically.<sup>35,48,292-294</sup> mfERG may therefore have a useful role in providing an objective measure of retinal function in research on the treatment for CSC.

### MACULAR HOLE

mfERG has been used for the objective assessment of macular function in patients with macular hole.<sup>7,106,201,216,251,283,295</sup> Patients with macular hole were found to have marked reductions in mfERG response densities in both the foveal and perifoveal regions.<sup>283,295</sup> After successful macular hole surgery, improvement in foveal and perifoveal mfERG response densities could be observed.<sup>201,283</sup> Apostolopoulos et al assessed the correlation between OCT and mfERG findings in patients who had macular hole surgery.<sup>7</sup> It was found that although visual acuity significantly correlated with the foveal thickness measured by OCT, mfERG response densities did not correlate with visual acuity and foveal thickness. The mfERG findings suggested that retinal function remained impaired despite successful macular hole surgery.

mfERG has also been applied to investigate the potential adverse effects associated with macular hole surgery.<sup>106,216</sup> Oh et al found that none of the patients with visual field defects after macular hole surgery had specific abnormalities on mfERG and the findings suggested arteriolar occlusion is not a likely cause for the visual field defects.<sup>216</sup> Horio et al also used mfERG to evaluate the functional outcome in patients who underwent internal limiting membrane (ILM) peeling in macular hole surgery with or without indocyanine green (ICG) dye staining.<sup>106</sup> It was shown that there were no significant differences in P1 implicit time and amplitude ratios between the two groups. Weinberger et al also demonstrated that there was regular pattern of mfERG amplitudes after macular hole surgery with ICG-assisted ILM peeling.<sup>311</sup> The results suggested the cause of potential ICG-related retinal toxicity may be due to its effect on retinal ganglion cells rather than the outer retina. However, the lack of mfERG changes in these studies may also be due to insufficient sensitivity of the mfERG

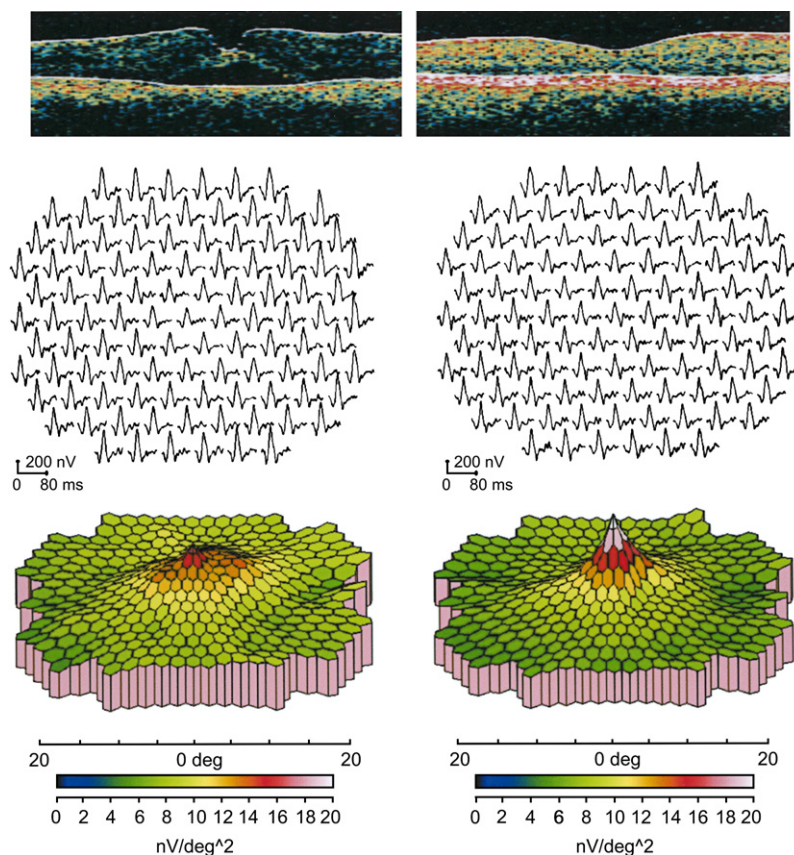


Fig. 5. Serial mfERG changes in a patient with acute central serous chorioretinopathy. *Top Left:* OCT demonstrating a pocket of subretinal fluid beneath the fovea. *Bottom Left:* mfERG trace array and three-dimensional topography plot demonstrating the diminished response at the central macula corresponding with the location of the subretinal fluid. *Top Right:* OCT of the patient three months after presentation with complete resolution of the subretinal fluid. *Bottom Right:* mfERG trace array and three-dimensional topography showing recovery of the central retinal response.

parameters in detecting such toxicity. Further studies may consider the use of other mfERG measurements such as second-order kernel responses and multifocal OP in evaluating the potential retinal damage associated with macular hole surgery.

#### EPIRETINAL MEMBRANE

Idiopathic epiretinal membranes (ERM) or macular puckers may cause visual impairment with patients developing decreased vision or metamorphopsia. mfERG has been applied in the assessment of macular function in patients with ERM.<sup>10,166,200</sup> (Fig. 6). Moschos et al performed mfERG in patients who underwent successful ERM surgery.<sup>200</sup> Preoperatively, there was reduction in the response densities in both the foveal and parafoveal regions, suggesting substantial functional alteration of the retina underlying the ERM. Postoperatively, significant increases in mfERG response densities were observed over time and the improvement continued

6 months after the operation. The authors suggested the improvement in mfERG responses may be due to resolution of the macular edema associated with the ERM. However, OCT was not performed in this study and it was uncertain whether mfERG findings correlated with macular thickness. In another study carried out by Li et al, both OCT and mfERG were performed in patients with ERM.<sup>166</sup> It was found that mfERG response amplitude was significantly lower with delay in implicit times in ERM patients. Although foveal thickness measured on OCT negatively correlated with visual acuity, no significant correlation was found between mfERG amplitude and both visual acuity and foveal thickness. Balayre et al also used mfERG to evaluate the retinal functional changes after ERM surgery with trypan blue staining and results demonstrated that trypan blue did not result in any obvious retinal toxicity.<sup>10</sup> The mfERG findings provided an objective measurement of the perioperative retinal function, and assisted in the understanding of the retinal pathophysiology in ERM.

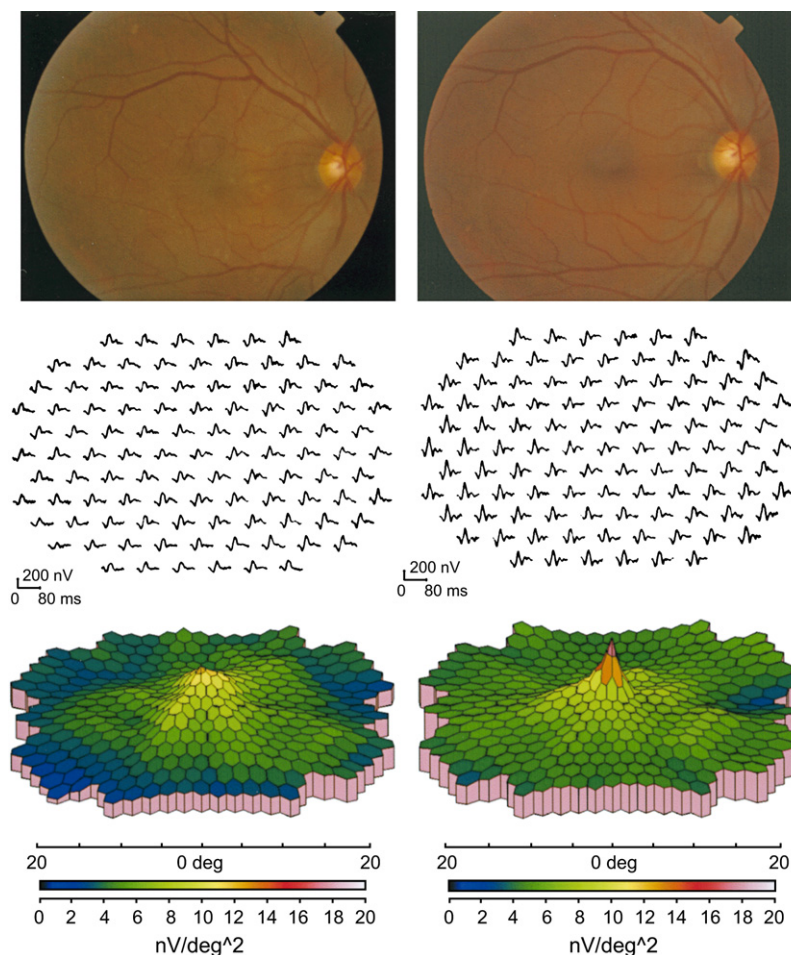


Fig. 6. Preoperative and postoperative mfERG in a patient with epiretinal membrane (ERM). *Left:* Fundus photograph, trace array and three-dimensional mfERG topography before ERM surgery. The visual acuity was 20/70 and mfERG demonstrated foveal and parafoveal reductions in retinal response amplitudes. *Right:* Fundus photograph, trace array, and three-dimensional mfERG topography of the patient 3 months after ERM surgery. The visual acuity improved to 20/30 and the mfERG responses improved after surgical removal of the ERM.

### RETINAL VASCULAR OCCLUSIONS

Branch retinal artery occlusion (BRAO) causes localized visual field defect due to damage to the inner two-thirds of the retina, involving the inner nuclear layer, inner plexiform layer, ganglion cells and the nerve fiber layers. mfERG has been used to document localized retinal dysfunction in patients with BRAO.<sup>88,218,313,318</sup> The areas of mfERG abnormalities generally correlated well with the localized defects detected on perimetry.<sup>88,313</sup> Studies have also been performed in BRAO patients to understand the influence of inner retinal damage on the first- and second-order mfERG responses.<sup>88,218</sup> Hasegawa et al demonstrated that there were significant reductions in both the first- and second-order response amplitudes in the affected area compared with the unaffected area.<sup>88</sup> The reduction was more marked for the second-order response and mapping of the second-order response correlated better with the perimetry findings

compared with the first-order response. This demonstrated that the second-order mfERG component may be a sensitive indicator for assessing inner retinal dysfunction caused by impairment of cells in the inner plexiform layer or retinal ganglion cells as observed in BRAO.

mfERG has also been used to assess the regional variation in recovery of retinal function after BRAO.<sup>116</sup> Doppler flow meter was used to assess the retinal microcirculation and results were compared with mfERG findings in the juxtapapillary and paramacular areas. It was found that while there were similar reductions in the mfERG amplitude and doppler flow ratios of the affected eye to the fellow eye in the juxtapapillary area, the mfERG amplitude ratio was lower in the paramacular area compared with the doppler flow ratio. This suggests recovery of retinal function after BRAO occurred faster in the juxtapapillary area compared with the paramacular area.



Similar to BRAO, branch retinal vein occlusion (BRVO) can cause visual field defect due to localized disturbance in retinal perfusion. mfERG has been applied to evaluate the extent of retinal dysfunction in patients with BRVO and was found to correlate with the visual field findings.<sup>113,313</sup> Thrombotic areas of the retina were also found to have significantly lower response amplitudes and longer mfERG implicit times compared with non-thrombotic areas.<sup>113</sup> The main mfERG abnormality at the central macula is the reduction of response amplitude, whereas delay in implicit time was the main abnormality in the quadrant affected by BRVO.<sup>114</sup> The foveal retinal thickness measured on OCT and visual acuity was also found to have a significant negative correlation with the P1 response amplitude.<sup>115</sup>

The retinal function after central retinal vein occlusion (CRVO) has also been evaluated using mfERG.<sup>50,149</sup> Kretschmann et al performed mfERG in patients with CRVO and reduced P1 amplitudes and delayed P1 implicit times were observed in both the affected and fellow eyes compared with normal controls.<sup>149</sup> Using wide-field mfERG (WF-mfERG), which allowed recording of mfERG responses from up to the central 90° of the retina, Dolan et al showed that mfERG abnormalities are common in both the affected and fellow eyes of CRVO patients.<sup>50</sup> Delays in P1 implicit times at the central and peripheral retina were found in 98% and 91% of eyes with CRVO, respectively. The mfERG changes observed in the fellow eyes were probably due to abnormal retinal function associated with systemic risk factors of CRVO such as hypertension, diabetes, and hypercholesterolemia. Significant correlations between central P1 mfERG amplitude and both 30 Hz photopic flicker amplitude and latency responses were also observed. Because the flicker amplitude has been shown to be a good predictor for neovascular complication in CRVO, further study will be useful in assessing the role of WF-mfERG measurements as prognostic indicators in patients with CRVO.

## TOXICITY DUE TO SYSTEMIC AGENTS

### Chloroquine and Hydroxychloroquine

Antimalarial drugs, such as chloroquine and hydroxychloroquine, are commonly used in the treatment of rheumatologic diseases, such as systemic lupus erythematosus and rheumatoid arthritis. Irreversible retinal toxicity may be associated with long-term use of the drugs, causing the development of bull's eye maculopathy in the late stage. mfERG has been used in the assessment of chloroquine and hydroxychloroquine retinal toxicity.<sup>130,162,190,192,204,234,285,303</sup> The most characteristic

mfERG findings specific to chloroquine and hydroxychloroquine retinal toxicity is the parafoveal reduction in P1 response amplitude and delays in N1 and P1 implicit times<sup>130,192,303</sup> (Fig. 7). Using mfERG, it has been shown that patients on long-term hydroxychloroquine therapy may have retinal functional abnormalities despite having normal visual acuity and absence of fundus abnormalities.<sup>192,204,234,285</sup> So et al demonstrated the presence of pericentral depression in mfERG response amplitudes in three (50%) of the six patients who had been on hydroxychloroquine for more than 5 years.<sup>285</sup> Moschos et al also showed that eight (40%) of the 20 patients who had been on hydroxychloroquine treatment for less than 5 years had mfERG abnormalities.<sup>204</sup> Hydroxychloroquine use was discontinued in patients who had severe reduction in mfERG responses and the mfERG abnormality returned to normal in some patients. This suggests that retinal dysfunction caused by hydroxychloroquine is potentially reversible. In another study by Maturi et al, mfERG abnormalities were found in 11 (58%) of the 19 patients who were on long-term hydroxychloroquine therapy.<sup>192</sup> All patients except one had normal Amsler grid testing and color vision. The authors identified four patterns of mfERG amplitude abnormalities including paracentral loss, foveal loss, peripheral loss, and generalized loss. The evolution of hydroxychloroquine retinopathy was demonstrated in one patient and there was gradual prolongation of P1 implicit time during follow-up. Lai et al reported the longitudinal mfERG changes in patients on hydroxychloroquine.<sup>162</sup> After a mean follow-up of 17 months, it was shown that there was slight but statistically significant increase in P1 implicit time in patients who continued taking hydroxychloroquine. Results also showed a significant moderate negative correlation between the total cumulative dose of hydroxychloroquine used and both the N1 and P1 response amplitudes, suggesting that the total dose of hydroxychloroquine might play an important role in influencing the mfERG abnormalities. Results from these studies demonstrated that retinal dysfunction is common in patients on long-term hydroxychloroquine therapy. The use of mfERG for evaluating hydroxychloroquine retinopathy appeared to detect retinal physiological changes earlier than other testing modalities and may enable documentation of preclinical stage of hydroxychloroquine retinopathy.<sup>192</sup>

Although it was commonly believed that the sites of hydroxychloroquine toxicity is at the RPE and photoreceptor levels, the exact mechanism of hydroxychloroquine toxicity remained uncertain. It has also been suggested that hydroxychloroquine



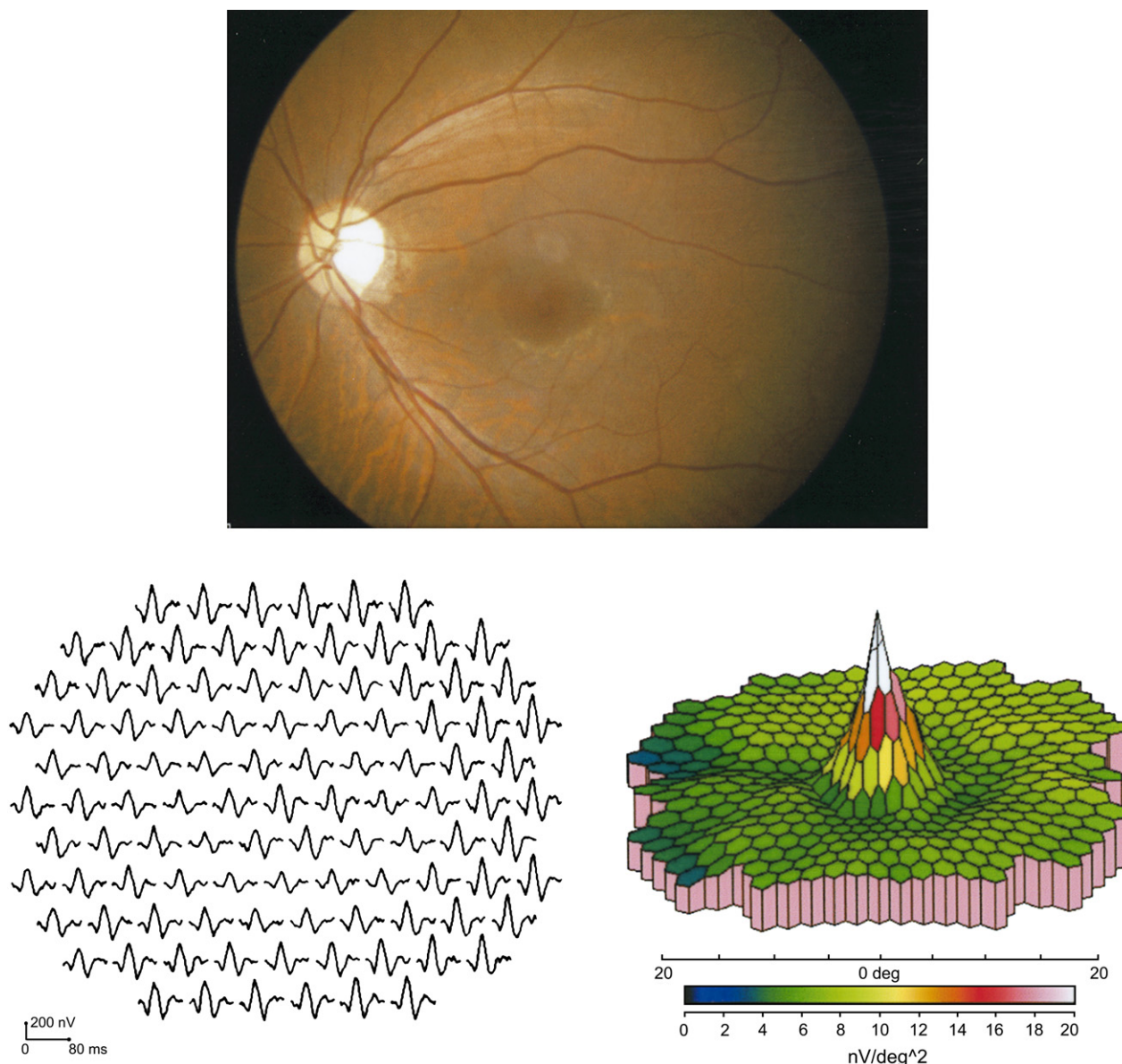


Fig. 7. mfERG findings in a patient with chloroquine retinopathy. *Top*: Fundus photograph of the characteristic bull's eye maculopathy in the left eye of a patient with visual acuity of 20/30 who has been on chloroquine therapy for 10 years. *Bottom*: Trace array and three-dimensional topography demonstrating the parafoveal loss in mfERG responses characteristic of toxic maculopathy caused by chloroquine or hydroxychloroquine.

may be toxic to the retinal ganglion cells. In order to investigate the effects of hydroxychloroquine to inner retinal function, Penrose et al used a special mfERG stimulus to measure the second-order response which evaluated the adaptation effects of the retina in patients taking hydroxychloroquine.<sup>234</sup> It was found that this protocol allowed earlier detection of focal abnormalities in hydroxychloroquine retinopathy. However, some patients still had abnormal first-order mfERG responses to the classic mfERG stimulus despite having normal second-order response to the new stimulus. Therefore the

use of this stimulus in assessing hydroxychloroquine retinopathy requires further evaluation.

### Vigabatrin

Vigabatrin is an irreversible inhibitor of gamma-aminobutyric acid (GABA) transaminase and is used in the treatment of epilepsy. One of the side effects associated with vigabatrin is persistent visual field constriction. Electrophysiological studies have suggested this might be due to the toxic effects of vigabatrin on the retina. Because the visual field

constrictions are often localized binasally, mfERG has been used to evaluate the retinal dysfunction topographically in patients taking vigabatrin.<sup>18,86,120,165,182,239,255</sup> Using mfERG, it was demonstrated that patients with visual field defects attributed to vigabatrin had reduced generalized or peripheral mfERG response amplitudes.<sup>18,86,120,165,182,239,255</sup> The abnormalities in mfERG response amplitudes appeared to correlate well with the visual field defects in some cases.<sup>86,239</sup> However, the abnormalities may also be more diffuse compared with the visual field findings.<sup>86,165</sup> Besch et al further investigated the multifocal OP and second-order mfERG responses in patients on vigabatrin who had visual field defects.<sup>18</sup> It was found that these patients had delayed multifocal OP and in cases with severe visual field defects, there were also delays in second-order mfERG implicit times. These findings suggested that vigabatrin-related visual field defects may be a result of inner retinal dysfunction of the retinal ganglion cells.

A limitation of conventional mfERG in the assessment of retinal function is the restriction of recordings of responses from the central 50–60° of the retina, and therefore it is unable to detect more peripheral retinal dysfunction caused by vigabatrin. The WF-mfERG was developed as a technique to objectively measure more peripheral retinal function and has been applied in the evaluation of visual field constrictions in vigabatrin patients.<sup>193,194</sup> McDonagh et al conducted a study to evaluate the use of WF-mfERG in patients taking vigabatrin.<sup>194</sup> Among all the WF-mfERG parameters, the most consistent overall predictor of bilateral visual field defects was the difference between the central and peripheral implicit times. Using this parameter, it was shown that WF-mfERG had 100% sensitivity and 86% specificity in detecting patients with visual field defect. This study demonstrated that WF-mfERG can objectively detect peripheral retinal dysfunction in patients taking vigabatrin and larger study is undergoing to validate these results.

## Others

### *Amiodarone*

Amiodarone is used in the treatment of cardiac arrhythmia and congestive heart failure. Long-term use of amiodarone has been associated with full-field and pattern ERG abnormalities. Shaikh et al performed mfERG in patients who had been on long-term amiodarone therapy to evaluate the potential retinal toxicity topographically.<sup>278</sup> It was shown that some patients had subnormal P1 amplitudes and mild prolongation in P1 implicit times. The authors believed that the mfERG

changes were probably age-related or due to testing variability and further studies should be performed to determine the extent of retinal toxicity associated with long-term amiodarone therapy.

### *Sildenafil*

Sildenafil is a drug used in the treatment of erectile dysfunction and one of the reported side effects is color vision disturbance. mfERG has been used to evaluate the acute effects of sildenafil on central retinal function.<sup>177</sup> Luu et al performed mfERG recordings in 14 healthy subjects given sildenafil.<sup>177</sup> At 1 hour after the intake of sildenafil, there were slight but significant reductions in P1 amplitudes and delays in P1 implicit times at all retinal eccentricities. The mfERG changes were largest in the central macula with around 20% reduction in P1 amplitude and 5–9% increase in P1 implicit times. The mfERG changes persisted for up to five hours after taking sildenafil in some patients. The mfERG findings provided objective evidence that sildenafil may have an acute effect in macular function which may account for the transient visual disturbances observed by the patients.

### *Deferoxamine*

Deferoxamine is a chelating agent used for iron overload in patients requiring long-term blood transfusion and its use may be associated with toxic retinopathy. Schmidt et al documented reduction in mfERG amplitude in the central retina in a patient who developed bull's eye maculopathy after deferoxamine therapy.<sup>267</sup> Kertes et al showed that there were bilateral reductions in response densities at the central retina which corresponded with the pigmented changes observed in deferoxamine toxicity.<sup>132</sup> After termination of the drug, the decline in retinal function stabilized as reflected by mfERG. Serial mfERG recordings allowed objective quantification and monitoring of retinal toxicity caused by deferoxamine.

### *Ethambutol*

Ethambutol is used in the treatment of tuberculosis and its use may cause toxic optic neuropathy. Studies have also demonstrated that ethambutol may be toxic at the retinal level and macular toxicity associated with ethambutol-related optic neuropathy has been documented using mfERG.<sup>163</sup> Lai et al reported generalised reduction in central mfERG responses in a patient with ethambutol-induced optic neuropathy.<sup>163</sup> The area of mfERG abnormality was more extensive than the central scotoma detected on automated perimetry, indicating diffuse impairment in macular function. After cessation of

ethambutol, increase in mfERG response paralleled with the improvement in visual acuity. Behbehani et al also reported mfERG response abnormalities in four patients with ethambutol associated visual loss.<sup>15</sup> Two of the patients had no visible optic nerve or fundus abnormalities. Analysis showed that patients had significant reduction in N1 response amplitude compared with controls. Based on these studies, mfERG may be a useful tool in the diagnosis and serial assessment of ethambutol-related retinal toxicity. Some of the findings however might also be related to eccentric fixation caused by ethambutol-induced optic neuropathy and therefore causing reduction in retinal response amplitude.

#### *Mercury*

Mercury is a potent neurotoxin that may cause retinal toxicity and mfERG has been used to evaluate the toxic effects of mercury to the central retina.<sup>307</sup> Ventura et al performed mfERG in workers of fluorescent-lamp manufacturing plants who had chronic exposure to mercury vapor.<sup>307</sup> It was found that the workers had significant reductions in N1 and P1 amplitudes at all retinal eccentricities and delay in P1 implicit time at the fovea compared with control. The mfERG findings provide objective evidence that chronic mercury exposure may result in retinal toxicity, causing outer segment and bipolar cell damage.

#### *Nefazodone*

Nefazodone is an anti-depressant which blocks postsynaptic serotonin type-2 (5HT<sub>2</sub>) receptors and its use has been associated with blurred vision and visual disturbances. Luu et al reported the use of mfERG in evaluating retinal dysfunction in a patient with severe bilateral visual loss three years after nefazodone therapy for eight weeks.<sup>174</sup> No abnormality was detected using conventional full-field ERG. The use of mfERG demonstrated severe depression in mfERG responses over the central retina with sparing of the nasal retinal responses, suggesting that nefazodone may cause central retinal toxicity.

#### *Thallium*

Thallium poisoning may cause visual impairment due to optic atrophy. mfERG has been applied to assess the retinal toxicity in a patient with chronic thallium poisoning in which the full-field ERG was normal.<sup>266</sup> Thallium poisoning led to reduction in central mfERG response amplitude with preservation of the responses from the mid-peripheral retina. The result suggested in addition to optic neuropathy, thallium poisoning may also result in

retinal toxicity at the central retina. However, eccentric fixation caused by the optic neuropathy might also have accounted some of the mfERG abnormalities.

#### *Miscellaneous*

Drugs such as methotrexate and rifabutin have been implicated to cause retinal toxicity and patients were found to have abnormal full-field ERG in which the responses improved on termination of the drugs.<sup>240,241</sup> mfERG recordings were carried out in these patients and the normal mfERG suggested that central retinal function was not affected in these patients. However, in the patient with methotrexate retinal toxicity, mfERG was performed only after the drug was stopped and therefore it was uncertain whether impairment in macular function occurred when the patient was still on treatment.<sup>241</sup> mfERG has also demonstrated that patients receiving antiviral therapy with alpha-2a interferon and ribavirin for chronic hepatitis C might develop subclinical retinal toxicity as shown by delayed central P1 response implicit times.<sup>45</sup>

### **TRAUMA**

#### **Phototoxic Retinopathy: Solar and Welding Arc Exposure**

Prolonged exposure to bright light, such as the sun and welding arc, may result in phototoxic retinopathy and mfERG has been used to assess the functional damage in phototoxic retinopathy.<sup>46,149,181,183,264</sup> Denk et al showed that there was persistent mfERG abnormality in a patient 9 months after phototoxic maculopathy caused by welding arc.<sup>46</sup> Mack et al also demonstrated the use of mfERG in detecting foveal dysfunction in four patients who had solar phototoxic retinopathy.<sup>181</sup> In another study by Schatz et al, mfERG together with OCT were used in the monitoring of solar retinopathy.<sup>264</sup> In both patients, the initial reductions in response amplitudes normalized at subsequent follow-up. These cases illustrated that mfERG can be useful in the assessment of phototoxic retinopathy especially in cases with absent or minimal fundus changes.

#### **Comotio Retinae and Traumatic Macular Hole after Blunt Trauma**

Comotio retinae and traumatic macular hole may occur after blunt trauma and mfERG has been used to evaluate the central retinal damage following blunt trauma.<sup>151,164,242</sup> Purvin and Maturi performed mfERG in a patient who developed bilateral central scotoma after motor racing

accident.<sup>242</sup> Clinical examination showed no evidence of pathology involving the optic disks and macula. However, the use of mfERG demonstrated marked reduction in central retinal response amplitude that corresponded to the scotoma observed. The use of mfERG in the absence of fundus abnormality confirmed a diagnosis of commotio retinae. Lai et al also studied the clinical course in a patient who developed commotion retinae and traumatic macular hole after being hit by a soccer ball.<sup>164</sup> At the initial presentation, mfERG showed a well-demarcated depression in retinal response corresponding to the visual field defect caused by the commotio retinae as well as depressed foveal response due to the traumatic macular hole (Fig. 8). The macular hole closed spontaneously after 4 months. The patient developed improvement in visual acuity but the paracentral scotoma persisted. Follow-up mfERG showed recovery of the foveal response as a result of spontaneous closure of the traumatic macular hole. However the well-demarcated area of reduced retinal response density persisted and the findings supported that permanent visual loss following commotio retinae may occur due to irreversible damage to the photoreceptors.

#### OTHER ACQUIRED RETINOPATHY

##### **Multiple Evanescent White Dot Syndrome (MEWDS) and Multifocal Choroiditis (MFC)**

Multiple evanescent white dot syndrome (MEWDS) is an acute unilateral multifocal retinitis characterized by numerous discrete white dots around the paramacular area at the RPE level. Patients usually complain of photopsia, scotoma with decreased vision, and visual field examination may reveal enlargement of the blind spot. mfERG has been used to evaluate the retinal function in patients with MEWDS and has demonstrated localized area of retinal dysfunction corresponding to the scotoma which extends from the blind spot (Fig. 9).<sup>23,40,58,108,217</sup> Furthermore, mfERG also showed more widespread retinal dysfunction compared with subjective visual field testing. The natural course of mfERG abnormalities in MEWDS have also been studied longitudinally and recovery of mfERG responses to normal level paralleled with resolution of symptoms and clinical findings.<sup>40,58,217</sup> Feigl et al showed that MEWDS patients who presented within seven days of symptoms had supernormal N1 and P1 mfERG amplitudes with normal implicit times.<sup>58</sup> This was followed by decrease in response amplitudes two weeks after onset of symptoms. The mfERG findings may reflect early photoreceptor disturbances associated with

MEWDS. The application of mfERG can assist in the evaluation of early stages of MEWDS as the retinal findings may be subtle and easily overlooked at the early stage.

mfERG has also been used to differentiate MEWDS with other ocular inflammatory conditions like multifocal choroiditis (MFC). Oh et al reported the use of mfERG in 14 eyes with MFC and 7 eyes with MEWDS.<sup>217</sup> mfERG demonstrated focal area of reduced retinal function corresponding to the blind spot enlargement in all patients with MEWDS, whereas only 50% of patients with MFC had focal loss in mfERG responses corresponding to the scotoma. MEWDS patients also had less global mfERG dysfunction compared with MFC patients. During follow-up, all MEWDS patients had nearly complete recovery of retinal function on mfERG whereas none of the patients with MFC had full recovery in mfERG responses. This finding indicated that MEWDS causes little permanent damage in retinal function whereas MFC may result in permanent retinal dysfunction. Watzke and Shults also reported that subnormal first- and second-order mfERG abnormalities persisted throughout the posterior pole in patients who recovered from MEWDS and MFC.<sup>310</sup> The abnormalities in second-order response were more severe compared with first-order response and this suggested that the inner retinal adaptive mechanisms are also affected in these patients.

##### **Acute Zonal Occult Outer Retinopathy (AZOOR)**

Acute zonal occult outer retinopathy (AZOOR) is a disease characterized by severe visual field loss and abnormal full-field ERG in the presence of normal fundus appearance and fluorescein angiography. mfERG has been used to evaluate the retinal function in patients with AZOOR.<sup>9,42,310,320</sup> Arai et al showed that mfERG responses were recordable only in the central retinal areas in a patient with AZOOR, which corresponded with the perimetry findings.<sup>9</sup> Yasuda et al also evaluated the role of mfERG in serial monitoring of visual function in a patient with AZOOR.<sup>320</sup> It was found that there was delayed recovery in mfERG response as compared with changes in visual acuity and perimetry. mfERG also demonstrated persistent retinal dysfunction after resolution of AZOOR clinically as subnormal first- and second-order mfERG responses were found in a patient 4 years after onset of bilateral AZOOR.<sup>310</sup> The mfERG abnormalities also extended beyond the areas of visual field defects in both eyes. The use of mfERG allowed the topographic assessment of retinal function in patients with AZOOR.



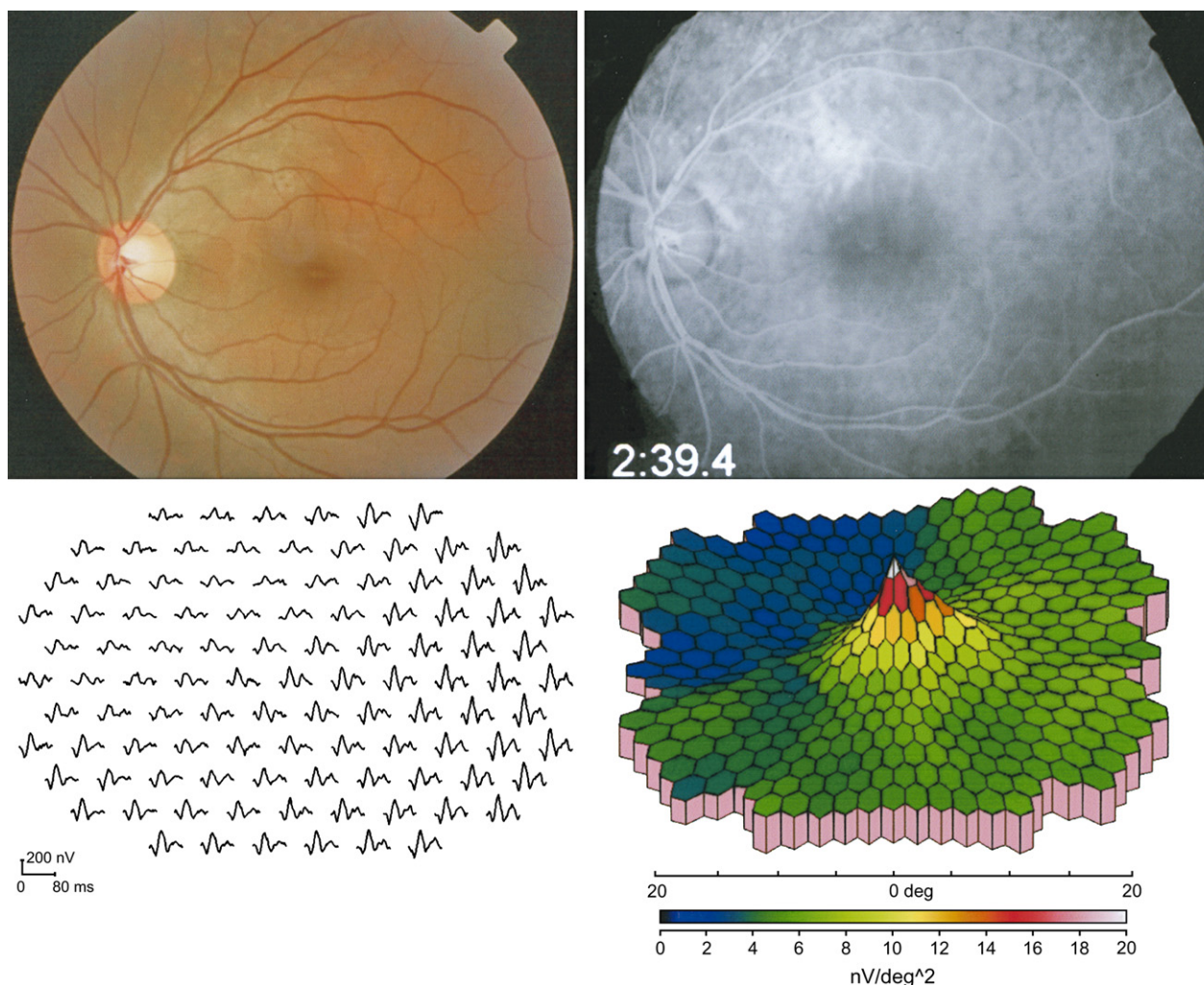


Fig. 8. mfERG findings in a patient after blunt trauma. *Top Left:* Fundus photograph of demonstrating commotio retinae and traumatic macular hole. *Top Right:* Mid-phase fluorescence angiography of the patient demonstrating areas of hyperfluorescence at the site of commotio retinae and at the macular hole. *Bottom Left:* mfERG trace array showing reduction of mfERG response at the fovea with a localized area of abnormal mfERG responses at the superior nasal retina. *Bottom Right:* Three-dimensional topography showing reduction of the foveal peak response density and a well-demarcated area of reduced response density due to commotio retinae.

### Acute Macular Neuroretinopathy (AMN)

Acute macular neuroretinopathy (AMN) is a rare condition that results in sudden onset of paracentral scotoma without usually affecting the visual acuity. Clinically, reddish brown deep macular lesions may be observed and fluorescein angiography findings are usually normal. mfERG has been used to objectively demonstrate the extent of retinal dysfunction in patients with AMN and patients were found to have localized areas of retinal dysfunction which corresponded to the scotoma.<sup>22,33,191,309</sup> The area of depressed retinal response may also be more diffuse compared with the scotoma, suggesting more diffuse retinal dysfunction can occur in patients with AMN.<sup>191</sup> mfERG also detected sub-clinical retinal dysfunction in the asymptomatic

fellow eye of a patient with AMN.<sup>309</sup> The mfERG findings indicated that AMN is a disease that affects mainly the outer retina at the photoreceptor or bipolar cell levels.<sup>22,191</sup> Because AMN patients may have relatively small scotoma, stimulus pattern with 103 or more hexagons should be used for recording as the 61-hexagon stimulus was unable to detect localized functional abnormality in a patient with AMN.<sup>59</sup>

### Acute Idiopathic Blind Spot Enlargement Syndrome (AIBSE)

Acute idiopathic blind spot enlargement syndrome (AIBSE) is a disease characterized by enlarged blind spot without visible changes in the optic disc and the peripapillary retina. The disease is

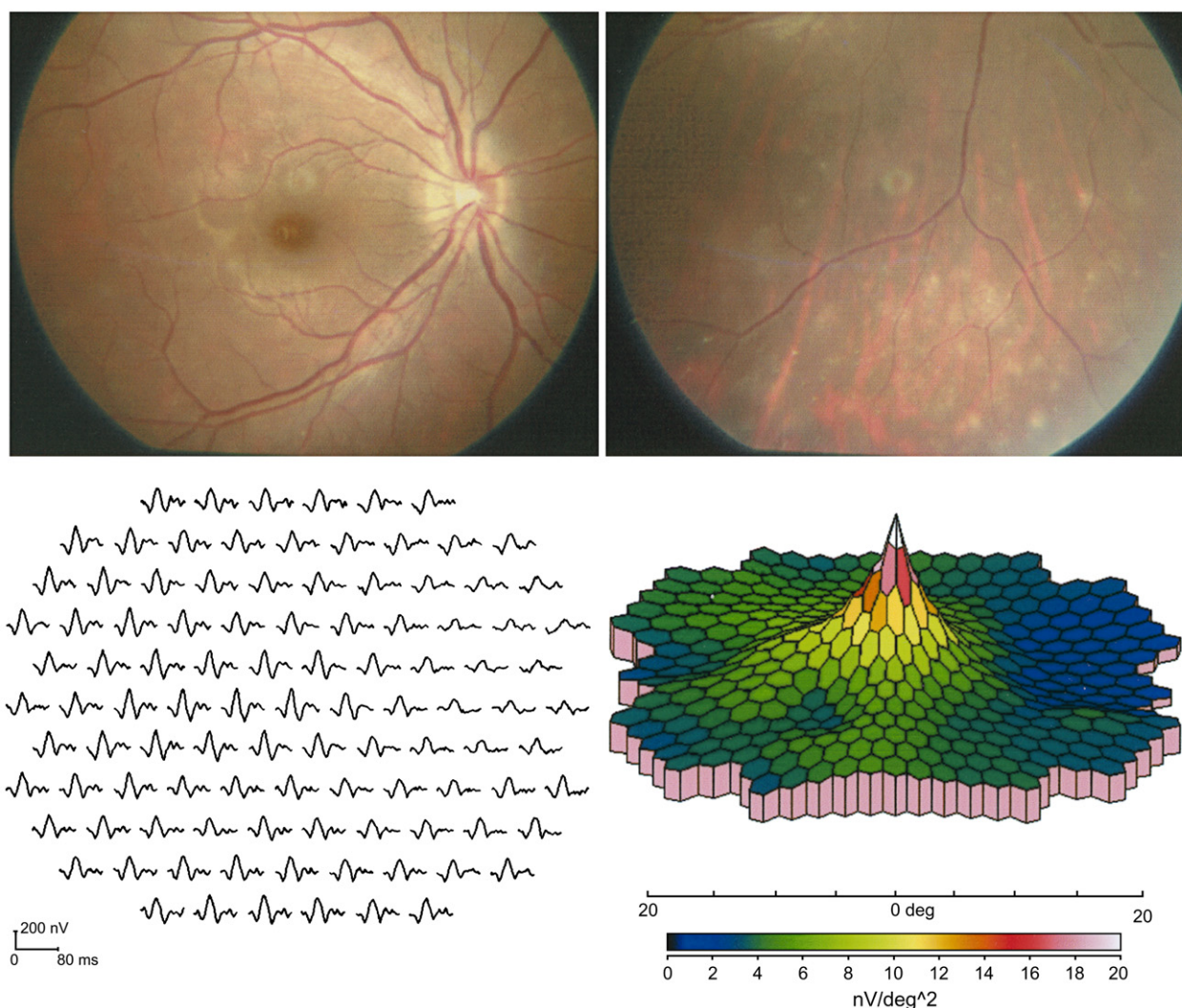


Fig. 9. mfERG findings in a patient with multifocal evanescent white dot syndrome (MEWDS). *Top, Left and Right:* Fundus photographs demonstrating the characteristic features of MEWDS with foveal granularity and multiple fine white dots at the level of retinal pigment epithelium in the mid-periphery. *Bottom, Left and Right:* Trace array and three-dimensional topography of mfERG responses demonstrating an area of reduced responses extending from the blind spot which corresponded well with the enlarged blind spot reported by the patient.

thought to be caused by peripapillary chorioretinal dysfunction and is diagnosed after excluding other conditions, such as MEWDS, AZOOR, and MFC.<sup>310</sup> Patients usually develop temporal visual field loss with normal visual acuity. mfERG has been shown to be useful in the evaluation of retinal dysfunction in patients with AIBSE.<sup>62,145,180,310</sup> Fletcher et al reported the use of a prototype mfERG in patients with AIBSE and loss of waveforms were found in retinal areas surrounding the optic disk.<sup>62</sup> Kondo et al also reported abnormal mfERG responses in areas corresponding to scotoma in patients with AIBSE.<sup>145</sup> The mfERG abnormality in the nasal retina persisted three months later despite resolution of symptoms clinically and mfERG enabled the detection of subclinical retinal dysfunction in the

patient. The mfERG findings confirmed retinal dysfunction as the main abnormality in this syndrome.

#### Antienolase Retinopathy and Melanoma-associated Retinopathy (MAR)

Autoimmune retinopathy can occur due to antibodies directed to retinal proteins and may be a paraneoplastic condition. mfERG has been demonstrated to be useful in assessing the retinal function of patients with antienolase retinopathy and melanoma-associated retinopathy (MAR).<sup>226,312</sup> Weleber et al demonstrated that patients with early antienolase retinopathy may develop central cone dysfunction only evident on mfERG.<sup>312</sup> mfERG has



also been used to assess retinal dysfunction in a patient with MAR and improvement in mfERG response amplitude of the central macula was observed after treatment of metastasis.<sup>226</sup>

### **Purtscher-like Retinopathy**

Purtscher-like retinopathy is characterized by sudden loss of vision with bilateral or unilateral patches of retinal whitening and hemorrhages in the posterior pole without a history of trauma. Haq et al performed mfERG in a patient with pancreatitis-associated Purtscher-like retinopathy.<sup>85</sup> It was found that there were reductions in both N1 and P1 amplitudes and this suggested that the outer retinal layers are affected in Purtscher-like retinopathy. This is in contrast with the common belief that Purtscher-like retinopathy mainly causes changes in the inner retina. The mfERG findings demonstrated that the outer retina is also damaged in Purtscher-like retinopathy, which may be secondary to infarctions of the choriocapillaries.

### **Pre-eclampsia and Choroidal Ischemia**

Patients with pre-eclampsia may develop transient vasospasm in choroidal circulation, resulting in choroidal ischemia and serous retinal detachment. Kwok et al performed serial mfERG in a patient with visual loss due to choroidal ischemia associated with pre-eclampsia.<sup>159</sup> Persistent reductions in response amplitude were found despite recovery in visual acuity and fluorescein and indocyanine green angiographies. mfERG allowed documentation of retinal dysfunction due to choroidal ischemia and was more sensitive compared with fundus angiography in demonstrating the retinal abnormalities.

### **Vogt-Koyanagi-Harada Disease**

Vogt-Koyanagi-Harada (VKH) disease is a bilateral granulomatous panuveitis that may result in visual loss due to generalized retinal atrophy caused by inflammation or exudative retinal detachment. Chee et al performed mfERG to investigate the visual function deficits in patients with convalescent VKH.<sup>36</sup> It was demonstrated that mfERG response amplitudes were significantly reduced with delays in implicit times throughout the macula in patients with large area of peripapillary atrophy (>2 disk areas). Patients with smaller area of peripapillary atrophy (<1 disk area) were also found to have reduced mfERG amplitude throughout the entire macula with delayed implicit times in the peripapillary region. These mfERG findings showed that retinal functional impairment can occur in VKH patients with normal visual acuity and no apparent retinal atrophy.

### **Miscellaneous Acquired Retinal Conditions**

mfERG has been used in the assessment of localized retinal dysfunction in uncommon diseases such as unilateral acute idiopathic maculopathy (UAIM),<sup>3,213</sup> idiopathic unilateral bull's eye maculopathy,<sup>215</sup> and high-altitude hypobaric hypoxic maculopathy.<sup>233</sup> mfERG allowed topographic analysis of retinal dysfunction and monitoring of the disease process in these cases. In a patient with pseudotumor cerebri, mfERG has also demonstrated that in addition to optic nerve damage, the visual loss may also be caused by central retinal damage as a result of long-standing retinal edema.<sup>124</sup>

## **Clinical Applications of mfERG in Hereditary and Congenital Retinal Diseases**

### **STARGARDT MACULAR DYSTROPHY AND FUNDUS FLAVIMACULATUS**

Stargardt macular dystrophy (SMD) and fundus flavimaculatus (FF) are hereditary diseases characterized by progressive visual loss in the first or second decades of life with progressive atrophy of the macula. Because the functional loss is initially limited to the macular region, full-field ERG and electro-oculography (EOG) are not useful in detecting early stages of SMD and FF. mfERG has been shown to be useful in documenting foveal dysfunction in patients with these disorders.<sup>52,70,149,150,153,253</sup> Kretschmann et al showed that 49 of 51 patients with SMD had severe reduction in mfERG response amplitudes in the central 5° of the retina.<sup>153</sup> Slight but significant increases in implicit times were also observed compared with normal controls. In another study by Gerth et al, all SMD patients were found to have markedly reduced mfERG response amplitude and most had delayed implicit times.<sup>70</sup> In order to evaluate the correlation between the areas of retinal dysfunction and scotoma in SMD patients, Rudolph et al analyzed the mfERG obtained from SLO stimulus and compared with the SLO microperimetry findings.<sup>253</sup> Area of reduced retinal function detected by mfERG using SLO stimulus correlated well with the size of scotoma detected on SLO microperimetry. These findings suggested that mfERG is useful in detecting central retinal dysfunction in SMD and is especially useful in patients with minimal fundus changes in which the diagnosis of SMD may be difficult.

## RETINITIS PIGMENTOSA / ROD-CONE DYSTROPHY

Retinitis pigmentosa (RP) is a diverse group of hereditary and sporadic disorders characterized by dysfunctions of photoreceptors and RPE. Because rod functions are usually impaired earlier and more severe than cone functions, RP is also known as rod-cone dystrophy. Conventional full-field ERG is used in the diagnosis of RP and patients may have severely abnormal or non-detectable scotopic ERG. As full-field ERG measures the mass response of the retina, it is unable to assess the central retinal function specifically. mfERG has been widely utilized to evaluate the central and regional variations of retinal dysfunction in RP patients.<sup>29,47,61,77,92,98,140,146,248,265,272,304,321</sup> mfERG is helpful in differentiating between affected and unaffected retinal areas and both amplitude and implicit time abnormalities were found to be dependent on retinal eccentricities.<sup>272</sup> RP patients were found to have significant reductions in response amplitudes at all retinal eccentricities and implicit times were generally within normal in the central areas but became significantly delayed towards the peripheral retina.<sup>29,61,98,272,274</sup> In patients with advanced RP, it is often difficult to detect full-field ERG waveform despite only slight reduction in visual acuity. mfERG is useful in demonstrating small residual central retinal function that might be preserved in these patients.<sup>77,92</sup>

Using special parameters, Holopigian et al studied both the cone-mediated and rod-mediated mfERG in RP patients.<sup>92</sup> Results demonstrated that whereas the cone-mediated mfERG response amplitudes and implicit times had significant correlations with the extent of visual field loss, the rod-mediated mfERG findings showed no correlation. This finding suggests that dysfunction of cone and rod systems may develop independently in RP patients. In another study by Hood et al, only implicit time changes but not amplitude changes were found to be correlated with the locations of visual field sensitivity loss.<sup>98</sup> mfERG implicit time measurements are therefore more important than amplitudes parameters in assessing the location of retinal dysfunction in patients with early RP.

mfERG is also useful in the assessment of central retinal dysfunction in patients with various subtypes of RP such as sector RP,<sup>223,270,321</sup> Usher syndrome (US),<sup>272,276</sup> and Bietti crystalline retinopathy.<sup>119,121</sup> Patients with sector RP may have subnormal scotopic ERG with normal photopic ERG.<sup>223,270,321</sup> The mfERG abnormalities generally correspond well with the visual field and morphological findings.<sup>223,270,321</sup> Locations without visible RP pigmen-

tary changes may also exhibit abnormal mfERG responses due to more diffuse area of functional loss.<sup>321</sup> mfERG enabled the topographic assessment of retinal function in patients with various subtypes of US. Seeliger et al found that while US type II and RP patients had significant delays in mfERG implicit times, US type I patients had no or only mild delay in implicit times.<sup>276</sup> The differences in mfERG implicit times between US types I and II patients were most marked in the peripheral areas. Analysis of mfERG implicit times can therefore assist the differentiation of subtypes of US, which goes along with differences in the degree of sensorineural hearing loss, and has important clinical significance as US types I and II are associated with different severity of sensorineural hearing loss.

mfERG has also been performed to map the localized retinal dysfunction in carriers of X-linked RP.<sup>304</sup> Vajaranant et al demonstrated localized mosaic pattern of mfERG abnormalities may be present in X-linked RP carriers, including a patient with normal visual field, full-field photopic ERG, and clinical findings.<sup>304</sup> mfERG can therefore provide an objective measurement of retinal function to study the phenotype of various genetic expressions in RP.

Because conventional mfERG can only record the responses from the central 50–60° of the retina, retinal dysfunction might not be detected in early stages of RP if it is limited to the peripheral retina. This can be overcome with the use of WF-mfERG, which allows the detection of early retinitis pigmentosa with more peripheral retinal dysfunction.<sup>49</sup>

## CONE DYSTROPHY AND OCCULT MACULAR DYSTROPHY

Cone dystrophy is an inherited retinal disorder that predominantly affects the cone system, whereas rod system function is mostly preserved. Patients with cone dystrophy are characterized by reduced visual acuity, abnormal color vision, and photophobia. Diagnosis of cone dystrophy is usually made by reduction of photopic full-field ERG and relatively normal scotopic ERG. Because mfERG can provide an objective measurement of central cone function, it is particularly useful in the assessment of cone dystrophy.<sup>80,93,131,149,152,154,169,282</sup> The main mfERG findings in patients with cone dystrophy include severe reductions in response amplitudes with delays in implicit times or complete absence of mfERG responses, especially in the central retina.<sup>93,131,152,154,169,282</sup> Holopigian et al evaluated both the cone- and rod-mediated mfERG in patients with cone dystrophy.<sup>93</sup> It was shown that patients had large reductions in cone-mediated mfERG



amplitude and delays in implicit time which were more marked in the central retina. The abnormalities in cone-mediated mfERG were more diffuse compared with the visual field defects. For the rod-mediated mfERG, the amplitudes and implicit times were within normal limits in most patients. Greenstein et al also demonstrated that patients with cone dystrophy had marked reduction in second-order kernel responses in areas of decreased visual field sensitivity.<sup>80</sup> This suggests that in addition to cone photoreceptor damage, there may be associated outer plexiform layer damage in cone dystrophy.

The topographic assessment of mfERG has further enabled the classification of cone dystrophy into peripheral and central types. The peripheral type of cone dystrophy was reported by Kondo et al in which mfERG demonstrated a predominant dysfunction in the peripheral cone with relatively preserved central cone function.<sup>142</sup> The central type of cone dystrophy is also known as occult macular dystrophy (OMD) and is characterized by progressive visual loss with normal fundus appearance and fluorescein angiography. Patients with OMD have normal full-field ERG but the focal macular cone ERG is abnormal. Because the retinal dysfunction is only localized to the macula, mfERG is very useful in the diagnosis of OMD.<sup>68,112,212,236,269,314,328</sup> The characteristic mfERG abnormalities in OMD include marked reductions in P1 response amplitudes in the central macula and minimal reduction towards the peripheral macula.<sup>236,314</sup> There are also slight but significant delays in P1 implicit times over the entire macular region. Because patients with OMD do not have visible fundus morphology, mfERG can allow detection of localized foveal cone dysfunction and differentiate OMD from functional visual loss.<sup>112</sup> Moreover, as focal macular ERG are more time-consuming to perform compared with mfERG, mfERG is the investigation of choice in diagnosing patients with OMD.

#### **BEST DISEASE AND ADULT ONSET VITELLIFORM MACULAR DYSTROPHY**

Best disease is an autosomal dominant progressive macular dystrophy associated with juvenile-onset of visual loss. An adult-onset form of the disease has also been identified and is known as adult onset vitelliform macular dystrophy (AVMD). Both diseases are due to different phenotype expressions caused by mutation of the VMD2 gene. The disease is a generalized disorder of the RPE causing excessive accumulation of lipofuscin, resulting in the characteristic egg-yolk macular lesions in later stages of the disease. EOG is typically abnormal in patients with Best disease but may be within normal

range in AVMD. Because these diseases predominantly affect the macula, mfERG is useful in the assessment of retinal function in patients with Best disease and AVMD.<sup>51,224,246,247,250,259,271</sup> Most studies have demonstrated that the majority of patients with Best disease and AVMD have reduced P1 amplitude in the central 5–10° of the retina with sparing of peripheral response amplitudes.<sup>71,224,246,247,250,271</sup> The mfERG implicit times are generally not affected in most patients. Saito et al reported generalized reductions in response amplitudes throughout the macula in 92% of patients with AVMD, suggesting the impairment in retinal function is not only limited to the central macula.<sup>259</sup> However, the generalized reduction in mfERG responses was only seen in 14% of eyes in the study by Renner et al and these findings may suggest a large variability in the extent of retinal dysfunction in AVMD.<sup>247</sup> Scholl et al also demonstrated that mfERG amplitude significantly correlated with visual acuity and the stage of disease.<sup>271</sup> Because mfERG abnormalities are often detected in Best disease and AVMD patients with good visual acuity, mfERG may serve as an indicator of the extent of retinal functional impairment in these patients.

#### **CENTRAL AREOLAR CHOROIDAL DYSTROPHY**

Central areolar choroidal dystrophy (CACD) is a macular dystrophy that may be sporadic or hereditary. It is characterized by the presence of bilateral symmetric round areas of well-demarcated choroidal, RPE, and retinal atrophy. Because CACD affects only the macula, full-field ERG is usually normal and is not useful in assessing patients with CACD particularly in the early stage. Several studies have evaluated the use of mfERG in patients with early and advanced stages of CACD.<sup>60,87,129,211</sup> Patients with advanced CACD were found to have significant reductions in P1 amplitudes in the central macula compared with controls.<sup>60,87,129</sup> mfERG allowed the documentation of localized retinal dysfunction that could not be detected by full-field ERG. Nagasaka et al studied both the first- and second-order mfERG responses in patients with early CACD.<sup>211</sup> Patients were found to have reduced first-order amplitude in the atrophic areas as well as the clinically normal areas, suggesting more diffuse impairment of retinal function as compared with the morphological changes. Although second-order kernels responses were also severely reduced, the ratios of second-order to first-order kernel amplitudes were relatively normal in areas free of atrophic changes. These findings suggest that the cause of retinal dysfunction in CACD is likely to be

pre-synaptic to the bipolar cells. The use of mfERG has improved the understanding of the pathophysiology in CACD.

### CHOROIDEREMIA

Choroideremia is an X-linked hereditary disease causing progressive degeneration of the RPE, choriocapillaries, and retina. mfERG has been used to assess retinal dysfunction in affected individuals as well as female carriers of choroideremia.<sup>43,254</sup> Rudolph et al performed mfERG in an affected patient and two female carriers of choroideremia.<sup>254</sup> In the affected patient, only a small mfERG response was recordable in the central fovea and waveforms were not recordable across the posterior pole, indicative of severe impairment in macular function. Reduced mfERG responses were also found in asymptomatic carriers of choroideremia. mfERG can therefore be utilized in the detection of functional abnormalities in carriers of choroideremia.

### CONGENITAL STATIONARY NIGHT BLINDNESS

Congenital stationary night blindness (CSNB) is a non-progressive retinal disorder characterized by night blindness, moderately reduced visual acuity, and myopia. The underlying defect in CSNB is thought to be due to defects in the neurotransmission from rod photoreceptors to on-bipolar cells. Kondo et al performed mfERG in patients with complete type of CSNB to assess the retinal origins of each mfERG component.<sup>141</sup> For the first-order kernel response, the response amplitudes were found to be normal in CSNB patients whereas the implicit times were delayed. CSNB patients also had severely reduced or absent second-order responses due to abnormality in the postsynaptic on-pathway and this led to subsequent delay in implicit times for the first-order kernel response. These findings emphasized the importance of measuring mfERG implicit times as patients with CSNB commonly had normal fundus findings and the diagnosis of CSNB may be missed if only mfERG amplitudes were analyzed. mfERG has also been performed in patients with Oguchi disease, a rare form of CSNB.<sup>322</sup> The mfERG was found to be within normal limit as the disease predominately affects the rod. The results showed that the central cone functions are relatively preserved in Oguchi disease and is consistent with the finding of normal S-cone ERG in patients with Oguchi disease.

### X-LINKED RETINOSCHISIS

X-linked retinoschisis (XLRs) is a bilateral hereditary vitreoretinal dystrophy due to mutation of

the RS1 gene. XLRs is characterized by microcystic changes at the macula, resulting in visual loss in young men. Patients with XLRs have abnormal scotopic full-field ERG with the characteristic negative waveform due to selective reduction of the b-wave. mfERG has been performed in detecting localized macular dysfunction in patients with XLRs and patients were found to have significantly reduced P1 response amplitude in the central macula.<sup>109,207,235</sup> Muscat et al demonstrated that mfERG is a very sensitive tool in XLRs which enabled detection of localized retinal dysfunction in a patient who had normal full-field ERG in one eye.<sup>207</sup> Piao et al found that some patients with XLRs also exhibited large reductions in mfERG amplitudes outside the fovea with significant delays in first-order implicit times in all retinal locations.<sup>235</sup> Second-order kernel analysis also showed absence of waveform and the ratio of amplitudes of the second-order kernel to the first-order kernel was significantly reduced. The findings suggested that XLRs caused inner retinal impairment and resulted in wide-spread cone-system dysfunction.

### ACHROMATOPSIA

Complete achromatopsia or rod monochromacy is a rare autosomal recessively inherited disease that causes severe visual loss and total color blindness. Patients with achromatopsia have absence of cone function and normal rod function. A subgroup of patient may have preserved S-cone and the condition is known as blue-cone monochromacy. mfERG in both types of achromatopsia showed no significant waveform recorded from the entire macula as the mfERG is mainly cone-driven.<sup>53</sup>

### ENHANCED S-CONE SYNDROME

Enhanced S-cone syndrome (ESCS) is a rare hereditary retinal disorder characterized by the absence of rod function and large-amplitude S-cone-mediated responses in photopic full-field ERG. mfERG has been used to assess the topographic distribution of the neural connections in patients with ESCS. Marmor et al reported the mfERG findings in a patient with ESCS and it was found that the mfERG responses consisted mostly of monophasic negative waveforms except near the central macula.<sup>186</sup> Ring analysis showed moderate delays in N1 and P1 implicit times in the central fovea. However in the peripheral macula, there were marked prolongations of N1 waveform with a very slow P1 peak at around 60 msec. Using colored stimulation, it was further demonstrated that ESCS patient had twice the normal amplitude to blue stimulus with normal amplitude to red stimulus.

Recording of multifocal off-responses also showed lack of off-response beyond the central 7° of the macula. These results demonstrated marked differences between the central and peripheral mfERG responses and indicated that S-cones may feed into different neural pathways in different retinal regions.

### KJELLIN SYNDROME

Kjellin syndrome is an autosomal recessive disease characterized by spastic paraplegia, mental retardation, amyotrophy, and central retinal degeneration. mfERG has been shown to be useful in detecting the central retinal dysfunction in a patient with Kjellin syndrome who had normal EOG and full-field ERG findings.<sup>67</sup>

### MATERNAL INHERITED DIABETES AND DEAFNESS

Maternal inherited diabetes and deafness (MIDD) is a mitochondrial inherited disease characterized by diabetes mellitus, neurosensory hearing loss, and retinal dystrophy. The fundus changes mainly involve the posterior pole and can range from mild abnormal pigmentation to extensive RPE atrophy. Because most patients had normal full-field ERG due to relatively intact gross retinal function, mfERG has been used to evaluate the central retinal function in patients with MIDD.<sup>17</sup> Patients were found to have reduced mfERG amplitudes with normal implicit times and in one MIDD patient, mfERG showed reduced P1 amplitude at the central macula despite normal pattern ERG. By analyzing responses from different retinal locations, mfERG was more sensitive in detecting subtle changes in macular function compared with pattern ERG. The locations of mfERG abnormalities also corresponded well with areas of the characteristic fundus autofluorescence abnormalities present in MIDD. The findings suggested the localized retinal dysfunction in MIDD is caused by loss of cone photoreceptor outer segment and RPE dysfunction.

### OTHER HEREDITARY RETINAL DISEASES

mfERG has also been used to demonstrate impairments in central and paracentral retinal functions in patients with other retinal dystrophies, such as malattia leventinese,<sup>69</sup> fundus albipunctatus,<sup>257</sup> Bothnia dystrophy,<sup>75</sup> and retinal diseases caused by various genetic defects, such as mutation of the serum retinol binding protein gene,<sup>273</sup> mutation of the peripherin/RDS gene,<sup>263</sup> and trinucleotide repeat expansion of the spinocerebellar ataxia type 7 (SCA7) gene.<sup>1</sup>

## Clinical Applications of mfERG in the Monitoring of Treatment for Retinal Diseases

### PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) with verteporfin has been demonstrated by randomized control trials to be effective in the treatment of subfoveal choroidal neovascularization (CNV) due to AMD and pathologic myopia. Several studies have used mfERG to provide an objective assessment of the changes in retinal function after PDT.<sup>118,147,161,203,205,220,256</sup> Palmowski et al demonstrated that there were improvements in parafoveal mfERG responses after PDT for CNV due to AMD.<sup>220</sup> In another study by Moschos et al, mfERG was performed in patients who had PDT for myopic CNV and it was similarly shown that mfERG response densities increased after PDT.<sup>205</sup> However, in patients who had PDT for CNV due to AMD, there were reductions in the mean retinal response densities in the foveal and parafoveal areas 6 months after PDT.<sup>203</sup> R  ther et al found a general reduction in P1 response amplitude and delay in implicit time after a median interval of 6 weeks post-PDT but the differences were not statistically significant.<sup>256</sup> These studies showed that various forms of macular functional changes can occur in patients who had PDT for CNV.

One of the side effects after PDT is the development of transient visual disturbances shortly after treatment. It is often difficult to detect these subtle non-specific changes objectively with visual acuity testing alone. mfERG has been performed to investigate the short-term changes in macular function after PDT. Jiang et al evaluated the mfERG findings at 3 and 7 days in patients who had PDT for CNV.<sup>118</sup> It was shown that with exception of the statistically significant delay in N1 implicit time for ring 5 at 7 days post-PDT, no other significant changes were observed. In another study by Lai et al, there were significant reductions in the mean N1 and P1 response amplitudes and delays in implicit times within 2 weeks after PDT.<sup>161</sup> The mfERG amplitudes and implicit times returned to pre-PDT level at 1 month after treatment. These mfERG findings may explain the early subjective visual disturbances after PDT in the presence of normal clinical findings.

### RETINAL SURGERY

#### Macular Hole and Epiretinal Membrane

As described in previous sections, mfERG has been shown to be useful in providing objective assessment of the preoperative and postoperative

macular function in patients undergoing macular hole and ERM surgeries.<sup>7,10,106,200,201,216,283</sup> mfERG has also been used to evaluate the potential retinal damage associated with macular hole and ERM surgery.<sup>10,106,216,311</sup>

### Retinal Detachment

mfERG has been used to investigate the changes in retinal function before and after retinal detachment surgery.<sup>202,262,316</sup> mfERG has the advantage compared with full-field ERG because it allows separate assessment of retinal function between the attached and detached retina. Sasoh et al evaluated the preoperative and postoperative changes in mfERG and visual field in patients who had retinal detachment surgery.<sup>262</sup> Preoperatively, patients had marked reduction in response density in the area of detached retina. Mild reduction in response density was also noted in the attached retinal area. Surgery resulted in less recovery in response density compared with visual field sensitivity. The mfERG implicit time however was not assessed in the study. In another study by Wu et al, it was found that retinal detachment surgery resulted in significant improvements in both the N1 and P1 response densities.<sup>316</sup> There were also slight decreases in implicit times but the changes were not statistically significant. Cazabon et al also reported the use of mfERG in evaluating unexplained visual loss after silicone oil removal in three patients who had vitrectomies for retinal detachment.<sup>25</sup> mfERG demonstrated reduced response at the central macula which correlated with the reduction in pattern electroretinogram amplitude, suggestive of macular dysfunction. The exact mechanism of visual loss however remained uncertain.

### Optic Disk Pit

Optic disk pit may result in visual loss due to serous macular detachment, and macular buckling has been proposed as a treatment option. Theodosiadis et al used mfERG for the preoperative and postoperative assessments in patients undergoing macular buckling surgery for serous macular detachment caused by optic disk pit.<sup>300</sup> Preoperatively, patients had reduced foveal and parafoveal response densities as a result of the macular detachment. After successful surgery, all patients had improvement in response densities and mfERG thus provided an objective measure of macular function in these patients.

### Arteriovenous Decompression and Radial Optic Neurotomy for Retinal Vein Occlusion

Patients with BRVO or CRVO may develop visual loss due to macular edema, hemorrhage or ischemia. Treatment with laser photocoagulation may not be effective in BRVO and vitrectomy with arteriovenous decompression has been proposed as an alternative treatment option. mfERG has been applied to assess the preoperative and postoperative macular function in BRVO patients who underwent arteriovenous decompression surgery.<sup>171,196</sup> Mester and Dillinger reported improvement in mfERG responses in 7 patients who had vitrectomy with arteriovenous decompression but the details of the mfERG response amplitudes and implicit times findings were not reported.<sup>196</sup> Lu et al also showed that there were improvements in both the central and peripheral retinal response densities after arteriovenous adventitial sheathotomy for BRVO.<sup>171</sup> For patients with ischemic CRVO, mfERG has also been used to evaluate the retinal functional changes following radial optic neurotomy (RON).<sup>189</sup> It was shown that RON did not improve visual function in terms of mfERG changes despite a reduction in macular thickness. mfERG can therefore provide an alternative measure of macular function in addition to other traditional outcome such as visual acuity and fluorescein angiography.

### Retinal transplantation

Retinal transplantation with RPE and/or retina has been proposed for the treatment of diseases such as RP and AMD. mfERG was used to determine the electrophysiological changes at the transplantation site after surgery.<sup>243–245</sup> Radtke et al reported the presence of transient mfERG responses at the transplantation site in a RP patient who had undergone retinal sheet transplantation.<sup>243</sup> However, in subsequent studies, no changes in mfERG recordings were detected after retinal transplantation despite one patient who developed visual improvement.<sup>244,245</sup> The poor preoperative visual acuity of light perception in most patients might have accounted for the lack of mfERG changes.<sup>245</sup> Another reason may also be due to the inability of mfERG to extract clear signals from the retinal transplantation site due to poor signal-to-noise ratio.<sup>244</sup> Future refinement in the technical parameters of mfERG may enable its application in assessing the efficacy of retinal transplantation objectively.

mfERG has also been used to assess the retinal function after transplantation of autologous RPE cells in patients with subfoveal CNV due to AMD.<sup>2,19</sup> Abri et al demonstrated that there was good



correlation between visual acuity and mfERG findings in patients who had autologous RPE cell transplantation.<sup>2</sup> Binder et al also showed that patients who underwent combined subretinal membrane excision with simultaneous transplantation of autologous RPE cells had significantly higher mfERG responses than patients who had membrane removal alone.<sup>19</sup> These results suggested that mfERG is a useful tool for the objective assessment of retinal function after autologous RPE cell transplantation.

### **Focal laser and pan-retinal photocoagulation**

Focal laser photocoagulation is commonly performed for the treatment of various macular disorders such as macular edema caused by diabetic retinopathy and BRVO. Greenstein et al used sf-mfERG to assess the effects of focal laser photocoagulation in patients with diabetic macular edema.<sup>78</sup> Most patients had no change in terms of visual acuity and visual field sensitivity. However, mfERG showed that patients had reduced amplitude and increased implicit times at 8 to 12 weeks after laser treatment. Timing measures were more affected compared with amplitude changes and the impairment in mfERG responses also extended beyond the area of laser photocoagulation. The findings suggested that although no change was found in terms of visual acuity, mfERG demonstrated that laser photocoagulation for diabetic macular edema might result in some retinal damage caused by laser energy or due to generalized alteration in retinal metabolism. Martidis et al also applied mfERG to investigate the effects of laser photocoagulation for the treatment of subretinal nematode.<sup>188</sup> Despite the patient having an initial visual acuity of 20/20, pre-laser mfERG demonstrated decreased mfERG response amplitude at the fovea due to retinal toxicity caused by the worm. Successful laser treatment of the worm resulted in recovery of both the foveal and perifoveal response amplitudes.

Lövestam-Adrian et al also evaluated the macular function using mfERG before and after pan-retinal photocoagulation (PRP) for proliferative diabetic retinopathy.<sup>170</sup> It was found that although there were no significant changes in visual acuity and macular thickness on OCT, there were significant reductions in mfERG response amplitudes of the central rings at 6 months after PRP. The finding suggested retinal functional impairment may occur in the untreated macula following PRP.

### **Others**

mfERG has been applied to investigate the changes in retinal function after interferon  $\alpha 2a$

treatment for patients with ocular Behcet disease.<sup>287</sup> Stübiger et al demonstrated reduction in central mfERG response amplitudes in patients with ocular Behcet disease due to macular edema or secondary atrophic changes.<sup>287</sup> Delayed P1 implicit times were also observed in patients with severe recurrent uveitis. After treatment with interferon alpha-2a, the response amplitudes improved in patients with macular edema and the implicit times normalized in patients without chronic atrophic changes. The mfERG findings had no correlation with visual acuity but appeared to correlate well with the duration and severity of ocular diseases.

Shimada and Horiguchi have also used mfERG to assess the retinal function after transpupillary thermotherapy (TTT) for treating subfoveal CNV.<sup>280</sup> Results demonstrated significant reduction in the P1 response amplitude within the first minute after TTT. There was also significant prolongation of P1 implicit time at 15 minutes then at 24 hours and 7 days after TTT. The mfERG abnormalities were possibly due to an early thermal effect, followed by other physiological responses. In another study by Ladewig et al, mfERG was performed to investigate the retinal functional changes after prostaglandin E1 infusion for the treatment of dry AMD.<sup>160</sup> It was demonstrated that post-treatment mfERG response amplitude increased by 20% in 3 patients, unchanged in 2 patients, and reduced by 10% in 2 patients. Because no statistical analysis was carried out, the extent of mfERG changes after treatment remained uncertain. Luu et al also carried out mfERG to evaluate the retinal functional changes in children receiving atropine eye drops for myopia and mfERG showed no significant changes in retinal function after 2 years of treatment.<sup>176</sup>

## **Clinical Applications of mfERG in Glaucoma, Ocular Hypertension, and Optic Neuropathy**

### **PRIMARY OPEN-ANGLE GLAUCOMA**

Primary open-angle glaucoma (POAG) is a common cause of visual impairment, and perimetry is the most commonly used method in the diagnosis and monitoring of glaucomatous damage. One of the main limitations of perimetry is the subjective nature of the assessment and therefore false positive and negative results are not uncommon. In view of the ability of mfERG to objectively measure retinal responses topographically, studies have attempted to use mfERG to evaluate the functional changes in glaucoma.<sup>26,28,64,89,97,221,227,260,306</sup> Chan and Brown showed that glaucoma patients had significant reductions in both the first- and second-order

kernel response amplitudes compared with control.<sup>28</sup> However, it was unclear whether the mfERG findings were representative of the visual field defects as no correlation analysis with visual field findings was performed in the study. Hasegawa et al evaluated the relationship between changes in first-order kernel mfERG responses and visual field loss in patients with glaucoma.<sup>89</sup> It was shown that POAG patients had small but significant changes in P1 and N2 implicit times compared with control. However, there were no significant differences in response amplitudes between the POAG and control groups. The implicit times but not response amplitudes correlated with mean sensitivity values of static perimetry. Similarly, Hood et al also found significantly longer mean P1 implicit times in patients with glaucoma compared with control but some patients still had normal implicit times despite visual severe field loss.<sup>97</sup> Using a 50% low-contrast stimulus instead of the conventional mfERG stimulus, Chan showed that the oscillatory component on the descending limb of the first-order kernel response was reduced in two patients with POAG.<sup>26</sup> The reduction in the oscillatory component also correlated with the quadrant with glaucomatous visual field loss.<sup>26</sup> In another study by Fortune et al, there were no significant differences between the response densities from the affected and relatively unaffected hemifields and this finding suggested a lack of spatial correspondence between mfERG and visual field findings.<sup>64</sup> Palmowski et al also demonstrated that despite significant delays in mfERG implicit times in the glaucoma group, overlaps of response parameters exist between the control and POAG patients.<sup>221</sup> These results implied that mfERG is not very reliable in the detection and monitoring of functional loss caused by glaucoma.

Studies have also evaluated the role of second-order kernel mfERG responses in the assessment of glaucoma. Hood et al showed that there was no significant difference between the amplitude ratio of the second-order to the first-order response in glaucoma patients compared with control.<sup>97</sup> In another study by Sakemi et al, it was demonstrated that neither first- nor second-order kernel mfERG response showed changes that reflected early glaucomatous visual field defects.<sup>260</sup> Palmowski et al also showed that although there was significant correlation between second-order mfERG response and visual field findings, the serial changes were small over time and mfERG was not sensitive enough in assessing functional changes in POAG.<sup>227</sup> These results suggested that although changes in second-order kernel responses are due to abnormality in adaptation mechanisms of the inner retina, retinal ganglion cells are not necessarily

damaged in the process of second-order response abnormality and thus is not very useful in investigating glaucomatous damage.<sup>104</sup>

In view of studies demonstrating the lack of sensitivity in both the first- and second-order mfERG components in the assessment of glaucoma, further research was performed to investigate the role of specific mfERG components in the evaluation of glaucomatous damage. Hood et al analyzed the mfERG amplitude component at 8.3 msec after the first-order P1 peak to evaluate the inner retinal damage of the ganglion cells caused by glaucoma.<sup>97</sup> This component is suggested to be contributed by the inner retina in monkeys after blockage of retinal ganglion cell potentials by TTX and NMDA.<sup>95,96</sup> Ratio measures were calculated by dividing the amplitude at 8.3 msec after P1 by the P1 amplitude. Results showed that although the mean ratio was significantly lower in glaucoma patients compared with control, only 33% of patients had reduced ratios outside the normal range and therefore this parameter was not sensitive enough to detect glaucomatous changes. Studies have also evaluated a similar wavelet on the descending limb of the first-order P1 mfERG response called *s-wave* which was suggested to be useful in the assessment of glaucoma.<sup>137,206</sup> The *s-wave* can be enhanced using a low-frequency mfERG stimulus and the response is thought to arise from the retinal ganglion cells as it is significantly higher in amplitude at locations closer to the optic nerve and is absent in patients with optic neuritis.<sup>261</sup> Studies by Murai et al and Kobayashi et al showed that the *s-wave* amplitudes were significantly smaller in glaucoma patients compared with control.<sup>137,206</sup> Analysis also demonstrated significant correlation between the *s-wave* mfERG amplitude and visual field sensitivity.<sup>206</sup> However, the analysis was only done by hemifield and it was unclear whether good correlations exist between the *s-wave* parameters and visual field sensitivity for specific retinal locations. Therefore the use of mfERG *s-wave* in assessing glaucomatous damage remained uncertain.

Another approach to investigate the inner retinal dysfunction of the ganglion cells which may be altered in glaucoma is by the use of a special mfERG stimulus to enhance the contributions from the retinal ganglion cells and the ONHC.<sup>63,222,289</sup> Techniques which have been employed to enhance these components included insertions of three successive global flashes or alternating dark and global flashes in between the multifocal stimuli.<sup>63,222,281</sup> Palmowski et al demonstrated that patients with POAG had reduction in the nasal retinal response amplitude to the second of the three global flashes compared with control.<sup>222</sup> The

clinical application, however, is limited because many of the POAG patients still had amplitudes within normal limits. Fortune et al also showed that glaucoma patients had less asymmetry between nasal and temporal responses due to reduction of the oscillatory component of the induced response in the temporal retina.<sup>63</sup> However, due to the small size and complex origin of this mfERG oscillatory component, application of this technique in assessing glaucomatous damage appears to be limited.

### OCULAR HYPERTENSION

Chan and Brown reported the use of mfERG in assessing patients with ocular hypertension (OHT) who had normal automated perimetry findings.<sup>27</sup> It was found that patients with OHT had significantly lower first- and second-order kernel response amplitudes compared with controls. The second-order kernel response showed larger relative reduction compared with first-order response. The findings suggested that analysis of mfERG especially the second-order responses may be useful in the assessment of OHT patients. However, it was unclear as to the proportion of OHT patients who had abnormal mfERG and therefore the sensitivity of mfERG in detecting retinal dysfunction in OHT patients remained questionable.

### LEBER HEREDITARY OPTIC NEUROPATHY

Leber hereditary optic neuropathy (LHON) is a form of mitochondrial inherited optic atrophy that causes focal degeneration of retinal ganglion cells and nerve fiber layers. mfERG recordings with first- and second-order kernel analyses have been carried out to investigate the changes in inner retinal functions of the retinal ganglion cells in patients with LHON.<sup>158</sup> Results demonstrated that there was loss of a component at around 7.5 msec after the first-order P1 peak. Second-order kernel analysis also showed absence of features which decrease with distance from the fovea which are present in the control group. These results confirmed the presence of inner retinal contribution in both the first- and second-order mfERG waveforms.

## Future Developments of mfERG and Other Multifocal Techniques

### DEVELOPMENTS OF NEW RECORDING PARAMETERS

By altering the mfERG stimulus parameters, researchers can use mfERG to investigate various aspects of retinal electrophysiology at different retinal locations topographically. The use of eight

bright frames followed by eight dark frames allowed the measurement of multifocal on- and off-responses.<sup>138,144,175</sup> Multifocal OP can also be measured by using sf-mfERG with insertion of three dark frames between the multifocal stimuli.<sup>11-13,79,317</sup> Responses from ganglion cells and ONHC can also be enhanced by using alternating dark and global flashes between the multifocal stimuli.<sup>63,281</sup> By selecting the appropriate emission spectrum of the color stimulus, specific mfERG responses from L- and M-cones can be recorded topographically.<sup>4,135,156</sup> This technique of silent substitution can differentiate protanopes and deuteranopes from trichromat individuals and has helped in the understanding of different cone electrophysiological activities.<sup>4,156</sup> As described previously, apart from using mfERG for recording responses from the cone system, rod-mediated mfERG can also be recorded through dark-adaptation and insertion of dark frames between the multifocal flashes in order to study the topographical function of the rod system.<sup>37,38,55,56,92,93,102</sup>

Besides using the conventional m-sequence technique in the recording of mfERG, the use of an LCD stimulator has enabled another recording technique called the *cyclic-summation method*.<sup>168</sup> This method was found to have better signal-to-noise ratio and can provide faster recording time compared to the conventional m-sequence.<sup>168</sup> Further study comparing the two recording techniques will be useful in determining their reliability in the clinical setting.

The conventional CRT and LCD stimulating systems both have limitations in investigating the temporal processing mechanism due to restricted refresh rate duration of 13 msec or more.<sup>128</sup> The development of mfERG system with light-emitting diodes (LEDs) may enable more rapid stimulation and has the potential for analysis of temporal response at a resolution of 1 msec or less.<sup>284</sup> This technique will be useful in assessing the temporal retinal electrophysiological responses topographically.

### WIDE-FIELD MFERG

WF-mfERG was developed recently and has the potential to stimulate more peripheral retina compared with conventional mfERG. Whereas the testing field of conventional mfERG is around 50-60°, up to 90° of retina can be stimulated using the WF-mfERG. As mentioned in previous sections, studies have demonstrated that WF-mfERG is useful in the assessment of retinal function in patients with CRVO,<sup>50</sup> retinitis pigmentosa,<sup>49</sup> and in the evaluation of vigabatrin-associated retinal toxicity.<sup>193,194</sup> However, the system is not readily available at

present and future commercially available models should broaden the utilization of this technique.

### OTHER MULTIFOCAL TECHNIQUES

Multifocal VEP (mfVEP) is a tool developed for the objective measurement of cortical response topographically. The use of mfERG and mfVEP can differentiate between retinal and optic nerve diseases as mfERG are normal in visual loss caused by optic nerve disease alone.<sup>103</sup> The applications and details of the mfVEP are outside the scope of this review and readers can refer to a review by Hood et al.<sup>100</sup> Gränse et al used mfERG to demonstrate the macular function is normal in patients with dominant optic nerve atrophy due to mutation of OPA1 gene, whereas the mfVEP is abnormal.<sup>76</sup> Chen et al has also reported the use of mfERG and mfVEP in evaluating a patient with papillorenal syndrome and has confirmed that the visual field defects were due to retinal ganglion cell and optic nerve abnormalities rather than outer retinal dysfunction.<sup>39</sup> Studies on the use of mfVEP in glaucoma also appear to be promising as the mfVEP defects can reflect the changes in perimetry including glaucomatous visual field changes.<sup>103,146</sup>

Another technique which is based on multifocal electrophysiology technique is the multifocal pattern ERG (mfPERG). The stimulus is composed of hexagonal elements each with alternating triangles and was developed to evaluate ganglion cell function. MfPERG has been used in the assessment of chloroquine retinopathy and results showed that chloroquine maculopathy may cause marked reduction in mfPERG responses.<sup>214</sup> However, although mfPERG was thought to arise from the retinal ganglion cells, studies have shown conflicting results in using mfPERG in the assessment of glaucoma.<sup>136,286</sup> Further research is required in determining the application of mfPERG in various ophthalmic disorders.

### Conclusions

Since the introduction of mfERG a decade ago, mfERG has been used in a large variety of clinical applications. The main strength of mfERG lies in its ability to provide objective assessment in central retinal function topographically within a reasonable short recording time. Through the analysis of mfERG response amplitudes and implicit times at different retinal locations, localized areas of retinal dysfunction caused by acquired or hereditary diseases can be identified. Application of mfERG is particularly useful in patients with pathology limited to the central retina as the full-field ERG in these

patients are usually normal. The use of mfERG has also enabled clinicians to monitor the development of toxic retinopathy due to systemic therapy and to objectively monitor the efficacy of surgical and non-surgical treatment for retinal diseases, as the changes in retinal function might not be reflected by subjective measures. The use of different stimulus and analysis parameters further enhanced the ability to investigate specific components of retinal electrophysiology topographically. Future developments and consolidations of the mfERG techniques will likely broaden the use of mfERG in the clinical setting.

### Method of Literature Search

We conducted a search (January 1980–December 2005) of MEDLINE with the PubMed search engine. Search words included *multifocal electroretinography*, *multifocal electroretinogram*, *multifocal ERG*, *mERG*, *mfERG* and *mf-ERG*. We included all original articles and case reports that evaluated the clinical applications of mfERG in various ocular conditions in human. Further references were retrieved from the lists of references provided in individual articles. Publications with duplicated results were excluded. All articles with English abstract were included and no distinction was made on the basis of the non-English languages.

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