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CLINICAL STUDY

Application of multifocal visual evoked potentials in the assessment of visual dysfunction in macular diseases

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Abstract

Purpose **To evaluate the use of AccuMap multifocal visual evoked potentials (mfVEP) in visual dysfunction caused by macular diseases.**

Methods **Forty-eight eyes with known macular diseases underwent AccuMap mfVEP and microperimetry 1 (MP1) assessments. Evaluation of mfVEP abnormality was based on an amplitude deviation probability plot and the AccuMap Severity Index (ASI). Correlation analyses of the mean mfVEP amplitude corresponding to a radius of 2°, 5°, and 10° of the central visual field, minimum angle of resolution best-corrected visual acuity (BCVA), and MP1 mean sensitivity of the corresponding areas were performed.**

Results **Among the 48 affected eyes, AccuMap mfVEP detected an abnormality of the central visual field in 45 eyes, with a sensitivity of 93.8%. The mean mfVEP amplitudes within a radius of 2°, 5°, and 10° of the central visual field were found to be positively correlated with BCVA ($P<0.01$ for all groups). The mean amplitudes also positively correlated with the MP1 mean sensitivity value of the corresponding visual field ($P<0.01$ for all groups). In the group with stable fixation or predominantly central fixation, the mean mfVEP amplitudes did not correlate with the BCVA or the MP1 mean sensitivity value. Regardless of the fixation status, the ASI was found to correlate with both the BCVA and the total MP1 mean defect value.**

Conclusion **Objective perimetry using AccuMap mfVEP might be applied in the assessment of macular function, with the ASI offering a potentially useful indicator for evaluating macular dysfunction.**

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Keywords: macular disease; multifocal visual evoked potential; electrophysiology; microperimetry

Introduction

Macular disease is one of the leading causes of visual impairment, especially in the elderly age group. Currently available approaches to objectively evaluate macular function include conventional electrophysiological tests and newer multifocal techniques.[1–4] Owing to the relatively low sensitivity and specificity of conventional electrophysiological tests in macular diseases, multifocal techniques, especially multifocal electroretinograms, have gained increasing popularity in the evaluation of macular diseases. Although a large number of studies have evaluated the use of multifocal electroretinograms in evaluating macular dysfunction, few studies have assessed the use of multifocal visual evoked potentials (mfVEP) in macular diseases. The technique of mfVEP provides an objective measure of visual field defects that has been shown to have good agreement with the Humphrey perimetry test and has been used to identify glaucomatous visual field defects and optic neuropathy.[5–7] Another tool that might be useful in the assessment of macular disease is microperimetry, which measures the central retinal sensitivity.[8–10] The aim of our study is to evaluate the use of mfVEP in patients with known macular disease and compare them with microperimetry findings.

Materials and methods

Study design

This was a cross-sectional study in which patients with macular diseases were recruited from the Beijing Tongren Eye Center, Capital Medical University. Exclusion criteria included previous ocular surgery, macular laser photocoagulation, significant media opacities, glaucoma, optic neuropathy, diabetes mellitus, and other retinal diseases involving the peripheral retina. All patients underwent complete ophthalmic examination including ETDRS best-corrected visual acuity (BCVA) testing using minimum angle of resolution (logMAR) unit, slit-lamp biomicroscopy, and indirect ophthalmoscopy. Full-field electroretinography was performed in patients with a provision diagnosis of cone dystrophy in order to confirm the diagnosis. In patients with bilateral disease, only one eye was selected for analysis. Informed consent was obtained from all patients and all investigation procedures adhered to the tenets of the Declaration of Helsinki. The research protocol was approved by the Ethics Committee of Capital Medical University.

mfVEP recording and analysis

mfVEP recording was performed using the AccuMap Opera v.2 system (ObjectiVision, Sydney, Australia) as described previously.[5–7,11] Briefly, using a series of binary sequence of visual stimuli, individual VEP signals were extracted from 58 individual sites within the visual field (up to 24° of eccentricity and 33° nasally) using the spread-spectrum technique. The visual stimulus was displayed on a 21-inch cathode ray tube monitor with 75 Hz stimulation rate as 58 packed segments in a dartboard configuration. Each segment contained a checkerboard pattern (16 checks) with individual checks being proportional to the segment in size. In all 8, 20, 32, 44, and 56 segments covered the central 2°, 5°, 10°, 15.5°, and 24° fields, respectively. The central 1° was used to monitor fixation and therefore is not stimulated. Fixation was monitored by asking the patient to indicate when a randomly generated single-digit number, interspersed with other numbers in a random sequence, was seen within the central 1° of the stimulus. While the fixation target number was displayed 8–12 times during each mfVEP recording, the timing between its presentations was altered, depending on the subject's response rate. Runs with $\geq$30% missed or incorrect fixation targets were discarded and re-recorded. The same technician performed mfVEP testing in all subjects, paying particular attention to the placement of electrodes in order to ensure a high signal-to-noise ratio on the mfVEP tracings. The electrodes were put in an occipital cross-electrode holder placed over the inions, with electrodes 3 cm above, 6 cm below, and 4 cm on either side. Four channels were derived from different pairs of electrodes (vertical, horizontal, and two oblique).[11] Under dim room light, all patients were optimally refracted for near vision without the pupils being dilated. Patients were seated in front of the display monitor, with the cornea located 30 cm from the display monitor. The background luminance of the stimulus was 73.5 cd/m^2 and the luminance of the white and black checks were 146 and 1.1 cd/m^2, respectively (Michelson contrast of 99%). A proprietary trace improvement algorithm was used to determine when the required number of runs had been attained to provide an optimum tracing. In most cases, seven to nine runs of 55 s were sufficient to provide a recording with good signal-to-noise ratio.

Raw data were analyzed using the ObjectiVision Opera 2 system software. Peak-to-trough amplitudes for each wave within the interval of 60–180 ms were determined and compared among channels for every stimulated segment of the visual field. Signal amplitude and interocular asymmetry for each sector in the combined trace array were compared with an internal normative database and probability plots of abnormal sectors were constructed. A scotoma was considered to be present if there were three or more contiguous non-rim points of amplitude having $P<2\%$ in the amplitude deviation plot compared with the normal database, with at least one point having $P<1\%$, or at least three contiguous points having $P<1\%$ or two contiguous points having $P<0.5\%$ in the asymmetry plot. An AccuMap Severity Index (ASI) score was also displayed based on the total number of abnormal zones, relative severity, and asymmetry. By comparing the results with a built-in normative database of 100 patients, the ASI was classified as normal (within 95% confidence interval (CI), ASI 0–11), borderline (95–99% CI, ASI 11–19), or outside normal limits (outside 99% CI, ASI $>$19).

Microperimetry assessment

Fundus-monitored microperimetry was performed with MP1 (Nidek, Vigonza, Italy). A 4-2 staircase strategy with Goldmann III size stimulus was used, and 76 locations covering a 10° radius of the central visual field were examined. The mean retinal sensitivities at 12, 28, 44, and 76 locations covering the central 2°, 4°, 6°, and 10° fields, respectively, were evaluated. The background luminance was set at 1.27 cd/m^2 and the differential luminance at 0 dB stimulation was 127 cd/m^2. The maximum stimulus attenuation was 20 dB. The duration of the stimulus was 200 ms and the fixation target varied in size (2° or 4° cross) according to the patient's visual acuity. Fixation stability and fixation location were independently measured using the MP1 software. Stability of fixation

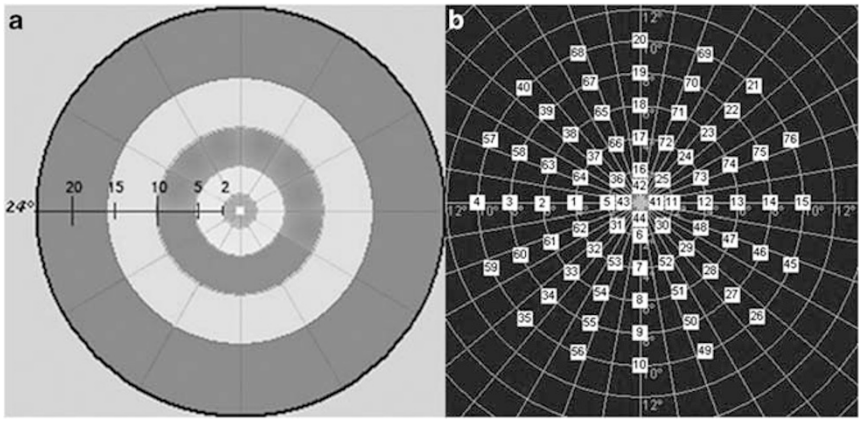

Figure 1 Eccentricities in AccuMap multifocal objective perimetry and MP1 microperimetry. (a) AccuMap multifocal objective perimetry showing that the visual field of 2°, 5°, and 10° radius contains 8, 20, and 32 segments. (b) For the MP1 microperimetry, 12, 28, 44, and 76 points cover the visual field of 2°, 4°, 6°, and 10° radius, respectively.

was classified as (i) stable if ≥75% of the fixation points were inside the 2° diameter circle, or (ii) relatively unstable if <75% of the fixation points were inside the 2° diameter circle. Based on the percentage of points lying inside the foveal circle, the location of fixation was also classified as (i) predominantly central if >50% of the fixation points were inside the 2° foveal circle, or (ii) predominantly eccentric if <25% of the fixation points were inside the circle. For comparison, radii are used in this study to represent the eccentricity of the visual field from the macular center unless specified otherwise.

Data analysis

The mfVEP recordings were analyzed separately, with the investigators masked to the clinical data and MP1 results. For the AccuMap mfVEP test, the mean amplitude across the whole stimulated visual field was calculated. As values of areas where signals were <60 nV could not be displayed, they were taken as 0 nV in the study. For the purpose of our study, individual segments were grouped into rings at different field eccentricities. The inner ring covered 2° radius of the central fixation and contained eight segments, the second ring covered 5° (20 segments), and the third ring 10° (32 segments) (Figure 1a). For the MP1 microperimetry test, retinal sensitivity values at different eccentricities were determined and the mean sensitivity was calculated as the arithmetic mean of all measured absolute thresholds in dB. The four detected rings corresponding to 2°, 4°, 6°, and 10° radius of the central fixation were calculated from 12, 28, 44, and 76 stimuli, respectively (Figure 1b).

Correlation analyses were performed between the central 2°, 5°, and 10° mfVEP amplitudes, ASI, mean sensitivity of the central 2°, 4° or 6°, and 10° of the visual field, the total mean defect of microperimetry, and the BCVA. In addition, the location and stability of fixation were classified and evaluated separately. The AccuMap mfVEP amplitude, mean sensitivity of microperimetry, and BCVA were compared between the different fixation groups. Comparisons between groups were analyzed with the two-sample *t*-test. Correlations between variables were assessed with the Pearson correlation analysis. A *P*-value of <0.05 was considered as statistically significant.

Results

Fixation stability and eccentricity

In all, 48 eyes of 48 patients (24 males and 24 females) with macular diseases were recruited. The mean age of the patients was 44.6 years (range, 19–68 years) and the diagnoses included central serous chorioretinopathy (26 eyes), neovascular age-related macular degeneration (9 eyes), idiopathic choroidal neovascularization (5 eyes), macular hole (3 eyes), macular epiretinal membrane (2 eyes), cone dystrophy (2 eyes), and acute macular neuroretinopathy (1 eyes). Among the 48 eyes, 45 (93.75%) had abnormality on the AccuMap mfVEP test and scotomas were detected within the central visual field (Figure 2). The mean ± standard deviation (SD) ASI score was 75.33 ± 52.47 and the mean ± SD MP1 mean defect was −4.55 ± 3.03. Of the 48 eyes, 28 (58.3%) were classified as having stable fixation and 20 (41.7%) as having relatively unstable fixation. For the location of fixation, 24 (50.0%) had predominantly central fixation and 24 (50.0%) had predominantly eccentric fixation. The mean ± SD logMAR BCVA in the stable group was

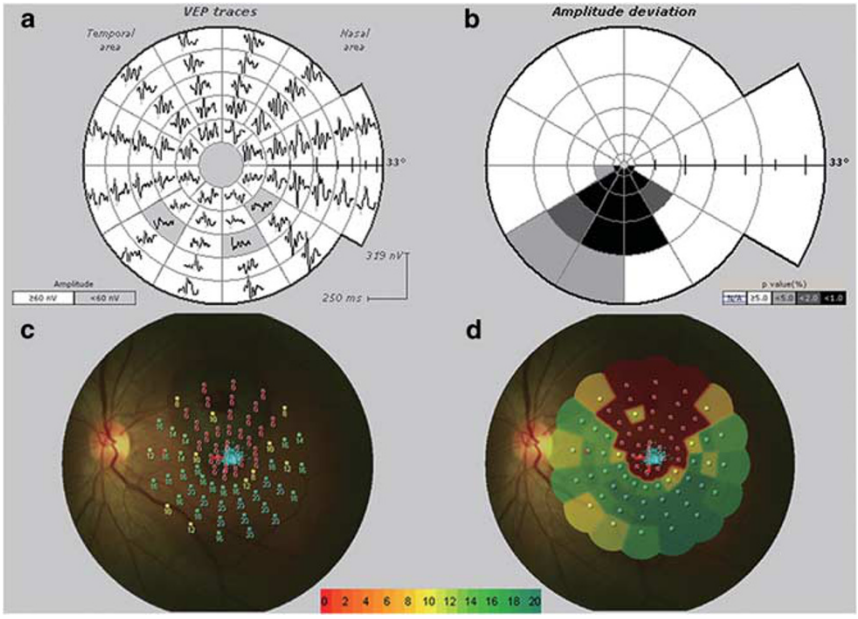

Figure 2 Comparison of AccuMap multifocal objective perimetry (a, b) and MP1 microperimetry (c, d) in a left eye with neovascular age-related macular degeneration. Subretinal hemorrhage associated with choroidal neovascularization resulted in reductions in mfVEP amplitude and retinal sensitivity. The shape and location of the absolute scotoma corresponded in both perimetry techniques when a visual field map was vertically revolved. (a) Raw signal tracing, (b) amplitude deviation probability plot of AccuMap multifocal objective perimetry, (c) retinal sensitivity map, and (d) pattern deviation plot of MP1 microperimetry.

0.19 ± 0.27 and was significantly better than 0.49 ± 0.35 in the relatively unstable group ($P = 0.002$). Similarly, visual acuity was also significantly better in the predominantly central group compared with the predominantly eccentric group, with a mean ± SD logMAR BCVA of 0.20 ± 0.27 and 0.43 ± 0.36, respectively ($P = 0.017$).

Correlation between mfVEP findings and visual acuity

The AccuMap mfVEP amplitude of the 48 affected eyes in the central 2°, 5°, and 10° of the visual field significantly correlated with the logMAR BCVA (Pearson's $r = -0.474$ to -0.481, $P = 0.001$ for all fields) (Table 1). Moreover, the ASI also correlated significantly with the BCVA (Pearson's $r = 0.733$, $P < 0.001$) (Figure 3a).

For the subgroup analyses, it was found that in patients with stable fixation, there was statistically significant correlation between the ASI and logMAR BCVA (Pearson's $r = 0.559$, $P = 0.002$), whereas the correlation was not significant between AccuMap mfVEP amplitude in all fields and logMAR BCVA ($P > 0.05$ for all groups). In the relatively unstable fixation group, both the ASI and the AccuMap mfVEP amplitude significantly correlated with the BCVA ($P < 0.01$ for all groups). In the predominantly central fixation group, the ASI significantly correlated with logMAR BCVA (Pearson's $r = 0.576$, $P = 0.003$), whereas the correlation was not significant between AccuMap mfVEP amplitude in all fields and logMAR BCVA ($P > 0.05$ for all groups). In the predominantly eccentric fixation group, both the ASI and the AccuMap mfVEP amplitude significantly correlated with the BCVA ($P < 0.05$ for all groups).

Table 1 Correlation between mfVEP amplitude, ASI, and logMAR BCVA

	Visual field (radius: deg)			*ASI*
	2	*5*	*10*	
Total (n = *48*)				
r	−0.474	−0.481	−0.476	0.733
P	0.001	0.001	0.001	<0.001
Stable fixation (n = *28*)				
r	−0.263	−0.220	−0.173	0.559
P	0.176	0.261	0.378	0.002
Relatively unstable fixation (n = *20*)				
r	−0.743	−0.800	−0.803	0.787
P	<0.001	<0.001	<0.001	<0.001
Predominantly central fixation (n = *24*)				
r	−0.368	−0.357	−0.303	0.576
P	0.077	0.087	0.150	0.003
Predominantly eccentric (n = *24*)				
r	−0.508	−0.512	−0.540	0.753
P	0.011	0.011	0.006	<0.001

Correlation between mfVEP amplitude and MP1 retinal sensitivity

The AccuMap mfVEP amplitude of the 48 affected eyes in the central 2°, 5°, and 10° of the visual field, respectively, significantly correlated with the MP1 mean sensitivity in the central 2°, 4° or 6°, and 10° visual fields (Pearson's $r = 0.437$–0.492, $P \leq 0.002$ for all groups), and the ASI also correlated significantly with the total MP1 mean defect (Pearson's $r = 0.724$, $P < 0.001$) (Figure 3b; Table 2).

For the subgroup analyses, in the stable fixation group, although the correlation was statistically significant between the ASI and the total mean defect (Pearson's $r = 0.602$, $P = 0.001$), the correlation was not statistically significant between the mfVEP amplitude and the mean sensitivity in any of the corresponding fields ($P > 0.05$ for all groups). However, in the relatively unstable fixation group, the correlation was significant between the mfVEP amplitude and the mean sensitivity in all groups (Pearson's $r = 0.715$–0.767, $P < 0.001$ for all groups), as well as between the ASI and the total mean defect (Pearson's $r = 0.602$, $P = 0.001$). For the predominantly central fixation group, the ASI significantly correlated with the mean defect (Pearson's $r = 0.607$, $P = 0.002$), whereas the correlation was not significant between the AccuMap mfVEP amplitude and the mean sensitivity in any of the corresponding fields ($P > 0.05$ for all groups). In the predominantly eccentric fixation group, the correlation was significant between the ASI and the total mean defect (Pearson's $r = 0.753$, $P < 0.001$), as well as between the mfVEP amplitude and the mean sensitivities of the corresponding fields (Pearson's $r = 0.489$–0.530, $P < 0.05$ for all groups).

Correlation between MP1 mean sensitivity and logMAR BCVA

For all 48 eyes, the MP1 mean sensitivity of the central 2°, 4°, 6°, and 10° significantly correlated with the logMAR BCVA ($P < 0.001$) (Table 3). These correlations remained significant even when patients were grouped into stable or relatively unstable fixation, as well as into predominantly central or eccentric fixation ($P < 0.001$).

Discussion

The AccuMap mfVEP system produces an objective visual field map through multiple recording channels to detect signals from all areas of the stimulated visual field. The system makes use of the underlying EEG amplitudes to reflect an individual's VEP response. This substantially reduces intersubject variability and allows more reliable comparison with a normal database for applying mfVEP in the detection of visual field changes clinically.[12] A number of studies have shown that AccuMap mfVEP can provide a good measurement of visual field defects in glaucomatous optic neuropathy,[5,13–15] optic neuritis,[7,16] compressive optic neuropathy,[6] and other conditions.[17–19] Strong correlation has been observed between areas of visual field loss on Humphrey subjective perimetry and mfVEP amplitude.[5,6,17] However, published reports that evaluated the use of mfVEP in macular diseases in comparison with MP1 microperimetry are scarce.

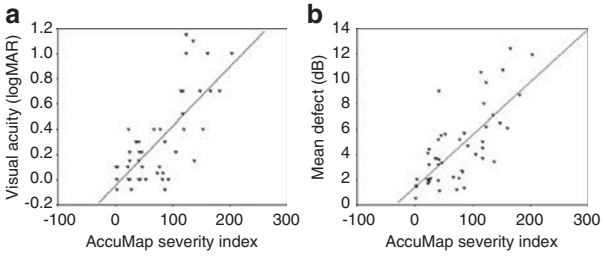

Figure 3 Scatter plot and correlation between (a) ASI and logMAR BCVA, and (b) ASI and mean defect of the central 76 points covering the central 10°.

Table 2 Correlation between mfVEP amplitude and MP1 mean sensitivity

AccuMap—MP1 visual field (radius: deg)		*Total* (n = *48*)	*Stable* (n = *28*)	*Relatively unstable* (n = *20*)	*Predominantly central* (n = *24*)	*Predominantly eccentric* (n = *24*)
2—2	*r*	0.492	0.293	0.767	0.381	0.530
	p	<0.001	0.131	<0.001	0.066	0.008
5—4	*r*	0.437	0.201	0.737	0.272	0.506
	p	0.002	0.304	<0.001	0.198	0.012
5—6	*r*	0.443	0.215	0.715	0.300	0.489
	p	0.002	0.272	<0.001	0.154	0.015
10—10	*r*	0.437	0.141	0.733	0.245	0.511
	p	0.002	0.473	<0.001	0.248	0.011
ASI—MD	*r*	0.724	0.602	0.719	0.607	0.753
	p	<0.001	0.001	<0.001	0.002	<0.001

Abbreviations: ASI, Accumap Severity Index; MD, mean defect.

Table 3 Correlation between MP1 retinal sensitivity and logMAR BCVA

	Visual field (radius: deg)	*2*	*4*	*6*	*8*	*10*
Total ($n=48$)	*r*	−0.793	−0.756	−0.741	−0.746	−0.742
	p	<0.001	<0.001	<0.001	<0.001	<0.001
Stable ($n=28$)	*r*	−0.733	−0.694	−0.686	−0.696	−0.698
	p	<0.001	<0.001	<0.001	<0.001	<0.001
Relatively unstable ($n=20$)	*r*	−0.758	−0.724	−0.694	−0.698	−0.691
	p	<0.001	<0.001	0.001	0.001	0.001
Predominantly central ($n=24$)	*r*	−0.777	−0.755	−0.746	−0.749	−0.738
	p	<0.001	<0.001	<0.001	<0.001	<0.001
Predominantly eccentric ($n=24$)	*r*	−0.757	−0.704	−0.682	−0.690	−0.691
	p	<0.001	<0.001	<0.001	<0.001	<0.001

The conventional pattern reversal VEP has been previously considered to be useful in assessing macular function. Patients with macular disease might demonstrate increased latency and/or reduced amplitude, especially at high spatial frequency.[2,20] Nevertheless, conventional pattern VEP has several limitations. Weinstein *et al*[21] have demonstrated that the central 2° of the macula accounts for approximately 65% of the response in the occipital cortex, suggesting that the spatial detail of the central visual field is poorly represented by conventional pattern. Moreover, pattern reversal VEP is also subjected to wide intersubject variability, and therefore we hypothesized that mfVEP might be more suitable for assessment of macular dysfunction.

Macular diseases can be associated with damage to photoreceptors and bipolar cells, causing impairment of visual signal transmission from photoreceptors to retinal ganglion cells.[22,23] Therefore, abnormal electrophysiological responses of the visual cortex captured by sensitive techniques might be used as indicators for macular diseases. Our results demonstrated that objective perimetry using AccuMap mfVEP allowed a highly sensitive (93.8%) detection of central visual field anomalies due to macular diseases. The mfVEP results also significantly correlated with subjective visual acuity. As visual acuity worsened, the mfVEP amplitudes of different eccentricities also reduced and the ASI value increased. This indicated that mfVEP abnormalities could reflect the changes in central visual acuity.

The scotoma in MP1 microperimetry is usually presented as a relative or absolute scotoma and not as a deviation probability plot. Although the shapes and locations of absolute scotomas in MP1 microperimetry were in good agreement with those in mfVEP of some patients, the topographic comparison between microperimetry and mfVEP in patients with relative scotomas might not be as easy as when using the Humphrey visual field.[5,6] We investigated the correlation of parameters at the corresponding visual field eccentricity between these two measures. It was found that the mean amplitude at different mfVEP field radii significantly correlated with the mean sensitivity in the corresponding MP1 location. These findings suggested that the two measures were consistent.

In our study, we classified the eyes based on stable or relatively unstable fixation, and predominantly central or eccentric fixation. It was found that mean visual acuity was significantly better in the stable group than in the relatively unstable group, as well as better in the predominantly central group than in the predominantly eccentric group. Eyes with poorer vision were therefore more likely to have less stable fixation, as well as to have predominantly eccentric fixation. One interesting observation in our study was the significant correlation between the mfVEP mean amplitude of different eccentricities and the BCVA or MP1 retinal sensitivity of the corresponding visual field in eyes with relatively unstable fixation group or predominantly eccentric fixation. In the stable fixation group or the predominantly central fixation group, the correlation was not statistically significant despite patients having better visual acuity. The main reason for this finding was the large variation of mean mfVEP amplitudes at different eccentricities among subjects and there was an absence of a maximal value, whereas the differential light threshold in MP1 had an upper limit of 20 dB stimulus and there was a narrower range of variation among the subjects. Patients with poor eyesight resulting from macular lesions generally showed a reduction in mfVEP amplitude, and a corresponding reduction in the fluctuation of amplitude across subjects was observed. This might explain the correlation between the two tests in the relatively unstable fixation group or the predominantly eccentric fixation group. Owing to the lower variation of MP1 retinal sensitivity and BCVA, they correlated with each other in every group. In contrast, in subjects with relatively good visual acuity, the mfVEP amplitude did not correlate with the BCVA because of the large fluctuation. These findings suggested that

patients with good fixation and central fixation might not have significant difference in mfVEP amplitude. Nonetheless, the ASI correlated with the mean defect and BCVA in all subgroups, suggesting that ASI is a better indicator of macular function than the mean mfVEP amplitude.

In summary, AccuMap mfVEP might be a useful objective method for the assessment of macular function, with the ASI offering a more reliable measuring tool than the mean mfVEP amplitude. Our study has several limitations. First, we did not evaluate the mfVEP latency changes as the abnormality assessed in our study was based on the amplitude deviation probability plot and the ASI. Further study might consider assessing the mfVEP latency changes in addition to the amplitude findings. Second, we did not perform multifocal electroretinograms or conventional pattern-reversal VEP analyses in the patients for comparison, as the main purpose of this study was to evaluate the correlations between mfVEP and microperimetry. Although mfVEP is an objective method of visual functional assessment, it cannot provide an entirely objective assessment for macular function, as responses arising outside the macula would still contribute to the mfVEP responses. Future studies might therefore consider evaluating the correlation between mfVEP and multifocal electroretinograms as an objective method of assessing macular diseases. Finally, the maximal peak-to-trough amplitude for each mfVEP response was determined within the interval of 60–180 ms and this measurement interval was by default selected by the computer software. The difference in measuring time might increase the intersubject amplitude variability and limit the reliability of the AccuMap testing measure. Nonetheless, as demonstrated in our study, the mfVEP method is highly sensitive (93.75%) in detecting patients with macular disease, and there was good agreement with the MP1 method in subjects with relatively poor visual acuity.

Summary

What was known before

- Multifocal visual evoked potentials (mfVEP) is an investigation technique that can provide an objective measure of visual field defects and has been used to identify glaucomatous visual field defects and optic neuropathy.
- MfVEP has been shown to have good agreement with the Humphrey perimetry test. However, its correlation with microperimetry has not been assessed previously.

What this study adds

- This study demonstrated that the mean mfVEP amplitudes positively correlated with the microperimetry mean sensitivity value of the corresponding visual field.
- In addition, the AccuMap severity index (ASI) was found to be potentially useful in patients with macular diseases.

Conflict of interest

The authors declare no conflict of interest.

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