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Retinal function as assessed by multifocal electroretinography and central perimetry before and after vitrectomy with conventional versus fovea-sparing internal limiting membrane peeling for idiopathic macular hole

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Purpose: *To perform multifocal electroretinography (mfERG)- and central perimetry-based evaluation of the function of the macula before and after vitrectomy with conventional internal limiting membrane (ILM) peeling versus fovea-sparing ILM peeling for idiopathic macular hole (IMH).*

Material and Methods: *This study included 70 patients (71 eyes) who received 25-G vitrectomy with conventional or fovea-sparing ILM peeling and gas tamponade with 20% SF6 or 15% C3F8 for stage-2 to stage-4 holes as per the classification by Gass. Eyes of study patients underwent optical coherence tomography angiography (OCTA) evaluation of IMH diameter and choriocapillaris perfusion density, ten-degree static perimetry and 20-degree 5-ring mfERG before and 1 month after surgery.*

Results: *Before surgery, eyes with IMH showed significantly reduced foveal light sensitivity and overall parafoveal sensitivity, increased Pattern Standard Deviation (PSD), and reduced retinal response density in mfERG rings 1 and 2 compared to fellow eyes. The foveal threshold sensitivity in the affected eyes was found to be correlated with minimal diameter of IMH ($r = -0.77$; $p < 0.05$) and the postoperative BCVA ($r = 0.66$; $p < 0.05$), whereas the overall retinal sensitivity, with the maximal diameter of IMH ($r = -0.56$), preoperative BCVA ($r = 0.6$) and postoperative BCVA ($r = 0.7$). MfERG retinal response density in ring 1 was significantly reduced ($p = 0.00001$) and correlated with the preoperative foveal threshold sensitivity ($r = 0.6$) and choriocapillaris perfusion density ($r = 0.39$). After macular hole closure, median BCVA (interquartile range) in the fovea-sparing ILM peeling group and the conventional ILM peeling group improved to 0.55 (0.35–0.7) and 0.43 (0.35–0.6), respectively. In addition, the foveal threshold sensitivity within 10-degree area in the former and latter groups improved, but was 13.6% ($p = 0.009$) and 15% ($p = 0.0001$), respectively, lower than in the fellow eyes (34.5 ± 2.9 dB). The overall retinal sensitivity in the fovea-sparing ILM peeling group improved more substantially, to 509.6 ± 13.9 dB, and almost reached the fellow-eye value (528.0 ± 25.8 dB). Moreover, the retinal response density in the conventional ILM peeling group improved in rings 1-5, whereas that in the fovea-sparing ILM peeling group, in rings 2-4, but not in ring 1.*

Conclusion: *In eyes with IMH, retinal photoreceptor function as assessed by perimetry and mfERG was found to be impaired at baseline and improved after macular hole closure. In the fovea-sparing ILM peeling group, the overall retinal sensitivity in the affected eyes improved more substantially than in the conventional ILM peeling group.*

Keywords:

vitrectomy, optical coherence tomography, idiopathic macular hole, internal limiting membrane, multifocal electroretinography, automated static perimetry

Introduction

An idiopathic macular hole (IMH) is a full-thickness defect of foveal retina from the internal limiting membrane (ILM) to the outer segment of the photoreceptor layer; it is accompanied by reduced visual acuity. In the Baltimore Eye study, a prevalence of 3.3 per 1000 was reported. It occurs almost three times more often in women than in men and develops usually in the seventh decade of life [1].

A vitrectomy with ILM peeling and vitreous gas/air tamponade is a gold standard for treating macular holes [2]. Fovea-sparing ILM peeling has been increasingly used recently; it preserves the parafoveal ILM which allows to reduce the risk of damage to foveal Müller cells [3–5].

Visual acuity (VA) is a major measure for assessing the function of patients with IMH. There are sensitive electrophysiological techniques for more accurate evaluation of the functional effect of IMH surgery. These include the full-field (Ganzfeld) electoretinogram and multifocal electoretinogram (mfERG), which provide objective retinal functional data and can be used to study local visual field defects in the macula. The mfERG was developed to provide a topographic measure of retinal activity and reflects the spatial relationship between the receptor cells and the cells supporting the retina [6–8]. Macular perimetry allows for the identification of defects in retinal receptor sensitivity, which provides more detailed knowledge on the functional state of the retina, too [9].

The purpose of the current study was to perform mfERG- and central perimetry-based evaluation of the function of the macula before and after IMH vitrectomy with conventional ILM peeling versus fovea-sparing ILM peeling.

Material and Methods

This was a prospective, open-label, interventional study. The study was conducted at the Vitreoretinal Department and Functional Study Laboratory of the Filatov Institute, conformed to the Declaration of Helsinki and local ethics committee approval was obtained. The study is part of the research project (state registration number 0122U001488).

Totally, 70 patients (15 males and 55 females) had an IMH surgery in 71 eyes. The mean age ± standard deviation (SD) was 65.7± 6.8 years. The median IMH duration (interquartile range (IQR)) was 3.0 (1.0-6.0) months, and, preoperatively, the mean BCVA (SD) in eyes with IMH was 0.19 (0.16).

Inclusion criteria were stage-2 to stage-4 holes as per the classification by Gass [9], ability to follow recommendations, and clear ocular media. Exclusion criteria were history of vitrectomy, myopia exceeding -6 diopters, wet age-related macular degeneration, glaucoma, diabetic retinopathy or other vascular choroidal and retinal disorders in affected or fellow eyes. Written informed consent to surgery (vitrectomy) was obtained from all study subjects.

A preoperative examination included visual acuity assessment, refractometry, tonometry, biomicroscopy, dilated fundus examination with a slit-lamp and 90 D lens, binocular indirect ophthalmoscopy with a 20 D lens, and macular optical coherence tomography (OCT; OPTOPOL Technology, Zawiercie, Poland) with the estimation of the maximal and minimal diameters of the macular hole and choriocapillaris perfusion density (reported previously [10]). In addition, the central visual field was assessed with a Humphrey Field Analyzer (model 750i, Carl Zeiss Meditec, Jena, Germany) and mfERG was recorded using a CRT monitor (Retiscan, Roland Consult, Wiesbaden, Germany).

Static perimetry measures differential light sensitivity (DLS) to a stimulus of varying intensity against a background of constant luminance. DLS is the ratio of background luminance (L b) to target luminance (L) at threshold (i.e., DLS = L b/L). Background intensity was maintained constant, whereas the stimulus presented by the perimeter varied in intensity between 0.08 and 10,000 asb. DLS characterizes retinal light sensitivity and is measured in log scale, which in Humphrey Field Analyzer is calculated as dB=10log10(10000/(A─31.6)), where A is the luminance of the stimulus in apostilbs and 31.6 apostilbs is the background luminance. Humphrey Field Analyzer Central 10-2 test helps to assess 68 points 2 degrees apart in the central 10-degree field of vision and was used to evaluate DLS in the macula. In addition, the foveal threshold was assessed.

The Humphrey field analyzer's statistical package (STATPAC) was used to produce in-depth analysis of visual field test results. The following indices were analyzed:

Overall retinal sensitivity for the four visual field quadrants (superior temporal, superior nasal, inferior temporal, inferior nasal);

Foveal threshold sensitivity;

Mean Deviation (MD), the average elevation or depression of the patient's overall field compared to the normal reference field (if the measured sensitivity is less than normal, minus sign will be given to the deviation value);

Pattern Standard Deviation (PSD), a measurement of the degree to which the shape of the patient's measured field departs from the normal, age-corrected reference field.

Central visual field test was performed in 41 eyes with IMH and 32 fellow eyes.

Patient eyes were presented with mgERG stimuli with hexagonal frames scaled to be larger with increasing eccentricity and containing 61 elements. P1 amplitude and P1 latency (the time from the onset of light stimulus until the P1 peak) were assessed in nV and ms, respectively. The 61-hexagonal mfERG stimulus pattern was divided into five rings for data analysis (1°–2°, 3°–5°, 6°–9°, 10°–15°, and 16°–20°). Topographic (3-D) response density plots depict the overall signal strength per unit area. Responses within a ring can be calculated as amplitude/unit area, whereby the summed responses in each ring are divided by the total area of hexagons in the ring and plotted as nv/deg2 (Fig. 1).

In an mfERG study, a Jet-Electrode was placed on the eye, and touched the sclera at the outer canthus behind the lower eyelid; a reference gold-cup electrode was placed just laterally to the outer canthus, and a ground electrode, on the patient's forehead 1.5 cm above the bridge of the nose. Preoperative data of eyes with IMH were compared with fellow eyes (controls) and postoperative data of eyes with IMH. In addition, the fovea-sparing group was compared against the conventional peeling group in terms of mfERG and central perimetry data.

All patients underwent a 25-G three-port pars plana vitrectomy (Constellation, Alcon, Switzerland) with the use of a wide-angle observation system (BIOM, Oculus, Weltzer, Germany). Conventional or fovea-sparing ILM peeling was used with subsequent gas tamponade with 20% SF_6 or 15% C_3F_8. The methodology and tamponade selection have been described in our previous reports [11, 12]. The macula was directly illuminated by the endoilluminator. The course of surgery as well as the timing of ILM peeling was reviewed using video analysis. Follow-up was performed to review the state of the macula at 1-1.5 months after surgery.

Thirty-four patients (34 eyes) had a conventional ILM peeling. Their mean age was 67.5 ± 6.7 years; median duration of macular hole (IQR), 3.0 (1.0–6.0) months; median BCVA (IQR), 0.14 (0.07 – 0.25); median minimal IMH diameter, 421 µm (287 µm – 459 µm); and median maximal IMH diameter, 805 µm (520 µm – 1048 µm). The mean duration of ILM peeling in the conventional ILM peeling group was 93.7 ± 17 s. Thirty-six patients (36 eyes) had a fovea-sparing ILM peeling. Their mean age ± SD was 64.14 ± 6.5 years; median duration of macular hole (IQR), 2.0 (1.0-8.0) months; median BCVA (IQR), 0.17 (0.1 – 0.25); median minimal IMH diameter, 367 µm (261 µm – 520 µm); and median maximal IMH diameter, 654 µm (568 µm – 806 µm). The mean duration of ILM peeling in the fovea-sparing ILM peeling group was 260.3 ± 25 s.

Statistical analyses were conducted using Statistica 8.0 (StatSoft, Tulsa, OK, USA) software and spreadsheets. Nominal data are presented as absolute numbers and percentages. The normal distribution of data was tested using the Kolmogorov–Smirnov test. Mean (M), standard deviation (SD), and 95% confidence interval (CI) values were calculated for normally distributed data. Student's t test was used to compare mean values of normally distributed data. The median (interquartile range (IQR)) values were calculated for non-normally distributed data. Mann-Whitney U test was used for the comparison of two samples when the underlying distributions were not normal. Spearman or Pearson correlation coefficients were calculated to assess correlations. One-way analysis of variance (ANOVA) was used to identify the factors characterizing the relationship between the input and output variables.

Results

The mean duration of ILM peeling was 2.8 times significantly longer in the fovea-sparing ILM peeling group than in the conventional ILM peeling group (260.3 ± 25 s versus 93.7 ± 17 s, respectively), and this difference was statistically significant ($p = 0.04$). Groups were not significantly different in terms of IMH duration or BCVA. The mean BCVA in the fellow eye was 0.79 ± 0.28.

The central visual field examination was performed in 41 eyes with IMH (27 eyes in the conventional ILM peeling group and 14 eyes in the fovea-sparing ILM peeling group) and 32 fellow eyes. At baseline, the retinal sensitivity in the four visual field quadrants, overall retinal sensitivity and foveal threshold sensitivity within 10-degree area were lower in eyes with IMH than in the fellow eyes, and these differences were statistically significant (Table 1).

One-way ANOVA found a significant impact of the presence of IMH on the foveal threshold sensitivity ($F = 38.2$, $p = 0.000001$).

In addition, eyes with IMH exhibited depressed overall retinal sensitivity compared to the normal reference sensitivity for that age ($p < 0.002$) and elevated PSD ($p < 0.001$) (Table 2).

The preoperative overall light sensitivity strongly positively correlated with the preoperative BCVA ($r = 0.6$) and the postoperative BCVA irrespective of the type of ILM peeling ($r = 0.7$), and moderately negatively correlated with the minimal and maximal diameter of IMH. In a similar fashion, the foveal threshold sensitivity mildlly positively correlated with the preoperative BCVA ($r = 0.37$) and stronger correlated with the postoperative BCVA irrespective of the type of ILM peeling ($r = 0.66$), and negatively correlated with the minimal and maximal diameter of IMH. Moreover, the PSD negatively correlated with the BCVA and choriocapillaris perfusion density (CPD), and positively correlated with the minimal and maximal diameter of IMH and the duration of IMH (Table 3).

MfERG showed lower P1-retinal response density amplitudes of ring 1 (1°-2°), ring 2 (5°-7°) and ring 3 (20°-23°) at baseline in eyes with IMH than in the fellow eyes, with P1 latency in the latter eyes being the same as in the

Table 1. Retinal sensitivity in the four visual field quadrants (superior temporal, superior nasal, inferior temporal, inferior nasal), overall sensitivity and foveal threshold sensitivity in eyes with IMH before surgery and fellow eyes

Visual field region	Eyes with IMH (1)	Fellow eyes (2)	p_{1-2}
	n=41	n=32	
Superior temporal (ST)	120.8±14.3	128.4±7.7	0.004
Superior nasal (SN)	117.9±10.8	128.7±7.4	0.0001
Inferior temporal (IT)	122.7±12.0	130.6±7.6	0.001
Inferior nasal (IN)	122.2±11.1	129.9±7.7	0.007
Overall sensitivity	483.6±45.4	517.6±29.3	0.007
Foveal threshold sensitivity	22.6±9.6	33.9±2.7	0.00001

Note: n, number of eyes; M ± SD, mean ± standard deviation; p, significance of difference; IMH, idiopathic macular hole

Table 2. Mean deviation (MD), the elevation or depression of visual sensitivity in the patient's overall field compared with that of the normal age-corrected reference field, and Pattern Standard Deviation (PSD), a measurement of the degree to which the shape of the patient's measured field departs from the normal, age-corrected reference field, in eyes with IMH and fellow eyes

Показники	Eyes with IMH (1), n=41	Fellow eyes (2), n=32	p_{1-2}
MD	-0.77 (-1.65–0.31)	0.64 (-0.42-1.34)	0.002
PSD	1.44 (1.31–1.83)	1.2 (1.02-1.41)	0.001

Note: IMH, idiopathic macular hole; n, number of eyes; MD, mean deviation; p, significance of difference; PSD, pattern standard deviation

former eyes. This indicated that photoreceptor and bipolar cell functions were significantly impaired but functions of the 3rd order neuron and neuroglia were at large well-preserved (Table 4).

Interestingly, retinal response density in ring 1 correlated with almost all indices of the central visual field and factors that may effect the functions (e.g., choriocapillaris perfusion density) (Table 5, Fig. 2). The strongest correlation was observed between the foveal threshold sensitivity and retinal response density in ring 1, which reflects a defect in the photoreceptor layer in the eye with IMH.

At the 1-month follow-up, macular hole closure was seen in 63 of 71 eyes (88.73%; 30/34 eyes (88.2%) in the conventional ILM peeling group and 33/37 eyes (89.2%) in the fovea-sparing ILM peeling group). In addition, in

Table 3. Coefficients r of correlations ($p < 0.05$) between central perimetry indices and functional and morphological indices of eyes with IMH

Показник	BCVA		IMH diameter		Choriocapillaris perfusion density	IMH duration
	Before surgery	After surgery	min	max		
Foveal threshold sensitivity	0.37	0.66	-0.77	-0.42	-	-
Inferior temporal region	-	-	-	-0.63	-	-
Inferior nasal region	-		-	-0.48	-	-
Overal light sensitivity	0.6	0.7	-0.40	-0.56	-	-
PSD	-0.47		0.42	0.44	-0.26	0.36

Note: BCVA, best-corrected visual acuity; IMH, idiopathic macular hole; PSD, pattern standard deviation

Table 4. Preoperative multifocal electroretinography (mfERG) indices in eyes with idiopathic macular hole (IMH) versus fellow eyes (M±SD)

mfERG ring	Index	Eyes with IMH (n=40)	Fellow eyes (n=39)	p
Ring 1	Retinal response density (nV/deg^2)	51.15±23.84	91.88±31.82	0.000001*
	Latency (ms)	41.80±5.66	43.55±2.86	0.7
Ring 2	Retinal response density (nV/deg^2)	37.42±11.39	48.35±19.47	0.004*
	Latency (ms)	40.61±3.39	40.40±34.0	0.75
Ring 3	Retinal response density (nV/deg^2)	25.20±8.53	29.01±9.51	0.08
	Latency (ms)	37.32±5.87	39.01±2.42	0.13
Ring 4	Retinal response density (nV/deg^2)	15.47±5.14	19.34±6.39	0.006*
	Latency (ms)	40.09±3.28	39.29±1.95	0.26
Ring 5	Retinal response density (nV/deg^2)	12.42±4.14	14.32±5.10	0.08
	Latency (ms)	40.69±3.16	40.15±2.20	0.41

Note: n, number of eyes; M ± SD, mean ± standard deviation; p, significance of difference; IMH, idiopathic macular hole

Table 5. Coefficients r of correlations (p < 0.05) of multifocal electroretinography (mfERG) indices

mfERG response density	IMH duration	BCVA	Chorio-capillaris perfusion density	Foveal threshold density before/after surgery	Visual field quadrants					MD
					ST	SN	IT	IN	Overall	
Ring 1	-	0.44	0.39	0.6/0.44	0.51	0.52	0.44	0.34	0.44	0.36
Ring 2	0.32	0.28		0.32	0.43	0.45	0.44	0.40	0.45	0.44

Note: BCVA, best-corrected visual acuity; IMH, idiopathic macular hole; IN, inferior nasal; IT, inferior temporal; mfERG, multifocal electroretinography; superior nasal, SN, superior nasal; ST, superior temporal

these 63 eyes, median BCVA (IQR) improved from 0.14 (0.07–0.25) to 0.5 (0.12–1.0). After IMH closure, visual functions (BCVA, foveal threshold sensitivity, and overall and quadrant retinal sensitivity in the central 10-degree field of vision) improved, and MD and PSD decreased, but did not reach those in the fellow eye. Moreover, retinal response density improved in all rings, and retinal response density in rings 2-5, but not in ring 1 (which, more than other, reflects the state of the foveola) reached those in the fellow eyes (Tables 6 and 7).

The characteristics under examination were assessed postoperatively in 39 eyes (27 eyes in the conventional ILM peeling group and 12 eyes in the fovea-sparing ILM peeling group). Comparisons between the conventional ILM peeling group and the fovea-sparing ILM peeling group are presented in Tables 8 and 9.

We assessed whether there were differences in the functional characteristics of macular light sensitivity and mfERG between the two groups. Median BCVA (IQR) in the fovea-sparing ILM peeling group and the conventional ILM peeling group improved to 0.55 (0.35–0.7) and 0.43 (0.35–0.6), respectively. At the 1-month follow-up, the foveal threshold sensitivity within 10-degree area in the former and latter groups improved, but was 13.6% (p = 0.009) and 15% (p = 0.0001), respectively, lower than in the fellow eyes (34.5 ± 2.9 dB) (Fig. 2).

In addition, at this time point, there was no significant difference in the retinal sensitivity in the four visual field quadrants between the two groups. However, the overall retinal sensitivity in the conventional ILM peeling group improved to 499 ± 32.5 dB and was significantly (p = 0.0016) lower than in the fellow eyes (528.0 ± 25.8 dB), whereas that in the fovea-sparing ILM peeling group improved more substantially, to 509.6 ± 13.9 dB (p=0,067), and almost reached the fellow-eye value. Moreover, the PSD changed not substantially in both groups, with no significant difference between them (Table 8).

Table 6. Central visual field indices in affected eyes before surgery and after macular hole closure and versus fellow eyesм

Visual field indices		Light sensitivity (dB), M±SD			p
		Affected eyes before surgery, (n=39)	Affected eyes after surgery (n=39)	Fellow eyes (n=39)	
Visual field quadrant	ST	120.8±14.3	123.9±10.8	131.6±9.52	p_1=0.44 p_2=0.03
	SN	117.9±10.8	125.8±7.4	131.67±7.6	p_1=0.003 p_2=0.007
	IT	122.7±12.0	125.4±7.9	132.6±8.3	p_1=0.77 p_2= 0.0009
	IN	122.2±11.1	127.4±7.9	132.1±7.5	p_1=0.1 p_2= 0.016
	Overall sensitivity	483.6±45.4	502.4±31.3	528.0±25.8	p_1=0.137 p_2=0.049
	Foveal threshold sensitivity	22.6±9.6	29.7±4.11	34.5±2.92	p_1=0.0004 p_2=0.0001
MD (Median (Q_{low}-Q_{Up})		-0.77 (-1.65–0.31)	-0.6 (-0.25–0.25)	1.1 (0.56–1.4)	p_1=0.45 p_2=0.02
PSD (Median (Q_{low}-Q_{Up})		1.44 (1.31–1.83)	1.6 (1.26–1.89)	1.22 (1.09–1.34)	p_1=0.11 p_2=0.008

Note: IMH, idiopathic macular hole; IN, inferior nasal; IQR, interquartile range; IT, inferior temporal; mfERG, multifocal electroretinography; M ± SD, mean ± standard deviation; n, number of eyes; p1, significance of difference between preoperative and postoperative values; p2, significance of difference between preoperative values in affected eyes and values in fellow eyes; PSD, pattern standard deviation; SN, superior nasal; ST, superior temporal

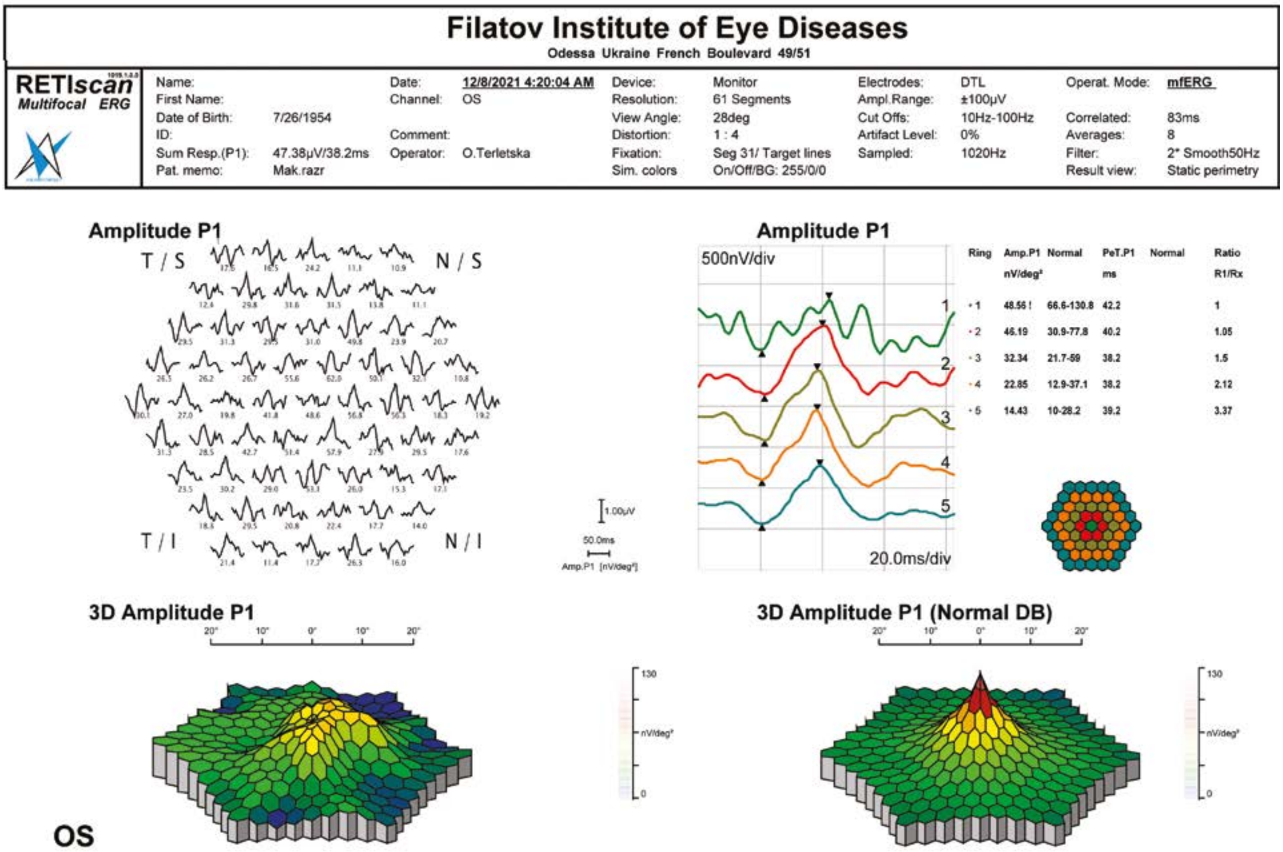

Fig. 1. Multifocal eletroretinography (mfERG) report (with 3-D response density topography plots for the presence and the absence of idiopathic macular holes shown at the right and the left, respectively)

We also analyzed changes in mfERG in both groups. The retinal response density in the conventional ILM peeling group was low before surgery but improved in all the five rings at month 1, whereas that in the fovea-sparing ILM peeling group improved in all the five rings, with the exception of ring 1, at month 1 (Table 9).

Discussion

ILM is still essential in the surgical treatment for IMH because it removes tangential and vitreomacular traction in the foveal area, stimulates glial cells, collagen secretion, basal membrane components, and inflammatory factors, thus leading to macular hole closure [13]. Nevertheless, the question of the use of ILM peeling during macular hole surgery is still controversial. Some researchers believe that ILM peeling affects the morphology and function of retinal Müller cells, which initiates a cascade of alterations, resulting in portoperative physiological and morphological abnormalities in the retina [14–16]. Therefore, fovea-sparing techniques have been increasingly used in macular hole surgery [3–5].

Some studies used mfERG and retinal light sensitivity assessed by static perimetry or microperimetry for a more subtle analysis of the functional results of macular hole surgery with conventional or fovea-sparing techniques. Reports on the macular light sensitivity after ILM peeling for macular hole closure are rather contradictory. In a study by Tadayoni and colleagues [17], spectral domain optical coherence tomography (SD-OCT) combined with scanning laser ophthalmoscopy (SLO) microperimetry was performed in 16 consecutive eyes after closure of an IMH, and the ILM was peeled in 8/16 eyes. Mean retinal sensitivity was lower and postoperative microscotomas were significantly more frequent after ILM peeling [17]. We beleive it important that, in that study, an automatic fundus eye tracking system enabled accurate projection of the stimulus, always onto the same point of the retina, which significantly improved the accuracy of the data obtained. Mitamura and Ohtsula [16] studied the relation between the dissociated optic nerve fiber layer (DONFL) appearance and ILM peeling and performed static microperimetry to explore the possible mechanisms underlying the DONFL appearance. The area of the DONFL appearance was limited to the area of ILM peeling. There was no difference in the microperimetry threshold value between the arcuate striae and the surrounding normal retina [16]. Qi and colleagues [18] evaluated the effect of ILM peeling surrounding macular holes for the function of retina by microperimetry-3(MP-3) in 44 eyes. Post-operative mean retinal sensitivity (MRS) in the selected normal retinal area increased in 37 patients but decreased in 7 patients. Patients with decreased MRS were significantly older than other patients.

Table 7. Multifocal electroretinography (mfERG) indices in affected eyes before surgery and after macular hole closure and versus fellow eyes

mfERG ring	Indices	Affected eyes before surgery, (n=39)	Affected eyes after surgery, (n=39)	Fellow eyes, (n=39)	p
Ring 1	Retinal response density (nV/deg^2)	56.7±24.0	68.7±27.6	92.7±29.0	p_1=0.07 p_2=0.007
	Latency (ms)	42.0±5.6	42.9±5.1	44.1±3.0	p_1=0.5 p_2=0.5
Ring 2	Retinal response density (nV/deg^2)	37.5±11.4	43.9±14.5	47.4±13.6	p_1=0.05 p_2=0.39
	Latency (ms)	40.6±3.4	40.1±3.2	40.8±3.27	p_1=0.5 p_2=0.77
Ring 3	Retinal response density (nV/deg^2)	25.3±8.6	32.4±9.3	33.5±8.8	p_1=0.001 p_2=0.69
	Latency (ms)	37.3±5.9	34.4±10.7	36.2±8.7	p_1=0.18 p_2=0.49
Ring 4	Retinal response density (nV/deg^2)	15.4±5.2	17.6±7.1	18.6±6.0	p_1=0.32 p_2=0.51
	Latency (ms)	40.1±3.3	40.3±3.1	39.9±2.6	p_1=0.8 p_2=0.63
Ring 5	Retinal response density (nV/deg^2)	12.4±4.1	13.2±6.1	14.0±5.0	p_1=0.6 p_2=0.5
	Latency (ms)	40.7±3.1	40.5±3.1	40.3±2.4	p_1=0.8 p_2=0.56

Note: IMH, idiopathic macular hole; mfERG, multifocal electroretinography; M ± SD, mean ± standard deviation; n, number of eyes; p1, significance of difference between preoperative and postoperative values; p2, significance of difference between preoperative values in affected eyes and values in fellow eyes

Ten-degree static perimetry was used in the current study. We found overall light sensitivity and foveolar sensitivity to be decreased, and PSD to be increased preoperatively in the affected eyes compared to fellow eyes. After macular hole closure, these characteristics and retinal sensitivity in the superior temporal and inferior temporal quadrants improved in the affected eyes, but did not reach the levels in fellow eyes. The foveal threshold sensitivity in the affected eyes was found to be strongly negatively correlated with minimal diameter of IMH ($r = -0.77$; $p < 0.05$) and positively correlated with the preoperative BCVA ($r = 0.66$; $p < 0.05$). In addition, at the 1-month follow-up, the foveal threshold sensitivity in the conventional ILM peeling group and the fovea-

Table 8. Mean deviation (MD) and Pattern Standard Deviation (PSD) before and after IMH vitrectomy with conventional versus fovea-sparing ILM peeling

Visual field index	Before or after surgery	Conventional ILM peeling		Fovea-sparing ILM peeling		p2
		Median (Q-Q)	p1	Median (Q-Q)	p1	
MD	Before surgery	-0.67 ((-1.96)–0.31)	0.3	-0.88 ((-1.65)–0.6)	0.3	0.95
	After surgery	-0.85 ((-2.65)–(-0.4))		-0.50 ((-2.39)–0.9)		0.4
PSD	Before surgery	1.72 (1.32–1.83)	0.2	1.35 (1.20–2.19)	0.3	0.5
	After surgery	1.68 (1.44–1.85)		1.43 (1.20–1.8)		0.1

Note: ILM, internal limiting membrane; IMH, idiopathic macular hole; IQR, interquartile range; MD, mean deviation; p1, significance of difference between preoperative and postoperative values; p2, significance of difference between the conventional ILM peeling group and fovea-sparing ILM peeling group; PSD, pattern standard deviation

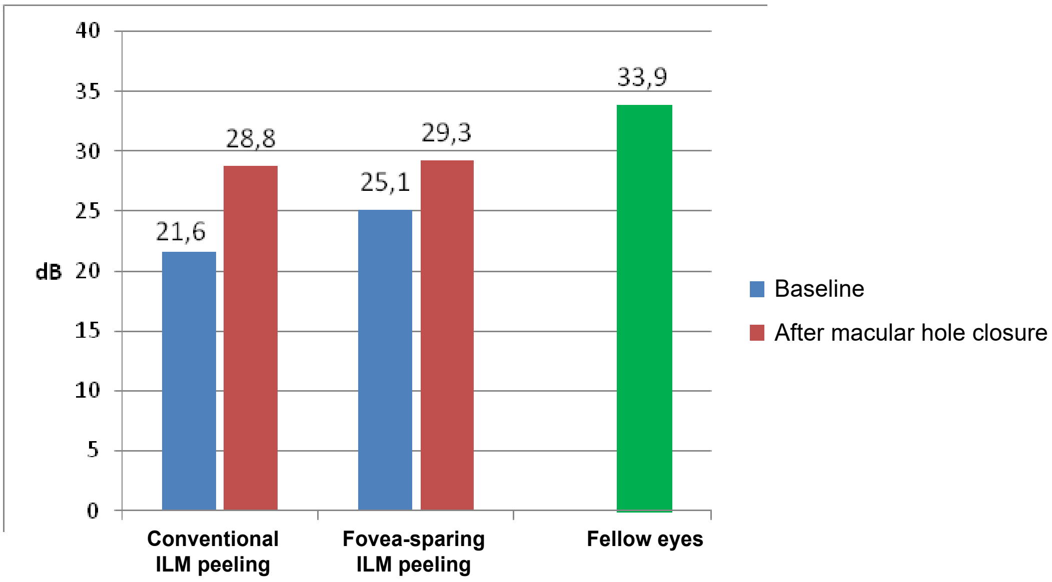

Fig. 2. Foveal threshold sensitivity in affected eyes before and after macula hole surgery with conventional versus fovea-sparing internal limiying membrane (ILM) peeling and in fellow eyes

sparing ILM peeling group improved, but was 15% (p = 0.0001) and 13.6% (p = 0.009), respectively, lower than in fellow eyes. This finding is somewhat different from that of Qi and colleagues [18]: compared with the fellow eyes without macular holes, the eyes that underwent surgery had significantly lower MRS in selected 28 points before surgery, and had an improvement in MRS reaching a similar level 4 after surgery. Retinal damage from ICG dye toxicity has been reported through in vitro and in vivo studies [19]. With regard to the period of restoration of retinal sensitivity, Jun and Kong [20] reported that, in Area 3, where both indocyanine green (ICG) staining and ILM peeling were performed, the MRS value significantly decreased three months after surgery compared with

Table 9. Multifocal electroretinography (mfERG) response density (nV/deg2) and latency (ms) before surgery and after macular hole closure (M±SD)

mfERG ring	Index	Conventional ILM peeling (n=25)		p1-2	Fovea-sparing ILM peeling (n=14)		p3-4
		Before surgery	After macular hole closure		Before surgery	After macular hole closure	
		1	2		3	4	
Ring 1	Response density	56.3±25.2	76.1±28.6 ↑	0.02	54.3±21.7	58.5±29.1	0.7
	Latency	41.7±6.0	41.7±5.7	0.9	42.7±5.0	44.8±3.5	0.3
Ring 2	Response density	37.6±11.9	44.8±17.4 ↑	0.1	37.5±11.0	42.6±10.0 ↑	0.3
	Latency	41.3±2.8	40.1±3.6	0.3	39.5±4.1	40.1±2.7	0.7
Ring 3	Response density	25.5±8.8	33.9±10.6 ↑	0.01	24.8±8.4	35.3±7.7 ↑	0.005
	Latency	37.2±4.7	33.8 ±10.3	0.2	39.1±1.3	33.7±8.7	0.18
Ring 4	Response density	15.2±5.3	17.9±7.9 ↑	0.2	15.7±5.0	17.3±6.0 ↑	0.5
	Latency	40.4±3.5	40.1±3.9	0.8	39.7±2.9	39.7±1.5	0.99
Ring 5	Response density	12.6±4.6	13.7±7.9 ↑	0.6	12.2±3.3	12.4±4.7 ↑	0.9
	Latency	40.9±3.2	41.0±3.7	0.9	40.6±3.1	39.8±1.6	0.5

Note: ILM, internal limiting membrane; M ± SD, mean ± standard deviation; mfERG, multifocal electroretinography; p, significance of difference baseline. However, the statistical significance was lost at six months postoperatively (baseline vs. follow-up: 26.63 ± 1.80 vs. 25.52 ± 1.95 dB, p = 0.059). We found that, in the fovea-sparing ILM peeling group, the overall retinal sensitivity in the affected eyes reached the levels in fellow eyes after surgery, which indicated better preservation of the parafoveal retina in these eyes compared to the affected eyes in the conventional ILM peeling group.

mfERG response is due to the outer retina cells, i.e., photoreceptors, ON and OFF bipolar cells and Müller cells [21]. In the presence of a full-thickness macular hole, electrophysiological dysfunction involves not only the foveola, but also the adjacent retina. Reduced retinal response density in ring 1 corresponds to the presence of a macular hole, and reduced retinal response density in ring 2 corresponds to the presence of macular edema and some delamination of macular hole margins [22]. We obtained similar results to the above findings, with a significantly reduced retinal response density in mfERG rings 1 (1°–2°) and 2 (3°–5°; approximately 1200 μm). That is, the diameter of ring 1 is the same as the mean minimal IMH diameter, and the diameter of ring 2 is the same as the mean maximal IMH diameter. In addition, we found a reduced retinal response density in ring 4. Interestingly, we found no abnormality in latency in any of the rings, which reflects the absence of functional abnormalities in retinal ganglion and neuroglial cells.

A combination of mfERG, retinal threshold sensitivity and OCTA studies allowed findings of some correlations between morphological and functional changes. The retinal response density in mfERG rings 1 and 2 correlated with the BCVA and foveal threshold sensitivity, demonstrating relationships of retinal functional characteristics. The choriocapillaris perfusion density was mildly but significantly correlated with the retinal response density in mfERG ring 1. That is, the preservation of well-functioning choriocapillaris, a major source of oxygen and nutrition to the photoreceptor layer, supports the electrophysiological response to stimuli. Yip and colleagues [23] reported on correlations of mfERG indices with morphological indices like minimal diameter of IMH. No generalized mfERG and OCTA study on IMH with the correlation analysis of mfERG and OCTA indices has been conducted [24].

We found that, at 1 month after surgery with macular hole closure, in the study sample, the retinal response density in ring 2, but not in ring 1, significantly improved and reached that in fellow eyes. In addition, the retinal response density in the conventional ILM peeling group was low before surgery but improved in all the five rings at month 1, whereas that in the fovea-sparing ILM peeling group improved in all the five rings, with the exception of ring 1 (the central ring), at month 1. It is likely associated with long ILM manipulation and, correspondingly, long illumination of the macula and possible resulting phototoxic effect [25]. In the current study, in both groups there was no change in mfERG latency in the affected eyes compared to fellow eyes. Moreover, in our study, fellow eyes with an intact macula were considered as controls. A study by Tuzson and colleagues [26] demonstrated that the mfERG indices in fellow eyes of patients with IMH were distinct from those in healthy eyes. The results of their statistical analysis pointed out significant differences for the ring ratios R1/R2, R1/R3, and R1/R4 between the fellow eyes of the patients who will have macular hole formation compared with the patients in whom one eye will remain intact. Their discriminant analysis showed that these three ring ratios together could be used as good predictors of any new case based on the mfERG data of the fellow eye.

It should be noted that reparation of the intraretinal neural network seems to continue up to one year after surgical closure of macular holes, and restoration of mfERG and central retinal perimetry after surgical closure of macular holes may require a long time [17, 27].

Conclusion

In eyes with IMH, characteristics of perimetry in the central 10-degree field of vision and mfERG undergo changes, with their forveal threshold sensitivity and parafoveal threshold sensitivity substantially reduced, and their retinal response density in mfERG rings 1 and 2 significantly reduced compared to those in fellow eyes, thus indicating a defect in the retinal photoreceptor layer. This was confirmed by the fact that the foveal threshold sensitivity strongly correlated with the minimal diameter of the macular hole, retinal response density in mfERG ring 1, and preoperative and postoperative BCVA. After IMH closure, functional indices substantially improved in both conventional ILM peeling and fovea-sparing ILM peeling groups. An advantage of fovea-sparing ILM peeling a macular hole surgery was that it resulted in a significantly greater improvement in the overall light sensitivity in the central field of vision compared to conventional ILM peeling.

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Disclosures

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Abbreviations: *IMH, idiopathic macular hole; ILM, internal limiting membrane; ERG, electroretinogram; BCVA, best-corrected visual acuity; RR, retinal response*