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Predictive value of pattern VEP, pattern ERG and hole size in macular hole surgery

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Abstract ● Objective: To describe pattern-reversal visual evoked response (PRVEP) and pattern electroretinogram (PERG) parameters in eyes with macular hole and their value for predicting postoperative visual outcome.

● Methods: Prospectively we studied 27 eyes (27 patients) with a full-thickness macular hole. Preoperatively the hole and rim were measured and the PRVEP and PERG were recorded. The preoperative parameters were correlated with postoperative visual outcome.

● Results: The macular hole was closed in 26 of 27 eyes. Sixteen eyes (59%) had an increase in visual acuity (VA) of two lines or more, 10 eyes (37%) remained within one line of preoperative VA and 1 eye (4%) had

a decrease in VA of two lines. Duration of symptoms was negatively correlated with preoperative VA ($R=-0.547$, $P=0.0038$) and postoperative VA ($R=-0.519$, $P=0.0065$) and positively correlated with hole area ($R=0.533$, $P=0.0061$) and rim area ($R=0.633$, $P=0.0009$). Only the PRVEP P100 latency of the 10' check size and the PERG N35 latency were significantly associated with visual outcome ($P=0.022$ and $P=0.042$ respectively). ● Conclusions: There was no association of either hole or rim size with postoperative visual outcome. Preoperative electrophysiology, however, is useful as a prognostic tool. Utilization is limited to the use of latency parameters of the response and is dependent on the check size of the stimulus.

Introduction

Vitreous surgery has become very successful in anatomically closing a full-thickness macular hole. Most patients postoperatively experience a decrease of the central scotoma and reduction of the metamorphopsia in successful cases. Postoperative visual outcome, however, varies to a greater extent. Therefore, preoperative objective methods that may predict postoperative visual acuity are potentially very useful for patient information, expectations and selection.

Both the pattern electroretinogram (PERG) and the pattern-reversal evoked potential (PRVEP) can be utilized as an objective measure of macular function. Sokol [21] in 1971 reported that both macular and non-macular cones contribute to the PERG. The PRVEP recording electrodes

are placed over the occipital cortex, an area that is known to receive macular projections; therefore, only macular cones are responsible for the electrical response if recorded with small check sizes and small stimulus fields. Consequently, Sokol showed the absence of the PRVEP in a patient with macular degeneration. Visual loss in patients with full-thickness macular holes has been attributed to loss of neurosensory retinal tissue and to the effect of the cuff of surrounding subretinal fluid in the pericentral macular area [19]. Kato et al. [10] found a reduced PRVEP amplitude in patients with idiopathic macular holes. In their study the PRVEP latencies showed no statistically significant difference between affected eyes and fellow eyes. Previous studies from our institute [2, 3] revealed that the PRVEP is very sensitive in detecting early macular pathologic conditions. In patients with macular

holes and in epiretinal membranes the PRVEP latencies were prolonged and the amplitude was reduced. Remarkably even in the fellow eye, with normal visual acuity, subnormal PRVEP amplitudes were found. Bass et al. [1] found significant VEP delays in 45% of patients with macular disease. Smith et al. [20] investigated the PERG and the PRVEP and for both modalities found a reduction of amplitude in macular hole patients. Johnson et al. [8] reported that eyes with lamellar holes had a normal P100 latency, but eyes with macular cysts and full-thickness macular holes had a prolonged P100 latency. Junghardt et al. [9] compared the PERG, the PRVEP and psychophysical functions in maculopathy and found that the strongest system (best correlations) consisted of visual acuity, static perimetry and PRVEP.

The goal of surgical treatment is to enhance vision by inducing a resolution of the subretinal fluid cuff. Although many studies have been published about the technique and results of macular hole surgery, little work has been done towards establishing the value of preoperative electrophysiology in obtaining acceptance criteria and predicting visual outcome. Mehta et al. [15] found that the preoperatively recorded PRVEP could objectively assess the function of the underlying macula in patients with macular gliosis and that the PRVEP was helpful in determining which patient would most likely benefit from vitrectomy with removal of the epiretinal membrane. The obtained PRVEP criteria were significantly associated with postoperative visual improvement. This was confirmed by the study [22] we carried out in a larger group of patients ($n=58$). In these patients the N80 PRVEP latency was significantly associated ($P<0.01$) with visual outcome. Accordingly, we decided to include preoperative electrophysiology and digital photography with measurement of macular hole size in our clinical protocol for the management of patients with full-thickness macular hole. The postoperative visual acuity was compared with preoperative measured parameters in order to find out whether these parameters were associated with visual outcome.

Methods

The initial study group consisted of 31 patients (31 eyes). We excluded four eyes: one developed a retinal detachment, one had extensive age-related macular drusen and two were operated on twice before the macular hole closed. The final study group consisted of 27 patients – 19 women and 8 men with a mean age 68.2 years – with stage III and IV full-thickness macular hole according to the Gass classification [4].

The follow-up period ranged from 2 to 9 months (mean 4.2 months, SD 2.0 months). Follow-up visual acuity was compared with preoperative visual acuity for all eyes and categorized into three groups:

1. Better: improved two lines or more from preoperative visual acuity
2. Same: within one line of preoperative visual acuity
3. Worse: decreased by two lines or more

We performed a routine ophthalmological examination, including best corrected visual acuity measurement using the Snellen chart, Amsler grid testing, slit-beam testing, slit-lamp examination and ophthalmoscopy. Hole and rim size were measured and areas calculated using the Topcon digital imaging system (ImageNet version 2.11.6, Topcon, Tokyo). The red-free images were acquired using a magnification angle of 35 deg. Contrast enhancement by image processing was applied in the macular region. The true size of the macular hole and rim was obtained by applying the method developed by Littmann [14]; we used refractive ametropia and the corneal radius to correct the data for magnification errors.

Recording and analysis of the PRVEP and PERG

PRVEP recording was performed, with pupils undilated, 1 day prior to surgery. The eyes were optimally refracted for viewing distance. For the PRVEP testing the active electrode was placed at position Oz, 2.5 cm above theinion, the referring electrode at T3, on the mastoid process.

Grounding was accomplished with an electrode on the earlobe (A1). Impedance, measured at 20 Hz, was kept below 5 k Ω .

The ambient illumination of the room was not standardized, though kept at mesopic level. PRVEPs were recorded monocularly, using a reversing checkerboard generated by a galvanometer-mirror system (Medilog VPS-20). The stimulus consisted of patterns of 34', 17' and 10' (min of arc). Field size was 9 deg, check contrast 80%, mean luminance of stimulus 40 cd/m². The ensemble average was obtained from 64 single responses of 500 ms duration; reversal rate was 2 Hz. The PRVEP latencies were measured as the time difference between the stimulus reversal and the first negative trough (N80) and the major positive peak (P100) of the response, respectively. The amplitude of the PRVEP was calculated from the difference (in microvolts) between the N80 trough and the P100 peak. This amplitude was termed as the "P100 amplitude". The electroretinogram was recorded monocularly with noncorneal Ag–AgCl skin electrodes [13]. To obtain low electrode impedance and reliable contact the skin was first cleaned with alcohol. The active electrode was placed on the lower lid of the eye under test. The reference electrode was put on the forehead, and an ear-clip ground electrode was placed on the contralateral earlobe. Electrode impedance was monitored and kept below 5 k Ω . The stimulus was generated with the same stimulator as described for the PRVEP protocol. The field size was adjusted to 18 deg and the check size to 34'. The resulting PERG was calculated by averaging 200 successive sweeps of 250 ms duration. Prior to the acquisition the patient was instructed to maintain fixation and to avoid blinking. If necessary the averaging process could be stopped temporarily in order to let the patient blink and take up the fixation.

The first negative peak of the PERG was labeled "N35". The N35 latency of the PERG was measured as the time difference between stimulus reversal and location of the N35 trough. In the same manner, latencies of the positive P50 and the negative N95 peaks were measured. The PERG amplitude was measured from the trough of the early deflection at around 35 ms (N35) to the following positive peak around 50 ms (P50).

Statistical methods

Statistical analysis was performed with the SAS statistical analysis software package (SAS Institute, Cary, NC, USA). Comparisons of the means of the PRVEP parameters in the groups with "better" and "same-worse" visual outcome were performed with a Student's *t*-test for normally distributed data and a Wilcoxon rank-sum test for the data that were not normally distributed. Spearman's correlation coefficient was calculated to measure the association between variables.

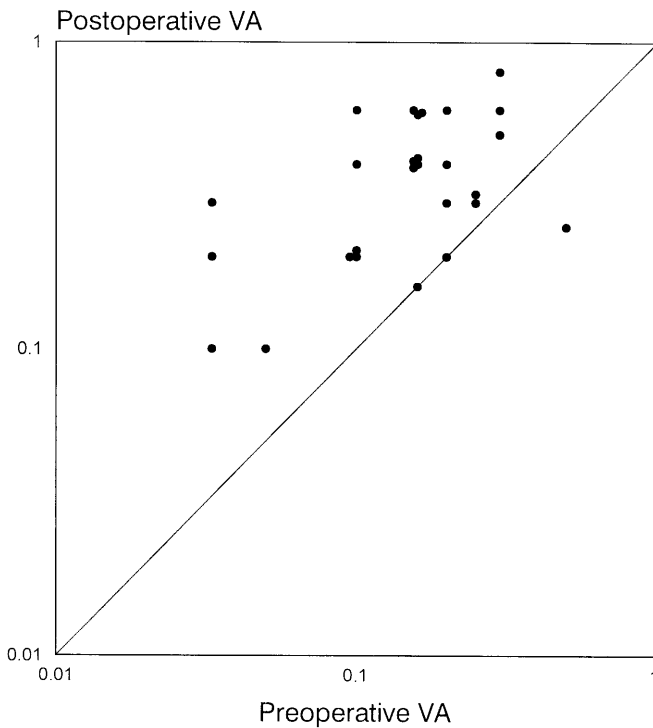


Fig. 1 Distribution of preoperative and postoperative visual acuity (VA) on a logarithmic scale

The association between electrophysiologic findings and postoperative visual outcome was estimated by forming contingency tables. Fisher's exact test was used for testing the null hypothesis that the variables under test and visual outcome were independent.

All eyes were operated on by standard three-port vitrectomy, inducing a posterior vitreous detachment, placing a drop of autologous platelet concentrate according to Gaudric et al. [5] on the posterior pole and gas tamponade with a gas-air mixture of 16% C_3F_8 . No efforts were undertaken to actively remove the internal limiting membrane. Prone positioning for 2 weeks after operation was advised.

Results

The macular holes were closed in 26 of 27 uncomplicated cases. Mean preoperative visual acuity was 0.16, mean postoperative visual acuity, 0.4. Distribution of preoperative and postoperative visual acuity is shown in Fig. 1.

Of the 27 patients, 16 (59%) had an increase in visual acuity of two lines or more, in 10 (37%) visual acuity remained within one line of preoperative visual acuity, and 1 (4%) had a decrease in visual acuity of more than two lines.

The mean area of the macular hole was 0.17 mm^2 (SD 0.10, range 0.03–0.47 mm^2), and the mean area of the surrounding rim was 0.53 mm^2 (SD 0.32, range 0.07–1.37 mm^2). In the total group we found that the area of the macular hole was significantly correlated with duration of symptoms (Spearman correlation $R=0.533$,

Table 1. Means and standard deviations of visual acuity (VA) hole and rim size and PRVEP and PERG parameters in eyes with a full-thickness macular hole (FTH; $n=27$) and the healthy contralateral eye ($n=10$). In the FTH group the PRVEP was recordable in 93% ($n=25$), 93% ($n=25$) and 74% ($n=20$) of the eyes for check sizes of 34', 17' and 10' respectively. The PERG (34' check size) was recordable in 74% ($n=20$) of cases. n.r. Not relevant

Parameter	FTH	Contralateral eye (VA=>0.8)
Preoperative VA	0.16 (0.1)	0.8 (0.1)
Postoperative VA	0.4 (0.2)	0.9 (0.1)
Hole area (mm^2)	0.170 (0.10)	
Rim area (mm^2)	0.532 (0.32)	
Duration (months)	5.5 (2.4)	n.r.
Follow-up (months)	4.2 (2.0)	n.r.
PRVEP		
N80 latency (ms)		
10 ^a	96.9 (7.3)	87.1 (7.4)
17'	89.4 (6.8)	83.7 (7.3)
34'	80.0 (7.3)	78.4 (8.7)
P100 latency (ms)		
10'	122.8 (8.5)	112.6 (8.1)
17'	118.3 (8.8)	108.4 (7.8)
34'	107.8 (9.6)	107.1 (10.9)
P100 amplitude (uV)		
10'	4.3 (2.6)	5.4 (3.3)
17'	4.8 (2.7)	6.1 (2.5)
34'	5.3 (2.7)	6.2 (3.1)
PERG (34')		
N35 latency (ms)	29.6 (5.0)	28.0 (3.6)
P50 latency	56.0 (4.0)	54.3 (2.8)
P50 amplitude (uV)	1.8 (0.7)	2.1 (0.9)

^a Check size

$P=0.0061$). The measured rim area was closely correlated even more with duration: $R=0.633$, $P=0.0009$). Duration was negatively correlated with preoperative visual acuity ($R=-0.547$, $P=0.0038$) and with postoperative visual acuity ($R=-0.519$, $P=0.0065$). We found no significant relation between either hole area or rim area and postoperative visual acuity. The mean latency and amplitude values of the PRVEP and the PERG are shown in Table 1.

As a reference we include the electrophysiology data of the healthy contralateral eye in Table 1. In the macular hole group the PRVEP was recordable in 93% of eyes for both the 34' and the 17' check size, and in 74% of eyes for the 10' check size. The PERG was recordable in 74% of eyes (34' check size).

A typical example of a PRVEP and PERG recording of an eye with a full-thickness macular hole and the contralateral eye is shown in Figs. 2–4.

The latencies of the PRVEP increase with reduction of the check size while the amplitude reduces for the smaller check sizes. In Table 2 we divide the patients into two groups according to their visual outcome. There was no difference in preoperative visual acuity between the patients who improved two lines or more and those who remained within one line of preoperative visual acuity.

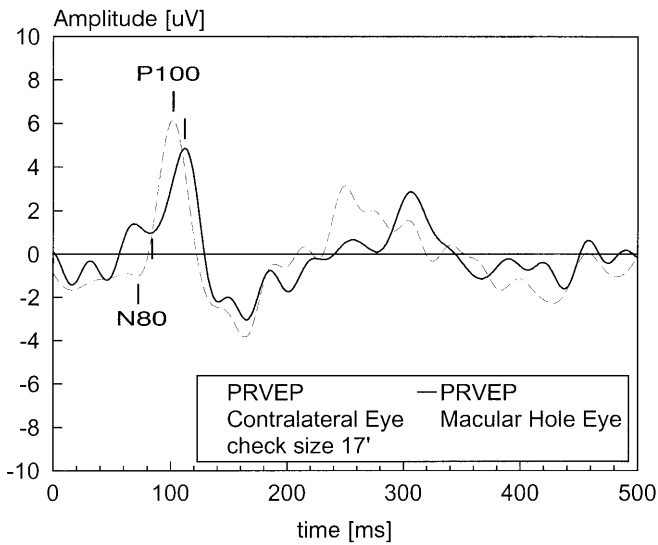


Fig. 2 Typical PRVEP response of an eye with macular hole (*solid line*) and the contralateral eye (*dashed line*). Stimulus check size 17'. Latency of the PRVEP response of the macular hole eye is prolonged and the amplitude reduced compared with the contralateral eye. Contralateral eye: N80 latency 72 ms, P100 latency 103 ms, P100 amplitude 7.2 μV ; macular hole eye: N80 latency 83 ms, P100 latency 111 ms, P100 amplitude 3.8 μV

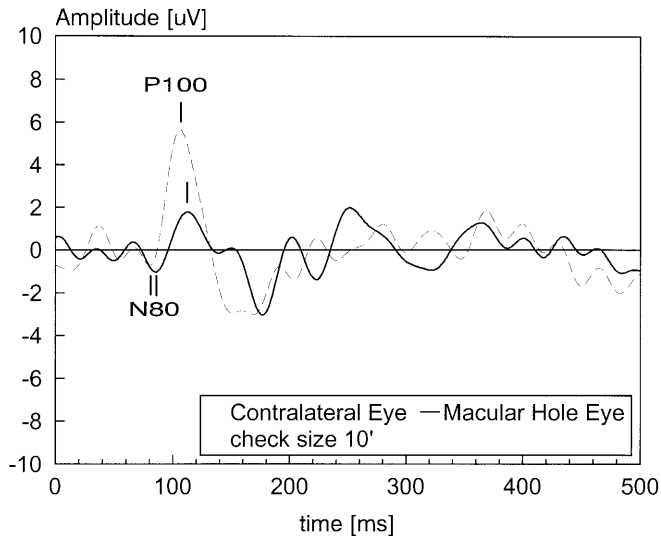


Fig. 3 Same patient as in Fig. 2. Stimulus check size 10'. Macular hole (*solid line*) and contralateral eye (*dashed line*). Latency of the PRVEP response of the macular hole eye is prolonged, and the amplitude is reduced compared with the contralateral eye. Contralateral eye: N80 latency 82 ms, P100 latency 107 ms, P100 amplitude 6.4 μV ; macular hole eye: N80 latency 86 ms, P100 latency 114 ms, P100 amplitude 2.8 μV

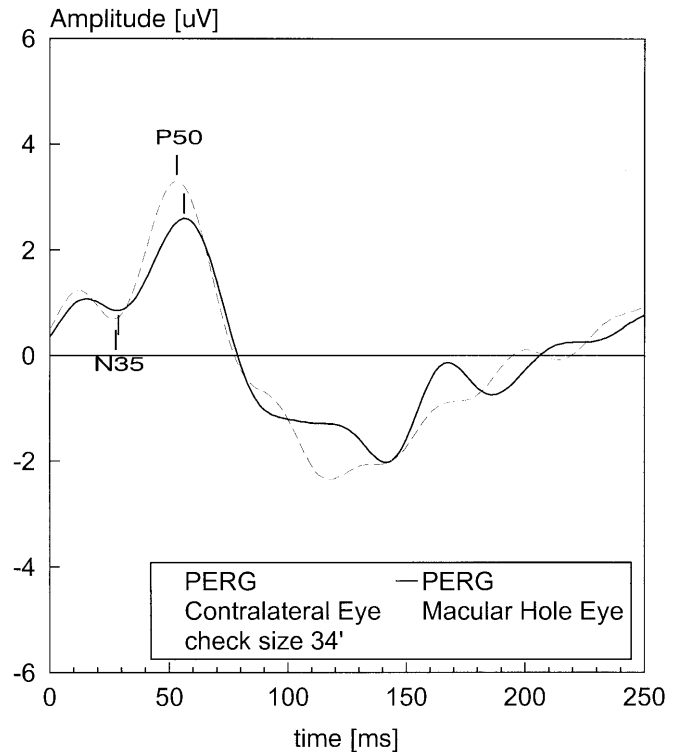


Fig. 4 PERG response of patient in Figs. 2 and 3. Stimulus check size 34'. Macular hole eye (*solid line*) and contralateral eye (*dashed line*). The latency of the PERG response of the macular hole eye has a small delay with respect to the contralateral eye. PERG amplitude of the macular hole eye is reduced. Contralateral eye: N35 latency 28 ms, P50 latency 54 ms, P50 amplitude 2.6 μV ; macular hole eye: N35 latency 30 ms, P50 latency 57 ms, P50 amplitude 1.7 μV

In patients with “same-worse” outcome we found a significant prolongation of the P100 latency of the 10' check size PRVEP compared with the “better” outcome group (P100 latency 128.8 ms vs 120.2 ms, $P=0.020$).

This suggests a prognostic value of the PRVEP latency for visual acuity outcome. Other differences in PRVEP latencies and amplitudes were not significant. The latency of the N35 trough of the PERG was significantly prolonged for the “same-worse” outcome group in comparison with the “better” outcome group (32.2 vs 27.4; $P=0.043$).

In PRVEP and PERG recordings the amplitude and latencies of the response as well as the recordability yield information about macular function. To combine both aspects we arbitrarily established a criterion for both PRVEP and PERG abnormality. The criterion was derived from PRVEP P100 latency and PERG N35 latency, because these parameters showed significant differences between the groups (Table 2). The PRVEP was assumed to be abnormal when the latency of the P100 was more than 128 ms or when the PRVEP was not recordable. The PERG was assumed to be abnormal when N35 latency exceeded the 30 ms limit or when the PERG was not

Table 2. Means and standard deviations of VA, PRVEP, PERG and size parameters. Subjects divided into two categories by visual outcome. In the "better" outcome group the PRVEP was recordable in 94%, 94% and 88% of the eyes for checksizes of 34', 17' and 10' respectively. The PERG was recordable in 63% of the eyes. In the "same-worse" outcome group the PRVEP was recordable in 91%, 91% and 60% of the eyes of checksizes of 34', 17' and 10' respectively. The PERG (34') was recordable in 82% of the eyes

Parameter	Visual outcome	
	"Better" (n=16)	"Same-worse" (n=11)
Age	67.2 (6.2)	69.6 (5.2)
VA preoperative	0.16 (0.1)	0.16 (0.1)
VA postoperative	0.5 (0.16)	0.2 (0.1)
Hole area (mm ²)	0.16 (0.07)	0.19 (0.14)
Rim area (mm ²)	0.55 (0.37)	0.503 (0.22)
Duration (months)	5.3 (2.6)	5.8 (2.2)
Follow-up (months)	4.6 (2.3)	3.6 (1.2)
PRVEP		
N80 latency (ms)		
10'	94.9 (7.3)	101.5 (5.4)
17'	87.6 (7.4)	92.1 (4.8)
34'	79.0 (6.9)	81.6 (8.1)
P100 latency		
10'	120.2 (8.1)*	128.8 (6.7)*
17'	117.5 (9.5)	119.5 (8.0)
34'	106.7 (9.2)	109.4 (10.4)
P100 amplitude (uV)		
10'	4.2 (2.7)	4.6 (2.5)
17'	4.7 (2.6)	5.0 (3.1)
34'	5.1 (2.6)	5.5 (2.9)
PERG (34')		
N35 latency (ms)	27.4 (4.0)*	32.2 (4.9)*
P50 latency	55.9 (3.3)	56.2 (4.9)
P50 amplitude (uV)	1.9 (0.7)	1.7 (0.8)

*Significant difference between the groups (Wilcoxon rank-sum test: $P < 0.05$)

recordable. Applying these criteria and associating them with visual outcome, 12 (80%) of the 15 patients with a normal PRVEP recording (P100) had a postoperative visual acuity increase of two lines or more; 8 (67%) of the 12 with a preoperative delayed or non-recordable PRVEP showed no increase in visual acuity (Table 3). For the PERG we found that 8 of 9 patients (89%) with a normal PERG visual acuity improved by operation, whereas 10 of 18 patients (56%) with an abnormal PERG did not experience an increase in visual acuity after surgery (Table 4).

Discussion

The pathogenesis of macular holes is not yet completely understood. Gass [4] proposed tangential traction as the main mechanism leading to a foveal dehiscence in the earliest stage. Kishi et al. [12] proposed intraretinal splitting by elevation of the anterior layer of the retina, possibly by tangential traction, as the first step in macular hole

Table 3. Relation of PRVEP findings and visual outcome

Visual outcome	PRVEP abnormal (P100>128 ms or non recordable)	PRVEP normal	Total
"Better"	4	12	16
"Same/worse"	8	3	11
Total	12	15	27

Statistics for 2X2 contingency table: Fisher's exact test $p=0.022$

Table 4. Relation of PERG findings and visual outcome

Visual outcome	PERG abnormal (N35 latency =>30 ms or non recordable)	PERG normal	Total
"Better"	8	8	16
"Same/worse"	10	1	11
Total	18	9	27

Statistics for 2x2 contingency table: Fisher's exact test $P=0.042$

development. Once a stage I macular hole is present its further course is dependent on the development of a posterior vitreous detachment. If a posterior vitreous detachment develops, the stage I hole will not develop further and will possibly even reverse with increasing visual acuity. Untreated, a stage II hole will, in 84% of cases, enlarge, concomitant with a two-line drop in visual acuity in 68% of cases [6].

Early recognition and possibly treatment at stage II are therefore vital. However, most patients, who have a healthy contralateral eye only present to the ophthalmologist once the visual complaints are quite significant, and a stage III or IV hole is already present in many cases.

Closing a stage III or IV macular hole with flattening of the surrounding rim by vitrectomy led to an increase in visual acuity of two lines or more in 59% of the patients in our study. Visual acuity, however, remains a subjective test, and the timing of establishing the final visual status influences the result because of the reparative process at the macula and progression of nuclear opacity after a vitrectomy with gas tamponade. From the scatterplot (Fig. 1) we can see that there is only a weak correlation between pre- and postoperative visual acuity ($R = 0.433$, $P = 0.024$). This correlation is comparable to the findings of Smiddy et al. [19]. They evaluated the utility of the potential acuity meter (PAM) and the laser interferometer (LI) to predict visual acuity after macular hole surgery. In 18 patients they found that the LI prediction as accurate in 70% of cases, and the PAM in 64% of the cases. In our study however, despite the weak correlation, we found no difference in preoperative visual acuity between the patients that improved two lines or more ("better" group)

and the patients that did not improve ("same-worse" group). This means that in our group the preoperative visual acuity has no value in predicting whether the patient will benefit by surgery.

Sjaarda et al. [17] stated that in eyes with full-thickness macular holes the visual loss is caused by the absence of retinal function in the area of the neurosensory defect, as well as reduction in retinal function in the surrounding area of neurosensory retinal detachment (rim). They performed microperimetry and demonstrated that the absolute scotoma corresponded to the neurosensory defect [18]. They also found that the size of the scotoma, determined by perimetry, is correlated with the patient's visual acuity as well as the duration of symptoms. We photographically measured the areas of the hole and the surrounding rim. Surprisingly, we found no correlation between either hole area or rim area and preoperative visual acuity. Both rim area ($R=0.633$, $P=0.0009$) and hole area ($R=0.533$, $P=0.006$) were correlated with duration.

The calculated areas were not correlated with postoperative visual acuity. In the "same-worse" group the mean hole area was slightly higher, though not significantly so. Accordingly, our conclusion is that the areas of the macular hole and of the rim do not have a prognostic value for visual outcome in patients such as ours.

Electrophysiology in relation to visual outcome

Kato et al. [10] investigated PRVEPs in 15 patients with idiopathic macular hole and found that the amplitude reduction and interocular delay of the PRVEP had no relation to the size of the macular hole or visual acuity. They concluded that estimation of the extent of the macular pathology from the VEP changes may be difficult because the PRVEP changes induced by a macular hole have a wide interindividual variation and have no relation to the size of the hole. Bemelmans et al. [3] proved in a larger group of patients (66) that the PRVEP latency is prolonged and the amplitude is reduced in macular hole, thereby indicating that the PRVEP could be applied to objectively measure the extent of the neurosen-

sory defect and may be capable of predicting visual outcome after macular hole surgery. As far as we know, no other studies have been published on the preoperative PRVEP and PERG in relation to postoperative visual outcome. In our group of patients with stage III and IV macular hole the P100 latency of response of the 10' check size stimulus was associated with postoperative visual outcome. The number of patients in whom reliable PRVEP responses could be recorded increases when larger check sizes are used. Katsumi et al. [11] found that the PRVEP was still recordable with a central scotoma of 4.0–5.0 deg, suggesting that the peripheral retina is responsible for the PRVEP recorded with larger check sizes. They also found that with a large central scotoma the PRVEP, though with much reduced amplitude, was still recordable with smaller check sizes. On the other hand, it is known that the utilization of PRVEP amplitude in measuring macular function is hampered by the large interindividual variability [2, 3]. Similar to the findings for the PRVEP are those for the PERG in predicting visual outcome. There is a small reduction in mean amplitude in the "same-worse" group (mean 1.9, SD 0.7 vs mean 1.7, SD 0.8). Probably because of the large spread in PERG amplitudes and the limited number of subjects the means are not significantly different. Holopigian et al. [7] found that the variability of the PERG amplitude within a single stimulus condition ranged from 30% to 67% of the mean value, thereby limiting the utilization of the amplitude in clinical practice. The latency of the P50 peak of the PERG is nearly the same in the two groups. In contrast, the latency of the N35 trough differs significantly between the groups, and the N35 criteria for latency and recordability are significantly associated with visual outcome ($P=0.042$). This suggests that the N35 and P50 are differently affected in disease and may be generated by different mechanisms. Our use of skin electrodes as opposed to foil or fiber electrodes may also influence the results [16]. Because nuclear opacity increases after a vitrectomy with gas tamponade, we expect an increase in the predictive power of preoperative PRVEP and PERG recordings after cataract extraction with intraocular lens implantation.

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