Focal Macular Electroretinograms before and after Removal of Choroidal Neovascular Lesions

Hiroko Terasaki, Tozo Miyake, Takashi Niwa, Yasuki Ito, Toshimitsu Suzuki, Masato Kikuchi, and Mineo Kondo

PURPOSE. To evaluate the changes in focal macular electroretinograms (fmERGs) after surgical removal of choroidal neovascular (CNV) lesions.

METHODS. Fourteen patients (14 eyes) with subfoveal or juxtapfoveal CNV associated with age-related macular degeneration and 1 patient with idiopathic CNV underwent vitrectomy and removal of the lesions. fmERGs elicited by a 15° stimulus were recorded before and 3 months after surgery. Optical coherence tomography (OCT) was performed to measure the foveal and parafoveal thickness before and 3 months after surgery.

RESULTS. Preoperative fmERGs were markedly reduced in all eyes. The mean amplitude of the b-wave in 15 eyes recorded 3 months after surgery increased significantly (P = 0.0022, Wilcoxon signed rank test). In all eyes except two with nearly nonrecordable a- and b-waves, the mean b-wave-to-a-wave ratio after surgery increased significantly in all eyes (P = 0.0330, Wilcoxon signed rank test). The percentage increase in the b-wave amplitude correlated significantly with the percentage decrease in the mean parafoveal retinal thickness (r = 0.688, P = 0.0076).

CONCLUSIONS. The decreased macular ERGs were partially recoverable in the early postoperative period. The decreased retinal edema after surgery may have contributed to this recovery. (Invest Ophthalmol Vis Sci. 2002;43:1540–1545)

Surgical removal of choroidal neovascular (CNV) lesions is undertaken to preserve or recover central neurosensory retinal function as an alternative to the relative destructive treatment by conventional laser photocoagulation in age-related macular degeneration (AMD). However, the postoperative visual acuity has sometimes been unchanged or even made worse when the lesion is located beneath the fovea (subfoveal CNV). The unimproved visual acuity probably results from a defective retinal pigment epithelium (RPE), although the surgery may be effective in preventing a further progression of visual loss.1,2

In the past several years, photodynamic therapy (PDT)3,4 and transscleral thermotherapy (TTT)5 have been used to destroy CNV lesions selectively with less damage to the RPE and the sensory retina for the predominantly classic CNV and occult CNV, respectively. Macular translocation surgery, an operation that moves the fovea from diseased RPE onto healthy RPE,6–8 also has the potential of improving or preserving central visual function in eyes with subfoveal CNV. In these new, promising treatments, not only the condition of RPE, but also the possibility of recovering retinal function is the key to performing the treatment. The atrophy of the sensory retina from long-term exudative changes is another cause of poor postoperative visual acuity. In surgical and other forms of treatments, knowledge of the effect of removal or inactivation of the CNV lesion on macular function will provide important information for future patients who undergo new treatment modalities.

To assess macular function, we recorded focal macular electroretinograms (fmERGs) before and after the surgical removal of a CNV lesion. fmERGs were selected, because they provide functional information over a larger area of the macula than that obtained from central visual acuity. We also evaluated the changes in foveal and parafoveal retinal thickness before and after surgery by optical coherence tomography (OCT) to compare the changes in function and morphology.

PATIENTS AND METHODS

fmERGs were recorded from 14 eyes of 14 patients with CNV associated with AMD and one patient with idiopathic CNV. fmERGs were recorded before and 3 months after vitrectomy for the removal of CNV between March 1999 and December 2000. The final follow up of these patients ranged from 5 to 27 months (14.2 ± 1.7 months, mean ± SE).

The standard Japanese visual acuity chart was used for acuity measurements, and the results were converted to Snellen visual acuity. The preoperative best corrected visual acuity ranged from counting fingers to 20/25. The size of the CNV lesion was measured on indocyanine green angiograms recorded by confocal scanning laser ophthalmoscopy (HRA; Heidelberg Engineering, Carlsbad, CA). The average size of the lesion was 0.94 ± 0.16 disc diameters (DD, range, 0.25–2.1 DD). The lesions were located subfoveally (beneath the fovea) or juxtapfoveally (beneath the fovea or juxtapfoveally, and the main part of the lesion was located on the RPE, in all cases).

OCT (Humphrey Instruments, San Leandro, CA) was performed before and 3 months after surgery, after the fmERG recordings. The images were cross-sectional scans passing through the fovea horizontally and vertically. The foveal thickness was calculated as the mean of the vertical and horizontal thicknesses at the fovea. The parafoveal thickness was calculated as the mean thickness at four points, 1 mm nasal, temporally, superiorly, and inferiorly from the fovea, according to the OCT images that passed through the fovea.

The surgical technique consisted of a standard three-port pars plana vitrectomy. The posterior hyaloid was separated from the retina after the cortical vitreous was removed. A retinotomy was made, and balanced saline solution was injected into the subretinal space with a 36-gauge subretinal cannula. The CNV membrane was removed through the retinotomy site by subretinal forceps. The irrigation pressure was increased to 60 to 80 mm Hg for 2 minutes, and fluid-air exchange was performed. Six eyes underwent intraocular lens surgery simultaneously, and four eyes underwent intraocular lens surgery 2 to 6 months after the first vitrectomy.

From the Department of Ophthalmology, Nagoya University School of Medicine, Nagoya, Japan.

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Corresponding author: Hiroko Terasaki, Department of Ophthalmology, Nagoya University School of Medicine, 65 Tsuruma-cho, Showaku, Nagoya 466, Japan; terasaki@med.nagoya-u.ac.jp.
The system and the techniques for recording fmERGs under direct fundus observation have been described in detail. Briefly, an infrared fundus camera, equipped with a stimulus light, background illumination, and fixation target, was used. The image from the camera was fed to a cathode-ray tube (CRT) monitor, and the examiner used the monitor to maintain the stimulus on the macula. The size of the stimulus spot was adjustable, and we selected a 15° spot stimulus centered on the fovea. The background light was delivered to the eye from the fundus camera at a visual angle of 45°. Additional background illumination outside the central 45° produced a homogeneous background illumination for nearly the entire visual field.

A Burian-Allen bipolar contact lens electrode was used for the electroretinographic recordings and allowed not only an extremely low noise level but also a clear view of the fundus displayed on the CRT monitor. The intensity of the white stimulus light and background light was 29.46 cd/m² and 2.89 cd/m², respectively.

After the patients' pupils were fully dilated with 0.5% tropicamide and 0.5% phenylephrine hydrochloride, fmERGs were elicited by 5-Hz rectangular stimuli (100-ms light on and 100-ms light off). A total of 512 responses were averaged by a signal processor. A time constant of 0.03 seconds with a 100-Hz high-cut filter on the amplifier was used to record the a- and b-waves, and the time constant was reduced to 0.003 seconds for recording the oscillatory potentials (OPs).

The amplitude of the a-wave was measured from the baseline to the peak of the a-wave. The amplitude of b-wave was measured from the trough of the a-wave to the peak of the b-wave. The amplitude of each OP wavelet was measured from a baseline drawn, as a first order approximation, between the troughs of successive wavelets to its peak.

The research was conducted in accordance with institutional guidelines and conformed to the tenets of the World Medical Association's Declaration of Helsinki. After providing sufficient information on other treatment options, including observation only, and information that macular electroretinography would bring little immediate benefit but would bring about the recovery of retinal function after surgery, an informed consent was obtained for the surgical removal of the CNV lesion and performance of fmERGs.

### Table 1. fmERG before and after Removal of CNV Lesion

<table>
<thead>
<tr>
<th></th>
<th>Before Surgery</th>
<th>After Surgery</th>
<th>Significance*</th>
<th>Normal Subjects (n = 112)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>a-Wave amplitude (μV)</td>
<td>0.47 ± 0.09</td>
<td>0.56 ± 0.08</td>
<td>0.14</td>
<td>2.10 ± 0.64</td>
</tr>
<tr>
<td>b-Wave amplitude (μV)</td>
<td>0.99 ± 0.14</td>
<td>1.67 ± 0.14</td>
<td>0.0022</td>
<td>4.89 ± 0.94</td>
</tr>
<tr>
<td>b/a Ratio</td>
<td>2.44 ± 0.27</td>
<td>3.74 ± 0.72</td>
<td>0.053</td>
<td>2.49 ± 0.64</td>
</tr>
<tr>
<td>a-Wave implicit time (ms)</td>
<td>25.4 ± 1.2</td>
<td>23.8 ± 0.8</td>
<td>0.3635</td>
<td>21.9 ± 1.7</td>
</tr>
<tr>
<td>b-Wave implicit time (ms)</td>
<td>55.4 ± 2.4</td>
<td>50.7 ± 2.1</td>
<td>0.0747</td>
<td>42.8 ± 2.1</td>
</tr>
</tbody>
</table>

*Significance (p) of difference between pre- and postoperative data (Wilcoxon signed rank test). The data for a- and b-wave amplitude were from 15 eyes, and the data for b/a ratio and implicit time were from 13 eyes with preoperative recordable a- and b-waves.

†Hayashi et al.
RESULTS

Visual Acuity and Complications

The best corrected visual acuity before surgery and at the time of the fmERG recording after surgery are shown below the waveform in Figure 1. The final postoperative best corrected visual acuity improved by at least two lines of the standard Japanese acuity chart in eight eyes and was maintained at the preoperative level in the other seven eyes. None of the eyes had a decrease in visual acuity at the final examination. The final best corrected visual acuity 5 to 27 months after surgery ranged from 20/1000 to 20/16. The preoperative log minimum angle of resolution (logMAR) correlated strongly with postoperative logMAR ($r = 0.716$, $P = 0.0044$).

Two patients experienced a retinal detachment after surgery because of a newly formed horseshoe-type retinal tear. One eye was treated successfully by cryopexy with gas tamponade, and the other eye by a revision of vitrectomy, endophotocoagulation, and gas tamponade with intraocular lens surgery. No other intraoperative and postoperative complications occurred in the other patients during the follow-up period. No recurrences of CNV developed in this relatively small case series.

Focal Macular ERGs

The amplitudes of the a- and b- waves and the oscillatory potentials were markedly reduced or nearly nonrecordable before surgery (Fig. 1). The implicit times of the a- and b- waves were prolonged in the 13 eyes with a measurable response. After surgery, the two eyes with preoperative nearly nonrecordable fmERGs (b-wave $< 0.5 \mu V$) had significant b-wave amplitude after surgery but with prolonged implicit times (patients 1, 2). The b-wave in patient 1 after surgery was $0.81 \mu V$ and that in patient 2 was $1.26 \mu V$. The markedly reduced b-wave amplitudes increased in patients 3 through 9; and the recovery of the a- and b-wave amplitude was not remarkable in patients 10 and 12, although the implicit time of the b-wave decreased. Patients 13 and 15 had relatively good preoperative fmERGs and showed an increase in the amplitudes of the a- and b-waves and the OPs after surgery (Fig. 1).

The mean amplitude and implicit times of the a- and b-waves elicited by the 15° stimulus before and 3 months after surgery are shown in Table 1 along with the data from 112 normal subjects (age 20–79 years; mean, 47) recorded with the same equipment and reported earlier.11

The mean amplitude of the a-wave in all 15 eyes was $0.47 \pm 0.09 \mu V$ (mean $\pm$ SE) before surgery and $0.56 \pm 0.08 \mu V$ after surgery. Although the a-wave amplitude increased in one half of the patients, the increase was not significant ($P = 0.14$, Wilcoxon signed rank test).

The mean amplitude of the b-wave in all 15 eyes was $0.99 \pm 0.14 \mu V$ before surgery and $1.67 \pm 0.14 \mu V$ after surgery. The mean b-wave to a-wave (b/a) ratio was $2.44 \pm 0.27$ before surgery and $3.74 \pm 0.72$ after surgery in the 13 eyes in which an a-wave was recordable before surgery. The increases in the b-wave amplitude and the b/a ratio after surgery were significant ($P = 0.0022$, $P = 0.0330$, respectively; Wilcoxon signed rank test). The postoperative mean b/a ratio was greater than the mean ratio $\pm$ SE in the normal subjects (Fig. 3, Table 1).

To try to determine the relationship between the fmERGs and visual acuity, a coefficient of correlation was calculated.
between the parameters of fmERGs and visual acuity (logMAR). Before surgery, the a- and b-wave amplitudes did not correlate with the logMAR; however, the postoperative a-wave and b-wave amplitudes correlated significantly with the postoperative logMAR ($r = 0.776, P = 0.0003; r = 0.520, P = 0.0458$, respectively).

The preoperative a- and b-wave amplitudes also correlated with the postoperative logMAR ($r = 0.706, P = 0.0023; r = 0.672, P = 0.0047$, respectively); however, the coefficient of correlation between the ratio of pre- and postoperative a-wave amplitudes and the difference in the pre- and postoperative logMAR was $r = -0.325$, which was not significant ($P = 0.2858$). Similarly, the correlation between the ratio of pre- and postoperative b-wave amplitudes and the pre- and postoperative logMAR value was low ($r = -0.053$) and not significant ($P = 0.8661$). The improvement in the b/a ratio also did not correlate significantly with the logMAR ($r = -0.303, P = 0.3225$).

The decrease in the implicit time of the a-wave after surgery compared with that before surgery in 13 eyes with measurable implicit times was not significant ($P = 0.3655$, Wilcoxon signed rank test). A decrease in the b-wave implicit time was seen in 8 of the 13 patients who had measurable implicit times before surgery (Fig. 4), however the mean decrease was not statistically significant ($P = 0.0747$, Wilcoxon signed rank test).

Again, the correlations between the changes in the implicit times of the a- and b-wave and the differences in pre- and postoperative logMAR were low and not significant ($r = 0.205, P = 0.5115; r = 0.211, P = 0.4986$, respectively).

**Optical Coherence Tomography**

The preoperative foveal and parafoveal retinal thickness measured by OCT was thicker than the thickness of normal eyes in all 15 eyes with CNV. After surgery, the foveal and parafoveal retinal thickness decreased in all cases. The mean foveal thickness was $333.6 \pm 49.8\mu m$ before surgery and $130.7 \pm 18.3\mu m$ after surgery. This difference was significant ($P = 0.0007$, Wilcoxon signed rank test). The mean parafoveal thickness was $353.1 \pm 21.9\mu m$ before surgery and $256.1 \pm 9.2\mu m$ after surgery. This decrease was also significant ($P = 0.0007$, Wilcoxon signed rank test; Fig. 5).

The percentage increase of the b-wave amplitude in 13 eyes with preoperative recordable b-waves correlated significantly with the percentage decrease in the mean parafoveal retinal thickness ($r = 0.688, P = 0.0076; \text{Fig. 6}$), but not significantly with the decrease in the mean foveal thickness ($r = 0.127, P = 0.6859$).

**DISCUSSION**

To date, the recording of changes in visual function after treatment for AMD have been based mainly on visual acuity measurements. The results of macular functional tests by subjective methods, such as contrast sensitivity, and objective methods, such as focal and multifocal ERGs, have been reported in AMD. Because visual acuity represents the function of only the foveal area of the retina and the ophthalmoscopic appearance of the fundus may not always reflect the physio-
logical state of the retina, it is necessary to assess the macular function more globally. For example, among patients with AMD with the same visual acuity, those with better contrast sensitivity have been reported to have a better ability to read.15

In fmAERG examinations, the responses elicited by a 3° or 4° stimuli correlated with visual acuity, whereas those elicited by a 10° or 20° stimulus do not always correlate.15 In these focal ERG studies, there have not been any studies examining the different components of the ERG. In addition, there are no reports about the changes in the different components after removal of CNV lesions except a brief case report after macular translocation surgery.15 In that report, the waveform of the ERGs were not presented.

Our method of recording the fmAERGs has two advantages. First, we can monitor the fundus during the recording. This is essential, because some of the patients have eccentric fixation or change the fixation point after the removal of the lesion. Thus, we would not know exactly where the responses originated unless we monitored the stimulus on the fundus. Another advantage is that we can obtain each component of the ERG as in the full-field photopic ERGs elicited by long-duration stimuli.

Bush and Sieving16 reported a major contribution from the off-bipolar cells to the a- and d-waves (off-response), whereas the on-bipolar cells contributed to the b-wave of the photopic ERGs over a range of stimulus intensities. To record each component of the macular ERG, long-duration stimuli are essential, otherwise, b- and d-wave cannot be separated. We used a 100-ms stimulus and thus were able to analyze the retina layer by layer.

Our findings demonstrated that all components of the fnmAERGs elicited by the 15° stimulus were markedly reduced, which suggested an impairment of macular cone function. This agrees with a histologic report that there is marked photoreceptor loss in eyes with AMD.17 Because a reduction of only photoreceptor function results in a decrease in the quantum catch by the cones, the relative degree of reduction of the a- and b-waves and the OPs should be proportional under this condition.18

The a- and b-waves and the OPs are considered to originate mainly from off- and on-bipolar cells and amacrine cells, respectively.16 In the patients in whom the degree of reduction of the a-wave, b-wave, and OPs is not equal, the damage to the off- and on-bipolar cells and amacrine cells may not be uniform under the dysfunctional cones. After surgery, the b-wave amplitude increased significantly without an accompanying increase of the a-wave in most of our patients. The selective recovery of the b-wave may suggest the recovery of inner retinal function, particularly the on-bipolar cells.16

To try to determine the mechanism for the inner retinal functional disturbance, we measured the foveal and parafoveal thickness by OCT. We used the mean thickness of 4 parafoveal points that were 1 mm from the fovea, because the fnmAERGs were elicited by a 15° stimulus that almost covered the macular area. In AMD, macular edema has been demonstrated histologically17 and more recently by OCT images.19,20 In our OCT images, the foveal and parafoveal retinal thickness was thicker before surgery and thinner after surgery. Our findings showed that the degree of recovery of the b-wave was significantly correlated with the decrease in the mean parafoveal retinal thickness. These results suggest that the inner retinal function is impaired by retinal edema, and the decreased thickness of the macular retina contributes to the early recovery of inner layer function of the macula. One hypothesis that can explain why the b-wave is reduced in areas of retinal edema is as follows. The b-wave arises mostly from a transient increase in potassium ions in the extracellular space, as a byproduct of neuronal activity. When the retina is edematous, the extracellular potassium concentration should be reduced, even if the neurons are not impaired—although they are usually impaired. Therefore, the b-wave can become smaller when the retina is edematous and recover more quickly after surgery.

The postoperative visual acuity (logMAR) correlated significantly with the preoperative visual acuity (logMAR) and the preoperative a- and b-wave amplitudes; therefore, better preoperative foveal and macular function resulted in better postoperative visual acuity. However, the degree of recovery in visual acuity and in the fnmAERGs varied.

In conclusion, we found that a substantial change in macular function occurred after the removal of CNV lesions and conclude that the preoperative changes are partially recoverable. However, it should be emphasized that a small number of eyes were studied and that this was a retrospective study. The decreased retinal edema after surgery may contribute to the recovered macular ERGs in the early postoperative period.

References


