



Transient Increase of Flicker Electroretinography Amplitudes after Cataract Surgery: Association with Postoperative Inflammation

Kumiko Kato, MD, PhD,¹ Ryunosuke Nagashima,¹ Hisashi Matsubara, MD, PhD,¹ Kengo Ikesugi, MD, PhD,¹ Hideyuki Tsukitome, MD, PhD,¹ Yoshitsugu Matsui, MD, PhD,¹ Takayasu Nunome, MD,¹ Masahiko Sugimoto, MD, PhD,¹ Daphne L. McCulloch, OD, PhD,² Mineo Kondo, MD, PhD¹

Purpose: To determine the characteristics and cause of the increase in the amplitude of flicker electroretinography (ERG) after cataract surgery.

Design: Prospective, observational clinical study.

Participants: Thirty patients who underwent cataract surgery.

Methods: Flicker ERGs were recorded with the RETeval system without mydriasis. The central macular thickness (CMT) was measured by OCT and the aqueous flare value (AFV) by laser flare-cell photometry. These examinations were performed before surgery and 1 day, 1 week, 1 month, 2 months, and 3 months after surgery. Linear regression analysis through the origin was used to compare the correlations between the relative changes in flicker ERG amplitudes and the changes in the CMT and AFV at different times after the surgery.

Main Outcome Measures: The amplitude of flicker ERGs, CMT, and AFV.

Results: The mean amplitude of flicker ERGs increased significantly by 31% at 1 week after surgery ($P < 0.001$); a significant increase in the amplitudes was not present at 3 months after the surgery. The mean AFV was significantly increased at 1 day after surgery ($P < 0.001$), and the CMT was significantly increased at 1 to 3 months after surgery ($P < 0.001$). The changes in flicker ERG amplitudes at 1 week after surgery were significantly associated with the changes in the CMT at 1 to 3 months after surgery ($P < 0.05$), and they were weakly associated with the changes in AFV at 1 day after surgery ($P = 0.05$).

Conclusions: These results suggest that the increase in the amplitude of flicker ERGs after cataract surgery is a transient phenomenon that has a peak at 1 week after surgery. The increase of flicker ERG amplitude was associated with measures that are frequently used to evaluate postoperative inflammation.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. *Ophthalmology Science* 2023;3:100243 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Supplemental material available at www.ophtalmologyscience.org.

Electroretinography (ERG) is widely used to diagnose inherited retinal diseases with dysfunctions of the inner and outer retinal layers.^{1–4} It is known that the characteristics of ERGs are important in evaluating the ischemic status of the retina in eyes with vascular diseases, including diabetic retinopathy^{5–7} and retinal vascular occlusions.^{8–10} Relevant to this study, ERGs have been used to detect retinal dysfunction associated with various types of intraocular inflammation.^{11–13}

Most studies on the effect of cataract surgery on ERGs have demonstrated that ERG amplitudes increased slightly after cataract surgery.^{14–16} Recently, Miura et al¹⁷ reported that the amplitude of flicker ERGs increased by 51% to 67% even though the degree of cataract was relatively mild. Similarly, Tanikawa et al¹⁸ reported that the amplitudes of all ERG components, including the rod and cone

responses, increased by 11% to 23% at 1 week after cataract surgery in eyes with mild cataracts. They attributed the increases to the removal of the light absorption effects of the cataract and/or the changes in the distribution of stimulus light scattering over the entire retina after the surgery.^{17,18}

Based on our clinical experience using ERGs in various ocular diseases, we developed a hypothesis that the increase of the ERG amplitude, particularly the flicker ERG amplitude, after cataract surgery may be a transient phenomenon that is caused by postoperative intraocular inflammation. This hypothesis was made because we have recently observed an increase of ERG amplitudes in eyes with nonischemic central retinal vein occlusion,¹⁰ mild diabetic retinopathy,⁷ and acute uveitis.¹⁹

To test this hypothesis, we performed a prospective clinical study of recording flicker ERGs before and periodically for up to 3 months after cataract surgery in patients with a mild degree of cataract. To determine whether there was a relationship between the change of ERG amplitude and postoperative intraocular inflammation, we also measured the aqueous flare value (AFV) using a laser flare photometer and central macular thickness (CMT) using OCT, both of which are widely used for evaluating postoperative intraocular inflammation after cataract surgery.

Methods

Study Design

This was a prospective, single-center study conducted at the Mie University Hospital between December 2019 and March 2021. The Medical Ethics Committee of Mie University Hospital approved the procedures used (no. 2019-156), and the procedures conformed to the tenets of the Declaration of Helsinki of the World Medical Association. All participants signed a written informed consent form after they were provided with information on the procedures to be used.

Subjects

The eligibility criteria were patients who required cataract surgery and were aged ≥ 50 years. Only eyes with relatively mild cataract with grade 1 to 2 nuclear, cortical, or posterior subcapsular cataract were included.²⁰ The exclusion criteria included eyes with diabetic retinopathy, retinal vein occlusion, epiretinal membrane, uveitis, and glaucoma receiving topical medications because these eyes are known to have a high incidence of developing cystoid macular edema after cataract surgery.^{21–23} Patients who had myopia of ≥ -6.0 diopters were also excluded. In the end, 33 eyes of 33 patients that underwent cataract surgery were studied.

Cataract Surgery

Cataract surgery was performed by 9 experienced surgeons (K.K., H.M., K.I., H.T., Y.M., A.I., T.N., M.S., and M.K.) in the Mie University Hospital. After topical or sub-Tenon capsule anesthesia with lidocaine hydrochloride, a standard microincision cataract surgery was performed including a 2.4-mm corneal or corneoscleral incision, continuous curvilinear capsulorhexis, phacoemulsification, and implantation of a foldable intraocular lens. Topical moxifloxacin and betamethasone were applied 3 times daily and bromfenac 2 times daily beginning postoperative day 1. At 1 month after the surgery, all eye drops were discontinued after we confirmed that there were no obvious ocular complications.

Protocols of Examinations

The best-corrected visual acuity was measured with a standard Japanese decimal visual acuity chart at 5 m. The intraocular pressure was measured with a noncontact automatic tonometer (CT-IP, Topcon). The CMT was measured with a spectral-domain OCT device (Spectralis, Heidelberg Engineering Inc), and the CMT was defined as the average thickness of the macula within the central 1 mm of the retina. The AFV was measured with a laser flare photometer (Kowa FC-1000 LFCM; Kowa Co, Ltd), and the value was expressed in photon counts/millisecond. These clinical examinations were performed before the surgery and 1 day, 1 week, 1 month, 2 months, and 3 months after the surgery.

Flicker ERG Recordings by RETeval

Full-field flicker ERGs were recorded with natural pupils using the RETeval system.^{24,25} Full-field stimuli were presented with a 60-mm diameter dome, and the white stimuli were created by a combination of 3 colored light-emitting diodes. In this study, we used a stimulus flash of 32 photopic Td-s, which we have reported to be less susceptible to the effects of a sequence of recordings of the tested eye than weaker stimuli.²⁶ The ERGs were detected with a special skin electrode array (Sensor Strip; LKC Technologies, Inc) that was placed 2 mm from the margin of the lower eyelid.

The amplitudes and implicit times of the fundamental component were automatically measured and displayed by the RETeval system using a special algorithm using discrete Fourier transformation and cross-correlation analysis. In this study, we analyzed the results of the fundamental component of the flicker ERG because it is known to be sensitive to various functional changes in the retina.^{27–30}

Relative Changes in the Amplitude of ERGs Compared with Baseline Value

The relative change (Δ) in the amplitude of the flicker ERGs after surgery was compared with the preoperative values (%) as follows:

$$\Delta (\%) = (\text{postoperative value} - \text{preoperative value}) / (\text{preoperative value}).$$

Statistical Analyses

Two-way layout analysis of variance was performed to examine if there was a significant change in the implicit times or amplitudes of the fundamental component of the flicker ERGs, CMT, and AFV during each postoperative time after surgery. Then, Dunnett's multiple comparison tests were used to identify which time points were significantly different from the baseline values before surgery.

To determine whether the degree of change of 2 different factors was significantly correlated, a linear regression analysis through the origin was performed.^{31,32} Thus, we examined whether the changes in the flicker ERGs at 1 week after the surgery were correlated with the changes in the AFV or the changes in the CMT at each time point after the surgery.

Multivariate linear regression analysis was used to determine if other factors were significantly associated with the changes in the amplitudes of the flicker ERGs at 1 week after surgery. The explanatory variables were age, sex, axial lengths, operation times, and baseline flicker ERG amplitudes. All statistical analyses were performed using the IBM SPSS Statistics software program (version 27.0.1). *P* values of < 0.05 were considered statistically significant.

Results

Clinical Characteristics of Patients Who Underwent Cataract Surgery

All 33 eyes underwent successful cataract surgery without any complications. After surgery, 1 patient could not visit the hospital as scheduled, and 2 patients were excluded because of missing test data. In the end, a total of 30 eyes were used for the final analysis.

The mean preoperative best-corrected visual acuity of the 30 patients (13 men and 17 women) who underwent cataract surgery was 0.32 ± 0.23 logarithm of the minimum angle of resolution units (range, 0–1.00), and the mean best-

corrected visual acuity at the final visit was -0.06 to 0.08 logarithm of the minimum angle of resolution units (range, -0.18 to 0.10). The mean age of the 30 patients was 72.3 ± 6.1 years (range, 55–82 years). The mean operation time was 18.2 ± 5.0 minutes, and there were no patients who had abnormal intraocular pressure elevation, abnormal ocular inflammation, cystoid macular edema, or endophthalmitis after the surgery.

Changes in Flicker ERG after Cataract Surgery

Representative flicker ERGs recorded before and 1 day, 1 week, 1 month, 2 months, and 3 months after cataract surgery are shown in Figure 1A. The fundamental component (red dotted line) is superimposed on the Fourier analyzed flicker ERGs (solid black line) using the first 8 harmonics. The actual values of the amplitudes and implicit times of the fundamental components are also shown in the rightmost column.

The amplitude of fundamental component of the flicker ERGs did not change significantly at 1 day after the surgery. However, it became significantly larger from $14.6 \mu\text{V}$ to $26.6 \mu\text{V}$ at 1 week after the surgery (Fig 1A, third row from the top). After that, the amplitude of the ERG gradually decreased. There was no significant change in the implicit times after the surgery.

To assess the changes in flicker ERG amplitude before and after cataract surgery quantitatively, we plotted the amplitude at each time point of the 30 subjects in Figure 1B. We found that amplitude of the fundamental component of the flicker ERGs was significantly larger than that at the baseline at 1 week after surgery ($P < 0.001$) with a mean increase from the preoperative value of 31.2%. After that, the amplitude of the flicker ERGs gradually decreased. At 2 months, just after the postoperative anti-inflammatory eye drops wore off, the amplitudes tended to increase slightly again and remained above the preoperative values (Fig 1B, red arrow). At 3 months after the surgery, the mean amplitude of the flicker ERGs decreased and was not significantly different from the preoperative value.

We also plotted the changes in the implicit times of the fundamental component of the flicker ERGs before and after surgery in Figure 1C. The implicit times became significantly but only slightly earlier at 1 day after the surgery ($P < 0.001$); however, there were no significant differences at any other time point.

There was no significant change in the pupillary diameter during RETeval flicker ERG testing at any test point after the surgery compared with the preoperative baseline (data not shown). We performed the same analysis using the reconstructed flicker ERG waveforms that are comprised of the first 8 harmonics, and similar trends were observed (Fig S1, available at www.opthalmologyscience.org).

Changes in AFV and CMT

Because we considered the possibility that the increase in the amplitude of the flicker ERG may be related to intraocular inflammation after the cataract surgery, we also analyzed the changes in the AFV and CMT in the same 30

eyes (Figure 2). The changes in the mean AFV before and after the cataract surgery are plotted in Figure 2A. We found that the mean AFV increased significantly only at day 1 after the surgery ($P < 0.001$); however, it did not significantly differ from preoperative values at all other time points after the surgery.

The mean CMT before and after the surgery is plotted in Figure 2B. We found that the mean CMT was significantly decreased at day 1 after the surgery ($P = 0.010$) but then began to increase gradually and reached the maximum at 2 months. The mean CMT was significantly thicker at 1 to 3 months after cataract surgery than that at the baseline ($P < 0.001$, Fig 2B). A color map of the retinal thickness recorded from 1 representative patient is shown in Figure 2C. The map shows a gradual increase of the CMT at 1 to 3 months after the surgery.

Correlations of Flicker ERG Amplitude with AFV or CMT

Next, we sought to determine whether the changes in the flicker ERGs after the surgery were correlated with 2 known indicators of postoperative ocular inflammation, the AFV and CMT, using a linear regression analysis through the origin.^{31,32}

The results of the standardized partial regression coefficients (β) and P values for the correlation between the changes in the flicker ERG amplitude (ΔERG) at 1 week after the surgery and the changes in AFV (ΔAFV) or the changes in CMT (ΔCMT) at each time point are shown in Table 1. We found that the ΔERG at 1 week after the surgery was significantly correlated with the ΔCMT at 1 to 3 months after the surgery ($\beta = 0.429\text{--}0.491$, $P < 0.05$, Table 1) with the strongest correlation at 2 months after the surgery (see also Fig 3).

We also noted that the ΔERG at 1 week after the surgery tended to be correlated with the ΔAFV at 1 day after the surgery, but this correlation was weak ($\beta = 0.354$, $P = 0.051$, Table 1). We performed the same analysis using the reconstructed waveform of the flicker ERGs, and similar trends were observed (Table S1, available at www.opthalmologyscience.org).

Factors Associated with Amplitude Increase in Flicker ERG after Cataract Surgery

Finally, to investigate the baseline factors of the patients who were associated with an increase in the flicker ERGs at 1 week after the surgery, we performed multivariate linear regression analyses (Table 2). The independent variables were sex, age, affected eye (right or left), axial length, operation time, and the baseline amplitude of the flicker ERGs. We found that only the baseline amplitude of the flicker ERGs was significantly and negatively associated with the ΔERG at 1 week after the surgery ($\beta = -0.560$, $P = 0.004$, Table 2). This indicated that the smaller baseline amplitude of flicker ERGs was associated with greater changes in flicker ERG amplitudes at 1 week after the surgery (see also Fig 4).

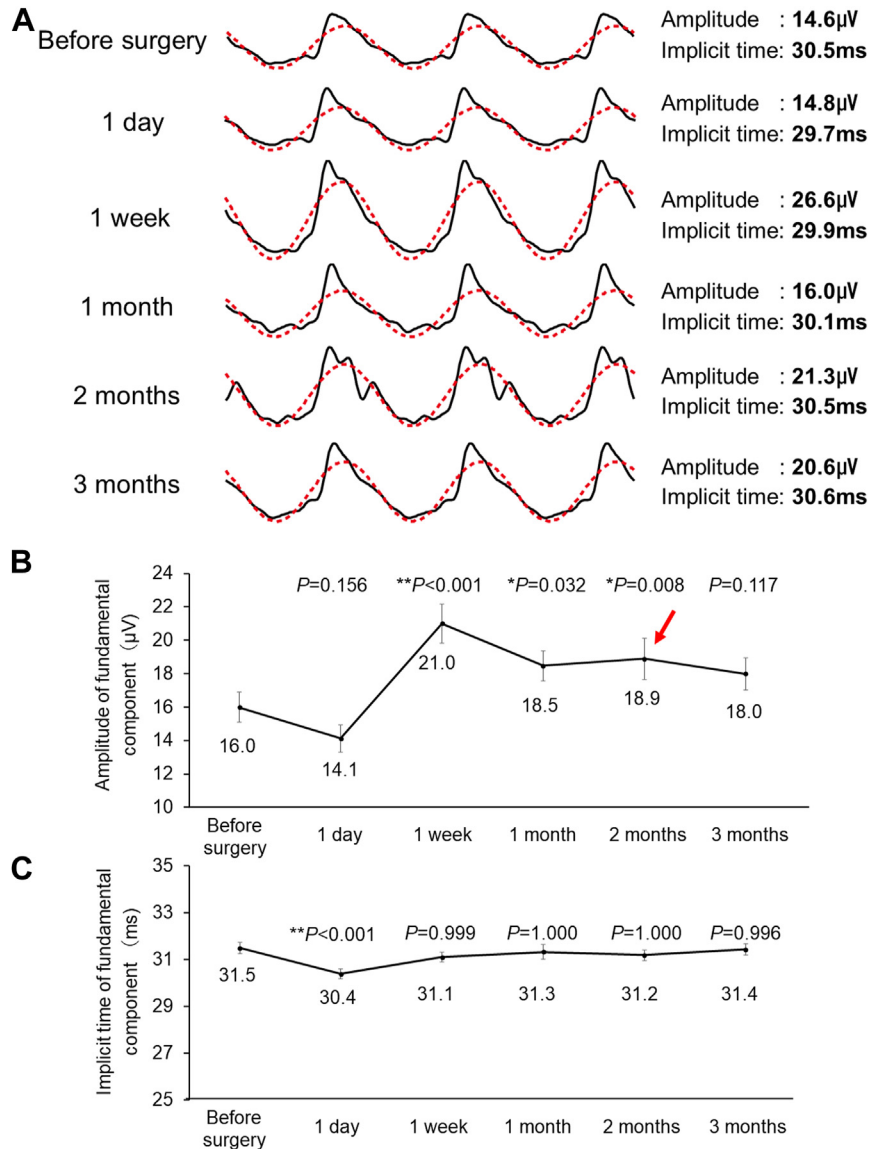


Figure 1. Changes in flicker electroretinography (ERG) before and after cataract surgery. **A**, Changes in flicker ERG before and after cataract surgery in a representative normal subject. The fundamental component (red dotted line) is superimposed on the reconstructed flicker ERG (solid black line) using the first 8 harmonics. Actual values of the amplitudes and implicit times of fundamental components are also shown in the rightmost column. **B**, Plot of the amplitude of the fundamental component of the flicker ERG before and at each time point after the cataract surgery. The bars indicate the standard error of the mean. $*P < 0.05$, $**P < 0.001$. **C**, Changes in the implicit times of the fundamental component of the flicker ERG before and at each time point after the cataract surgery. The bars indicate the standard error of the mean. $**P < 0.001$.

Discussion

Our results showed for the first time that the amplitude increase of flicker ERGs after cataract surgery is a transient phenomenon that peaks at 1 week after surgery (Fig 1). We also showed that the increase of flicker ERG amplitudes at 1 week after the surgery was significantly correlated with the changes in the CMT at 1 and 3 months after surgery, and it was weakly correlated with the changes in the AFV at 1 day after surgery (Table 1, Fig 3). In addition, we also noted that, after the postoperative anti-inflammatory eye drops were discontinued at 1 month after the surgery, the ERG

amplitude tended to increase slightly (Fig 1B, red arrow). These results suggested that the increase of the flicker ERG amplitudes after the cataract surgery was most likely caused by the postoperative intraocular inflammation rather than by the removal of light absorption or scattering effects of the cataract. These findings provide a new insight into this interesting electrophysiologic phenomenon of the eye.

The phenomenon of transient increases in the ERG amplitude has been reported in several pathologic conditions, including the early phase of intraocular iron foreign body³³ and in some eyes at the early stages of diabetic

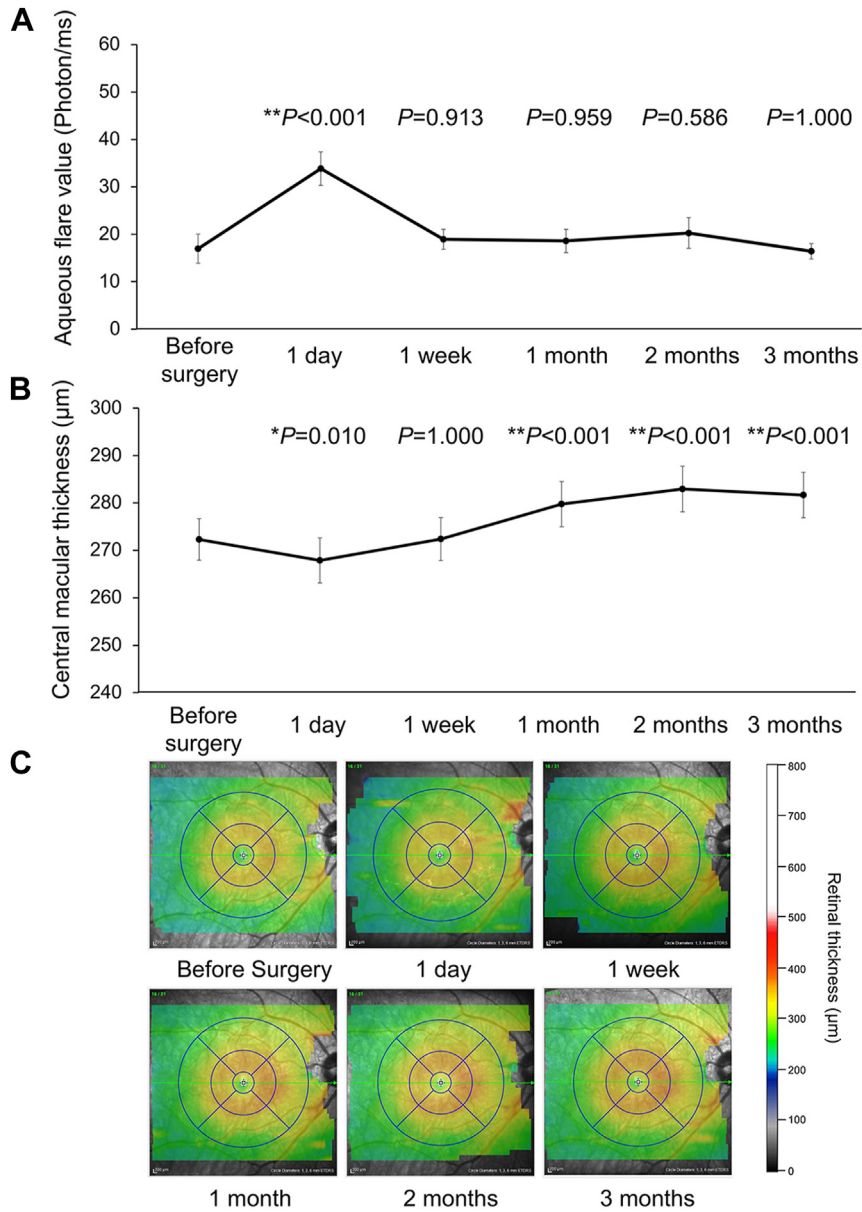


Figure 2. Changes in aqueous flare value (AFV) and central macular thickness (CMT) before and after cataract surgery. **A**, Plot of the AFV before and after each time point of cataract surgery. The bars indicate the standard error of the mean. **P<0.001. **B**, Plot of the CMT before and at each time point after cataract surgery. The bars indicate the standard error of the mean. *P<0.05, **P<0.001. **C**, Changes in the color map of retinal thickness before and at each time point after cataract surgery.

retinopathy.^{7,34} We also recently reported that “supernormal” ERG amplitudes were seen in some eyes with nonischemic central retinal vein occlusion¹⁰ and acute uveitis because of the lens fragments.¹⁹ Therefore, it would be reasonable to assume that the increase of ERG amplitudes was associated with the intraocular mediators produced by pathologic conditions, such as trauma, ischemia, or inflammation.

At present, what intraocular mediators are directly responsible for the amplitude increase of ERG under some pathologic conditions have not been determined. However, we have speculated that one major candidate may be nitric

oxide (NO). It is known that NO is produced in the eyes in various pathologic conditions, such as diabetic retinopathy, retinal ischemia, uveitis, and trauma.^{35–37} Nitric oxide is also known to be generated in the eye after cataract surgery.³⁸ Interestingly, Vielma et al³⁹ reported that the amplitude of all ERG components increased after intravitreal injection of NO in rats. They also showed that the ERG amplitudes of the cone responses increased by 47% after NO injection, a value that is comparable with the degree of flicker ERG increase after cataract surgery in our study of 31%.

The time course of the changes in the values of the flicker ERGs, CMT, and AFV after the cataract surgery is plotted in

Table 1. Correlation between the Changes in Flicker Electroretinography Amplitude at 1 Week and the Change of AFVs or CMT at Each Time Point

Time Point	Δ AFV	Δ CMT
1 day	$\beta = 0.354$ (CI, -0.001 to 0.629) $P = 0.051$	$\beta = -0.172$ (CI, -0.496 to 0.194) $P = 0.356$
1 week	$\beta = -0.080$ (CI, -0.423 to 0.282) $P = 0.667$	$\beta = -0.041$ (CI, -0.390 to 0.318) $P = 0.825$
1 month	$\beta = -0.250$ (CI, -0.555 to 0.114) $P = 0.174$	$\beta = 0.429^{\ddagger}$ (CI, 0.087-0.680) [‡] $P = 0.016^{*;\ddagger}$
2 months	$\beta = -0.157$ (CI, -0.484 to 0.209) $P = 0.400$	$\beta = 0.491^{\ddagger}$ (CI, 0.166-0.720) [‡] $P = 0.005^{*;\ddagger}$
3 months	$\beta = -0.166$ (CI, -0.492 to 0.200) $P = 0.371$	$\beta = 0.443^{\ddagger}$ (CI, 0.104-0.689) [‡] $P = 0.013^{\ddagger;\ddagger}$

A linear regression analysis through the origin was used. The standardized partial regression coefficient (β) and P value are shown.

AFV = aqueous flare value; CI = confidential interval; CMT = central macular thickness.

* $P < 0.01$.

[†] $P < 0.05$ was considered significant.

[‡]Indicate the time points when significant correlations were found.

Figure 5. We found that the time of the peak of the ERG amplitude was later than the peak time of the AFV but earlier than the peak time of CMT. It is widely believed that the surgical invasion causes blood–aqueous barrier disruption with leakage of inflammatory molecules and cells into the anterior chamber, which results in an increase of the AFV. These inflammatory mediators released by the anterior uvea gradually diffuse into the vitreous and increase the permeability of the perifoveal capillaries, resulting in intraretinal fluid accumulation and increase of the CMT.⁴⁰ At the same time, these inflammatory mediators may have acted directly or indirectly on retinal neurons, resulting in an increase in the flicker ERG amplitudes. If this was the case, it would not be too surprising if these

Table 2. Results of Multiple Linear Regression Analysis to Identify the Factors That Were Associated with the Changes in Flicker ERG Amplitude at 1 Week after the Surgery Compared with Preoperative Values (%)

Independent Variables	β	P
Age (yrs)	0.119	0.536
Sex (male/female)	0.261	0.170
Axial length (mm)	-0.037	0.846
Operation time (min)	0.002	0.993
Baseline flicker ERG amplitude (μ V)	-0.560	0.004*

The standardized partial regression coefficient (β) and P values are calculated for 5 independent variables, which were associated with the changes in flicker ERG amplitude at 1 week after the surgery compared with preoperative values (%).
ERG = electroretinography.
* $P < 0.05$ was considered significant.

electrophysiologic changes in the retina occurred earlier than the morphologic changes in the retina.

We also noticed that the degree of change in the flicker ERG amplitudes at 1 week after the cataract surgery was not uniform among the 30 eyes and ranged from -30% to +82% (Fig 4). We studied what kinds of background factors of the patients were associated with the degree of changes in ERG amplitude and found that it was dependent on the initial ERG amplitude; thus, the eyes with smaller initial ERG amplitudes tended to have a greater degree of amplitude increase (%) after the surgery (Table 2, Fig 4). Although the exact reason for this was not determined, we have one suggestion called the “ceiling effect of the ERG amplitude increase.” The ERGs arise from the electrical activities of the retinal neurons elicited by light stimuli, and the amplitudes can be increased in response to some intraocular mediators. However, there must be an upper limit of the maximal amplitude value. Therefore, the larger the initial amplitude is, the smaller the degree of increase is because of intraocular inflammation. An alternative hypothesis is that the eyes with larger preoperative flicker ERG amplitudes

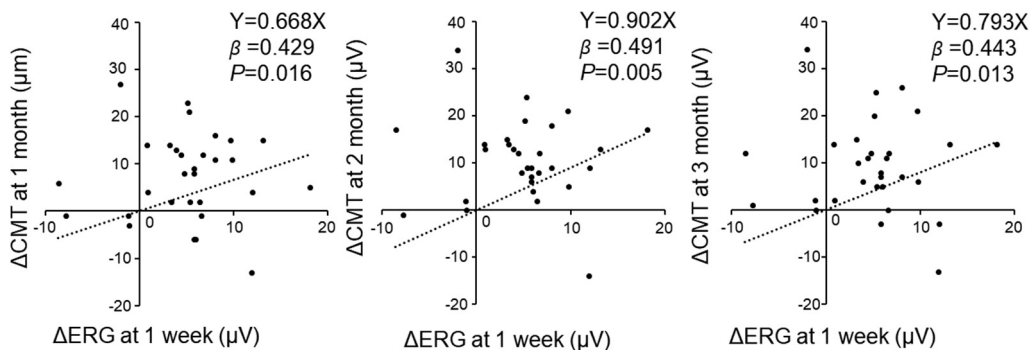


Figure 3. Plot of changes in central macular thickness (Δ CMT) at 1, 2, and 3 months after the surgery against the changes in flicker electroretinography (ERG) amplitude (Δ ERG) at 1 week. A linear regression analysis through the origin showed that the Δ ERG at 1 week was significantly associated with Δ CMT at 1 to 3 months after the surgery ($P < 0.05$) with highest correlation at 2 months after the surgery. Δ CMT = Central macular thickness.

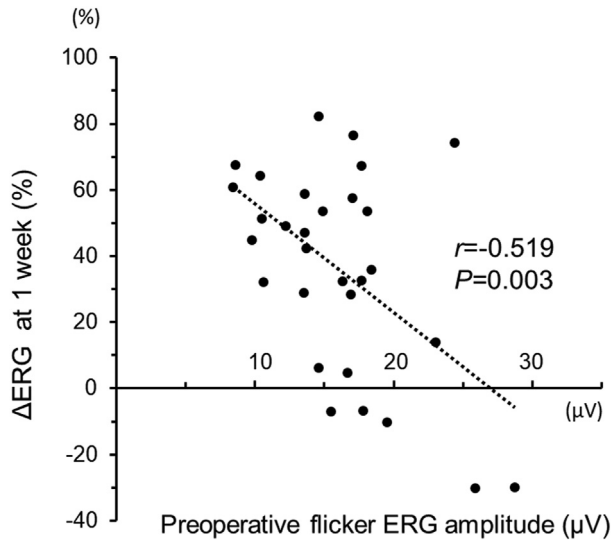


Figure 4. Plot of the changes in flicker electroretinography (ERG) amplitude (Δ ERG) at 1 week after the surgery against the preoperative flicker ERG amplitude. There was a significant negative correlation between the preoperative amplitude of the flicker ERG and Δ ERG at 1 week after the surgery ($r = -0.519$, $P = 0.003$).

may have already had some preoperative inflammations, so they were already enhanced.

Finally, we discuss the impact of the results on the functional evaluations using the ERGs before and after ophthalmic surgery. Electroretinograms are often examined before and after surgery to determine whether an improvement of retinal function has occurred after vitreoretinal surgery. However, our results clearly showed that the intraocular changes other than improvement of optical quality caused by the surgery can increase the amplitude of the ERGs transiently. Therefore, when an increase in ERG

amplitude is observed after surgery, it is necessary to determine whether the increase of ERG amplitude was caused by the improvement of retinal function because of the surgery or by the transient physiologic changes in the retina associated with the surgery. This would be especially important when the ERG is recorded within 2 to 3 months of the surgery.

There are several limitations in this study. First, although we suggested that the amplitude increase of flicker ERGs may be caused by some intraocular mediators produced by cataract surgery, we did not identify which cytokine or chemokine is responsible for the ERG amplitude increase. We also cannot deny the possibility that factors other than ocular inflammation, such as improvement in optical properties, may be involved in the increased ERG amplitudes. Second, we recorded only the flicker ERGs before and after the surgery. If all ERG components, including the a- and b-waves and the oscillatory potentials of the cone and rod responses, had been recorded, it would have been possible to determine which retinal neurons in the retina were responsible for the increase. Third, we examined the changes in the flicker ERGs for only 30 eyes before and after the uncomplicated cataract surgery. Therefore, we could not determine whether the changes in the ERGs could help in predicting which eyes will develop macular edema after the cataract surgery. We are currently continuing our prospective studies, including eyes prone to have inflammation and complications, to determine whether the ERG values can predict the development of macular edema after cataract surgery. The fourth limitation was that we followed up patients for only 3 months after the surgery. At 3 months after surgery, there was a residual increase in the central retinal thickness, and the amplitude of the ERG had not returned to baseline value. A follow-up at 6 months after surgery would have provided more interesting insights. We are in the process of developing a study plan with an extended follow-up period.

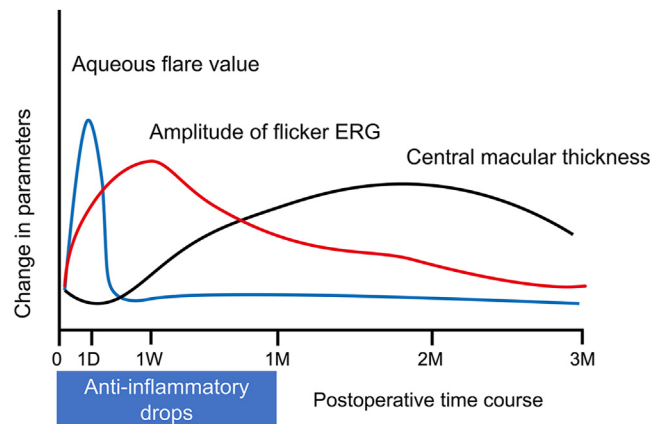


Figure 5. Schema showing the time courses of changes in the values of the flicker electroretinography (ERG) amplitude, central macular thickness (CMT), and aqueous flare value (AFV) after cataract surgery. The AFV (blue line) increased immediately at 1 day after the surgery and returned to baseline within 1 week. The amplitude of the flicker ERG (red line) showed a peak at 1 week after the surgery. The CMT (black line) gradually increased and peaked at 2 months after the surgery.

In conclusion, we demonstrated that the increase in the amplitude of flicker ERGs after cataract surgery is a transient phenomenon that peaks at 1 week after the surgery. We also showed that this ERG increase is significantly associated with the postoperative intraocular inflammatory process. Further studies are needed to determine what mediators are responsible for this ERG amplitude increase and whether the flicker ERG can be used to predict which eyes will develop macular edema after cataract surgery in the early stages or to evaluate the effect of anti-inflammatory medications on postoperative inflammation.

Footnotes and Disclosures

Originally received: June 18, 2022.

Final revision: October 27, 2022.

Accepted: October 28, 2022.

Available online: November 4, 2022. Manuscript no. XOPS-D-22-00132R2.

¹ Department of Ophthalmology, Mie University Graduate School of Medicine, Tsu, Japan.

² School of Optometry and Vision Science, University of Waterloo, Waterloo, Canada.

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s): K.K.: Honoraria — Senjyu Pharmaceutical, Santen Pharmaceutical, Otsuka Pharmaceutical, Kowa.

H.M.: Honoraria — Novartis Japan, Santen Pharmaceutical, Bayer Pharmaceutical.

K.I.: Honoraria — Novartis Japan, Santen Pharmaceutical, Bayer Pharmaceutical, Kowa, Otsuka Pharmaceutical, Seed, Senjyu Pharmaceutical, Alcon Japan.

Y.M.: Honoraria — Novartis Japan, Santen Pharmaceutical, Bayer Pharmaceutical, Kowa, Carl Zeiss, AMO Japan, Senjyu Pharmaceutical, Alcon Japan, Hoya.

M.S.: Honoraria — Novartis Japan, Santen Pharmaceutical, Bayer Pharmaceutical, Kowa, Daiichi-Sankyo, Wakamoto Pharmaceutical, Senjyu Pharmaceutical, Alcon Japan.

M.K.: Consultant — Senjyu Pharmaceutical, Ono Pharmaceutical, Chugai Pharmaceutical; Honoraria — Senjyu Pharmaceutical, Chugai Pharmaceutical, Novartis Japan, Alcon Japan, Santen Pharmaceutical, Bayer Pharmaceutical, Asahi-Kasei, Sanofi; Grants — Ministry of Education, Culture,

Acknowledgments

The authors thank Eriko Uchiyama, Daisuke Kurose, Asako Sugawara, Takumi Ohashi, Iroha Fujimoto, and Yuki Mizuno for performing ophthalmic examinations on our subjects. The authors thank Atsushi Ichio, Hiroko Enomoto, Yuka Yonekawa, Kouhei Sampa, Hitomi Suimon, and Yukiko Muramoto for recruiting subjects. The authors thank Norio Sugimoto of the Sugimoto data analysis service for critical discussion on statistical analysis. The authors also thank Professor Emeritus Duco I. Hamasaki of the Bascom Palmer Eye Institute of the University of Miami (Miami, Florida) for critical discussion and final manuscript revisions.

Sports, Science and Technology (grant-in-aid for scientific research C, grant no.: 18H02954 and 17K19721).

The authors have no proprietary or commercial interest in any materials discussed in this article.

HUMAN SUBJECTS: Human subjects were included in this study. The Medical Ethics Committee of Mie University Hospital approved the procedures used (No. 2019-156), and the procedures conformed to the tenets of the Declaration of Helsinki of the World Medical Association. All participants signed a written informed consent form after they were provided with information on the procedures to be used.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Kato, Kondo

Analysis and interpretation: Kato, Kondo, McCulloch

Data collection: Kato, Nagashima, Matsubara, Ikesugi, Tsukitome, Matsui, Nunome, Sugimoto, Kondo

Obtained funding: N/A

Overall responsibility: Kumiko Kato

Abbreviations and Acronyms:

AFV = aqueous flare value; **CMT** = central macular thickness;

ERG = electroretinography; **NO** = nitric oxide.

Keywords:

Aqueous flare value, Cataract surgery, Central macular thickness, Electroretinography, Inflammation.

Correspondence:

Kumiko Kato, MD, PhD, 2-174 Edobashi, Tsu, Mie 514-8507, Japan. E-mail: k-kato@med.mie-u.ac.jp.

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