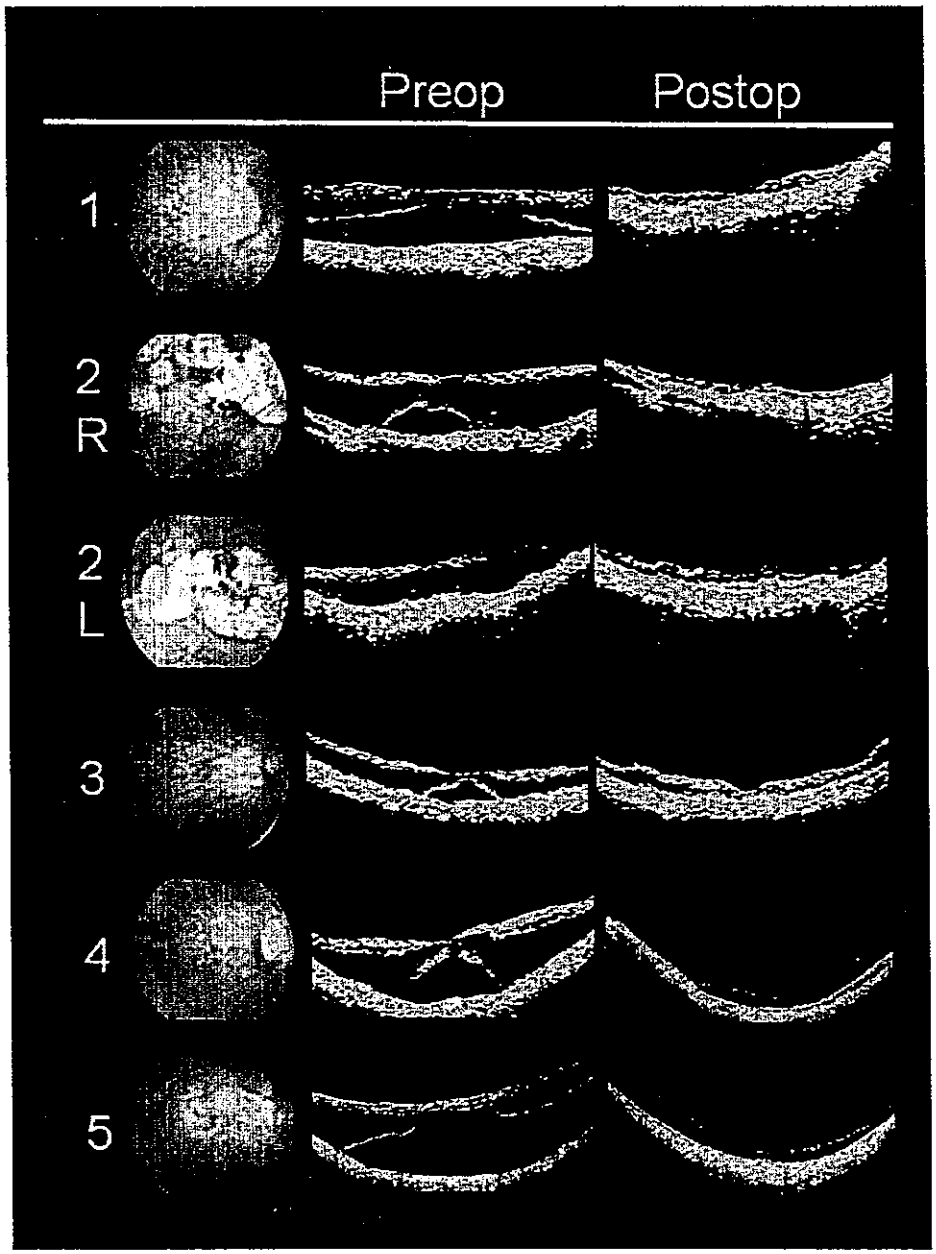


FIGURE 1. Postoperative fundus photograph (left), optical coherence tomography findings in the fovea before (middle), and 6 months after (right) surgery in the six study eyes. Subretinal fluid disappeared, and the fovea completely reattached in five eyes of four patients. Subretinal fluid remained but was reduced in case 4. Both eyes were involved in case 2. L = left; R = right.

The SLO microperimetry results in the three eyes (case 1, right eyes of case 2 and case 3) are shown in Figure 3. The functioning retinal area enlarged (Figure 3A) and fixation stabilized (Figure 3B) in all cases.

DISCUSSION

AFTER PERFORMING VITRECTOMY IN SIX EYES OF FIVE PATIENTS, the visual acuity improved in all eyes. Although we removed the crystalline lens from all patients, the visual improvement seemed to result from retinal reattachment and not from lens surgery. The fact that only the left eye of case 2 had a mild cataract, but all others had a clear lens before surgery, supports this. In addition, the scotoma decreased, and fixation stabilized after surgery based on SLO microperimetry results in three eyes. These observations suggest that visual improvement occurred because of the recovery of foveal function.

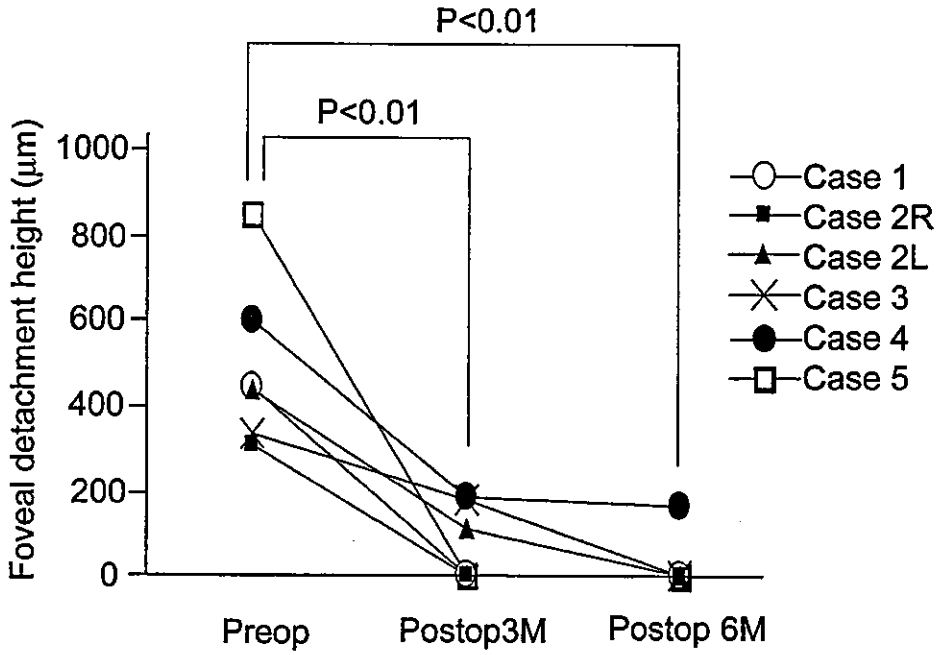


FIGURE 2. The time course of the height of the foveal detachment in all study eyes. The height was measured by optical coherence tomography. In all cases, the foveal detachment decreased after surgery. The height was significantly lower at 3 and 6 months after surgery ($P < .01$ for both comparisons). Both eyes of case 2 were involved. L = left; R = right.

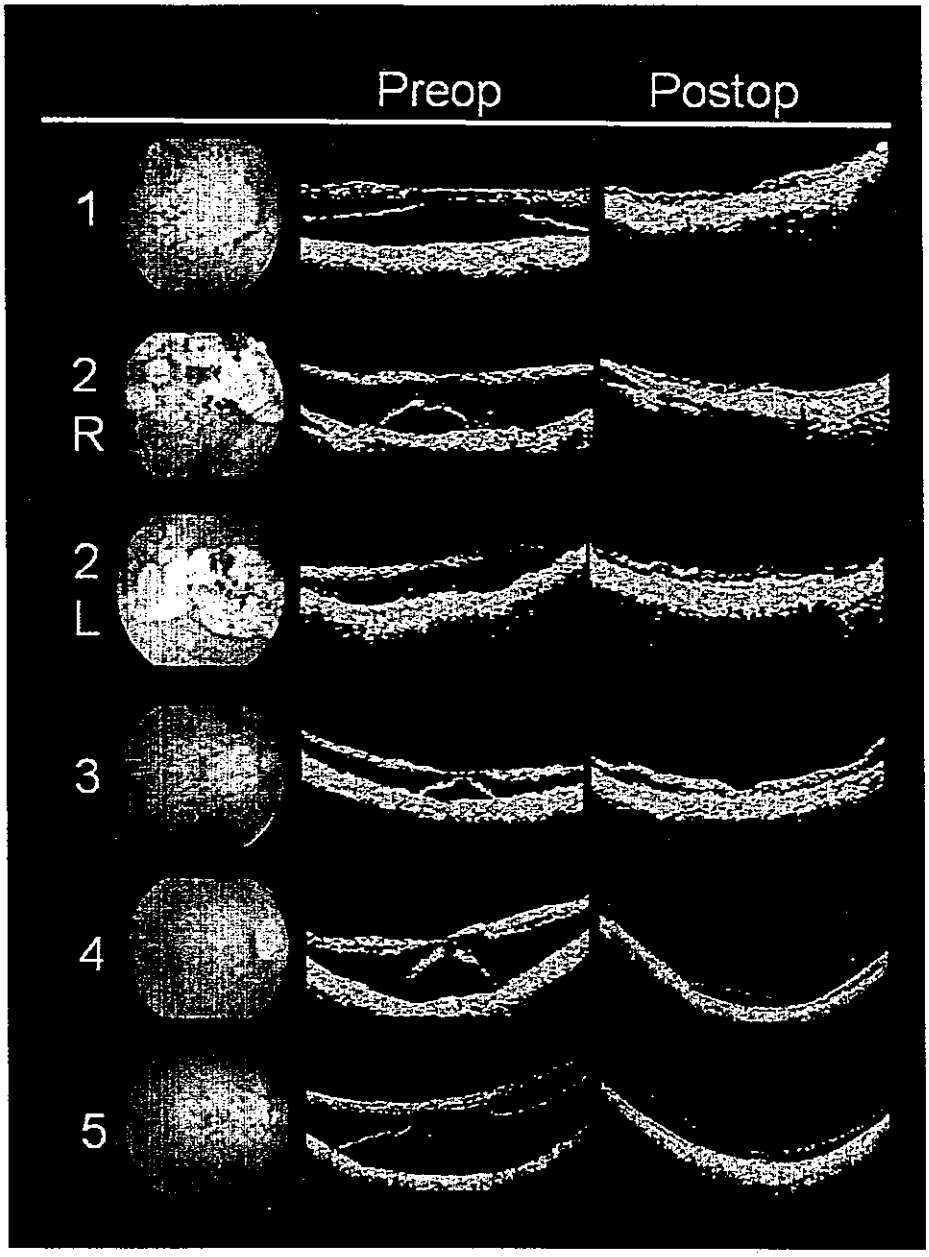
Vitrectomy sometimes results in poor visual outcome. In fact, one patient who underwent vitrectomy for myopic foveoschisis developed a macular hole.[7] In addition, we reported that myopic foveoschisis with an early macular hole is likely to result in enlargement of the macular hole and retinal detachment,[4] and macular holes tend to persist after vitrectomy in myopic eyes.[14] Based on these observations, we had confirmed the absence of a macular hole in patients using OCT before surgery, and none of our patients developed a macular hole after surgery. We believe that patients must be examined using OCT to detect a macular hole before surgery.

The mechanisms of myopic foveoschisis are poorly understood. Postoperative resolution in our patients suggests that the vitreous cortex may have contributed at least partially to the myopic foveoschisis, indicating the vitreous traction is pathogenetic of the disease. However, it is still uncertain if vitreous traction is involved in this disease. We tried to evaluate the presence/absence of posterior vitreous detachment by biomicroscopic examination and OCT; however, it was difficult. We believe that the status of the vitreous is a major subject that needs to be investigated.

Although Kuhn[15] suggested that an ILM is responsible for the macular detachment in highly myopic eyes, the present study did not prove the necessity for ILM peeling to treat the disease. For example, foveal detachment could be treated simply by creating a vitreous detachment and gas tamponade. There is also a growing body of evidence that simply ICG or ICG-assisted ILM peeling may be toxic to the neural retina as well as to the retinal pigment epithelium.[16–18] Thus, we should confirm the necessity for these surgical manipulations to establish an ideal surgical approach.

It is uncertain what type of myopic foveoschisis is suitable for vitrectomy. Reportedly, most patients with myopic foveoschisis do not develop a macular hole.[2] In addition, there was a case report in which myopic foveoschisis spontaneously resolved.[19] These observations suggest that only patients with symptoms should undergo surgery. Baba and associates[2] reported that none of seven patients complained of visual impairment. However, this does not agree with our experience that nine (82%) of 11 eyes were symptomatic in our clinic. In addition, the surgical effect is uncertain for inner retinoschisis[2] because it was not detected in any study eyes. Further investigations are needed to determine the incidence and natural course of myopic foveoschisis.

Finally, the surgery enabled resolution of the retinal detachments and subsequent visual improvement. However, this is a small study, and further study is necessary to confirm the surgical benefits.



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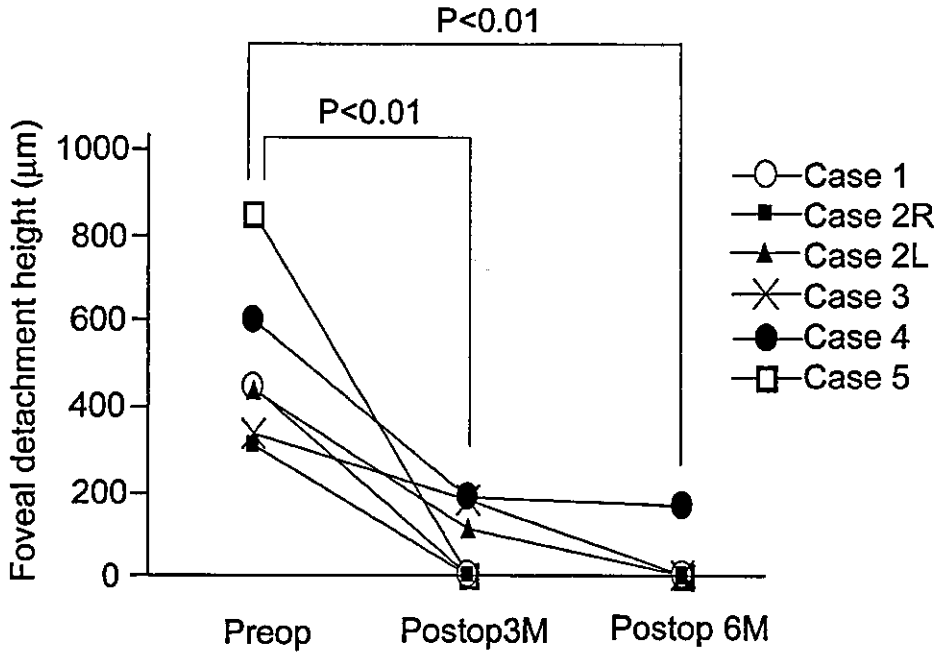

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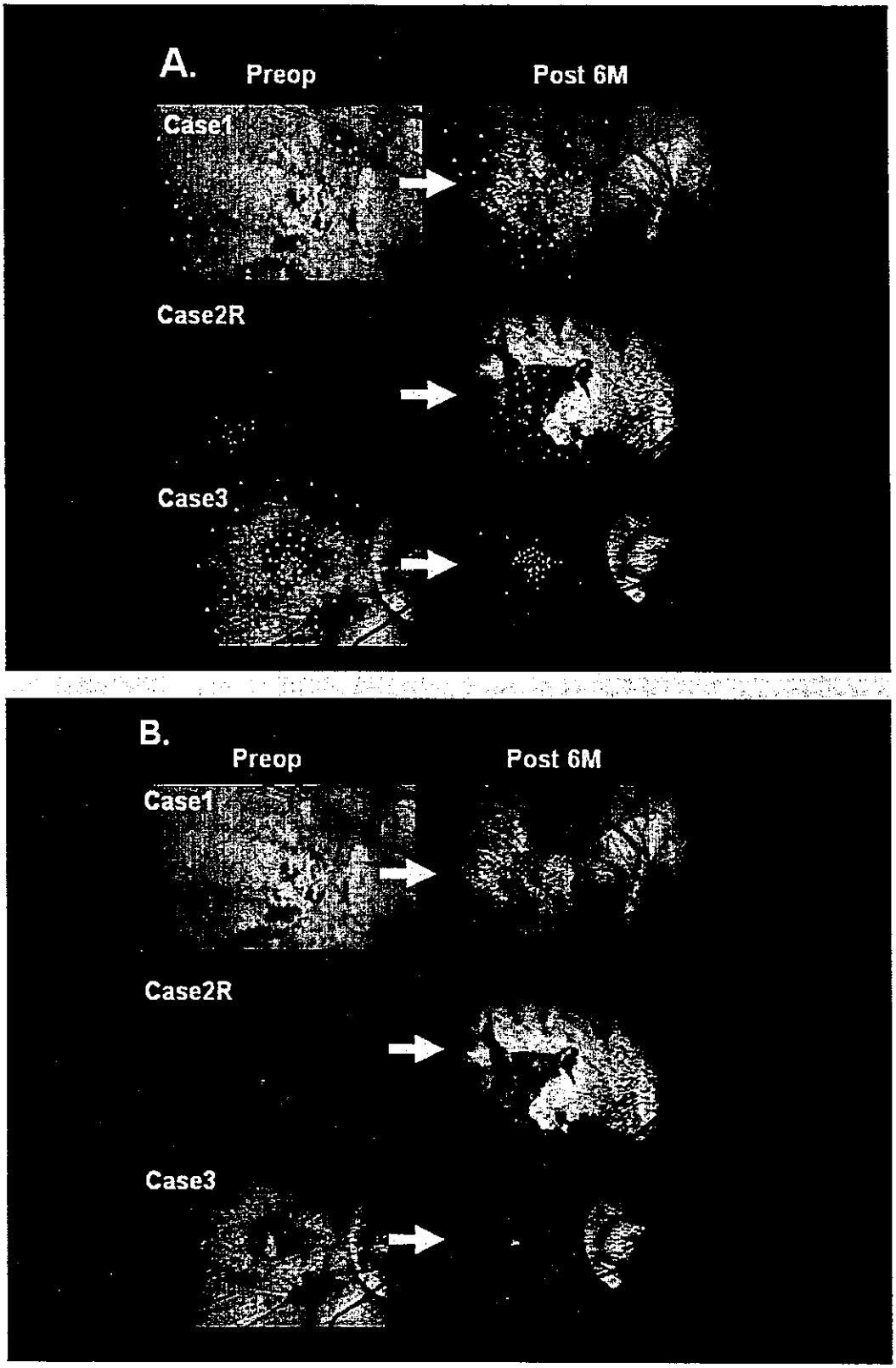

FIGURE 3. The preoperative and postoperative scanning laser ophthalmoscope microperimetry in case 1, and the right eye of cases 2 (case 2R), and case 3. (A) The green dots indicates the stimuli detected by the patient, and the red indicates the undetected stimuli. The scotoma has decreased in all eyes. (B) Green dots indicate the fixation point, which stabilized after surgery in all eyes. R = right.

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MACULAR TRANSLOCATION SURGERY AND RETINAL CIRCULATION TIMES

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ATSUSHI HAYASHI, MD,* TAKASHI FUJIKADO, MD,* YASUO TANO, MD*

Purpose: To quantify and compare the retinal circulation times before and after macular translocation surgery.

Methods: In nine patients undergoing macular translocation with 360° retinotomy, arm-retina and arteriovenous passage times were quantified from preoperative and postoperative scanning laser fluorescein angiograms. A control group of eight patients who had not undergone any intraocular surgery was also evaluated. The time that between injection into the antecubital vein and the appearance of fluorescein at two selected points on superotemporal and inferotemporal arteries near the disk provided the arm-retina time. For the arteriovenous passage time, 50% of the maximal fluorescence time difference was assessed from the intensity curves of arteries and corresponding veins at the same points for the arm-retina time. Postoperative measurements were obtained an average of 10.6 months after surgery.

Results: No significant difference was noted between preoperative and postoperative values of the arm-retina time (mean ± SD: 14.41 ± 2.73 seconds versus 14.67 ± 3.85 seconds, respectively; $P = 0.84$) or that of the arteriovenous passage time (2.66 ± 0.74 seconds versus 2.47 ± 0.68 seconds, respectively; $P = 0.37$) in the study group. The arm-retina time (14.96 ± 2.01 seconds) and arteriovenous passage time (2.44 ± 0.68 seconds) in the control group did not differ from preoperative and postoperative arm-retina times ($P = 0.65$ and $P = 0.85$) and arteriovenous passage times ($P = 0.54$ and $P = 0.93$) in the study group. The arteriovenous passage time correlated with the degree of retinal rotation around the optic disk in the study group ($r = -0.70$; $P = 0.04$).

Conclusion: Macular translocation surgery does not alter retinal macrocirculation in the long term.

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Macular translocation surgery offers gains in visual acuity for patients with subfoveal choroidal neovascular membranes who are otherwise destined to become legally blind. Surgery involves displacement of the functional sensory retina of the macula away from the subfoveal pathologic lesion to a new location over a healthier bed of retinal pigment epithelium to recover visual function there. During this procedure, the entire retina is detached from the retinal pigment epithelium and rotated about the optic nerve.[1,2]

Ocular perfusion is already defective in age-related macular degeneration (AMD),[3–5] and the effects of extensive retinal manipulation as well as altered retinal anatomy might contribute to further ocular hemodynamic derangement. The aim of this study was to

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measure and compare the retinal circulation times before and after macular translocation surgery.

Patients and Methods

Nine patients (six males and three females) with recently diagnosed subfoveal choroidal neovascularization secondary to AMD were evaluated in this study. Patients' ages ranged from 55 to 79 years (average, 67.4 years). Eight patients (five males and three females) with the same severity of AMD who had not undergone any intraocular intervention served as the control group. Controls' ages ranged from 65 to 78 years (average, 74.1 years).

Surgery, as described elsewhere,[2] included entire retina detachment followed by a 360° retinotomy, mobilization and rotation of the retina around the optic nerve head (28–70° against the retinal pigment epithelium), and reattachment with silicone oil tamponade in its new location following excision of the subfoveal neovascular membrane.

Fluorescein videoangiography with the disk centered in the 40° field was performed with a Rodenstock scanning laser ophthalmoscope (Munich, Germany) after injection of 5 mL of 10% sodium fluorescein into the antecubital vein with a 5-mL saline flush. The angiogram was recorded on DV videotape, digitized into a series of frames (spatial resolution, 480 × 480 pixels), and processed off-line; five frames per second were selected and evaluated. The measuring areas (7 × 7 pixels each) were located on the four main temporal vessels at distances between 0.5 and 1 disk diameter away from the disk rim. Over the area of interest, dye dilution curves were plotted against time by means of software (MatlabR12; The MathWorks, Inc., Natick, MA). Each area to be measured was manually reset on the vessels in the next frozen image, and in each image, the area of interest was maintained at a constant position where possible. From the dilution curves, arm-retina and arteriovenous passage times were determined. The time between the injection into the antecubital vein and the appearance of fluorescein at two selected points on superotemporal and inferotemporal arteries provided the arm-retina time, as previously described.[6] The half-maximal (50% of the peak fluorescence intensity) time difference at the temporal arteries and corresponding vein was used to determine the arteriovenous passage time. The half-maximal value, showing the best reproducibility, reflects the macular and more peripheral circulation.[7]

Times for the late postoperative measurements were decided according to a previous study as at least 6 months after the procedure.[8] All the measurements were obtained from noncomplicated eyes without silicone oil or any media opacity between 7 and 14 months after macular translocation (average, 10.6 months). The data obtained from the superior and inferior temporal quadrants were averaged as a representative macrocirculatory value for the posterior pole.

In all subjects, intraocular pressure, systemic blood pressure, and heart rate were measured just before each angiogram. In the study group, four patients who had a history of systemic hypertension were receiving medication before and after surgery. Another patient had undergone percutaneous transluminal coronary angioplasty for myocardial infarction 4 years before the operation. One other patient had a history of a transient cerebral ischemic attack 3 years before the macular translocation surgery. In the control group, three patients were hypertensive and taking antihypertensive medicine at the time of fluorescein angiography. One of these three controls also had diabetes mellitus that was under control and a history of angina pectoris. Another hypertensive control had a left ventricular hypertrophy. A fourth control had a diagnosis of ventricular premature beats. Another control had undergone an operation for intracerebral hemorrhage several years ago. The rest of the controls had no apparent systemic disease.

Patients were excluded from the study if they were unable to give informed consent or had a history of allergy to sodium fluorescein or radiographic dyes.

Paired *t*-test, unpaired *t*-test, and Pearson correlation analysis were used to analyze the data. Differences were significant at $P < 0.05$.

Results

During two angiograms obtained preoperatively and postoperatively, no significant differences in systolic and diastolic blood pressures, heart rate, and intraocular pressure were detected in the study group (Table 1; $P = 0.11$, $P = 0.09$, $P = 0.14$, and $P = 0.74$, respectively). Control group values were not different from study group preoperative measurements ($P = 0.24$, $P = 0.49$, $P = 0.57$, and $P = 0.61$, respectively) or postoperative measurements ($P = 0.45$, $P = 0.37$, $P = 0.09$, and $P = 0.77$, respectively).

In the study group, the arm-retina time was 14.41 ± 2.73 seconds preoperatively and 14.67 ± 3.85 seconds postoperatively. There was no statistically significant difference between the values ($P = 0.84$). Preoperative and postoperative arteriovenous passage times were 2.66 ± 0.74 seconds and 2.47 ± 0.68 seconds, respectively. No statistical significance was encountered between the two measurements ($P = 0.37$) (Figure 1).

In the control group, the arm-retina time was 14.96 ± 2.01 seconds and the arteriovenous passage

Table 1. Systemic and Ocular Parameters for Subjects

Parameter	Study Group		Control Group
	Preoperative	Postoperative	
Systolic blood pressure (mmHg)	138.5 ± 16.4	126.6 ± 12.7	128.3 ± 17.1
Diastolic blood pressure (mmHg)	80.8 ± 6.1	71.4 ± 10.3	77.8 ± 3.6
Pulse (beats/min)	66.1 ± 7.2	62.6 ± 8.9	68.3 ± 7.9
Intraocular pressure (mmHg)	13.3 ± 3.6	13.0 ± 3.9	12.5 ± 3.0

Data are mean ± SD.

time was 2.44 ± 0.68 seconds. These values did not differ from the study group preoperative and postoperative arm-retina time ($P = 0.65$ and $P = 0.85$, respectively) and arteriovenous passage time ($P = 0.54$ and $P = 0.93$, respectively).

The arteriovenous passage time correlated with the degree of retinal rotation around the optic disk ($r = -0.70$; $P = 0.04$). No correlation was detected with the degree of retinal rotational and the arm-retina time ($r = -0.46$; $P = 0.21$). Macular translocation generally seemed to result in more favorable outcomes in terms of stable retinal circulation times in eyes with the retina rotated between 28° and 47° around the optic disk (Figure 2).

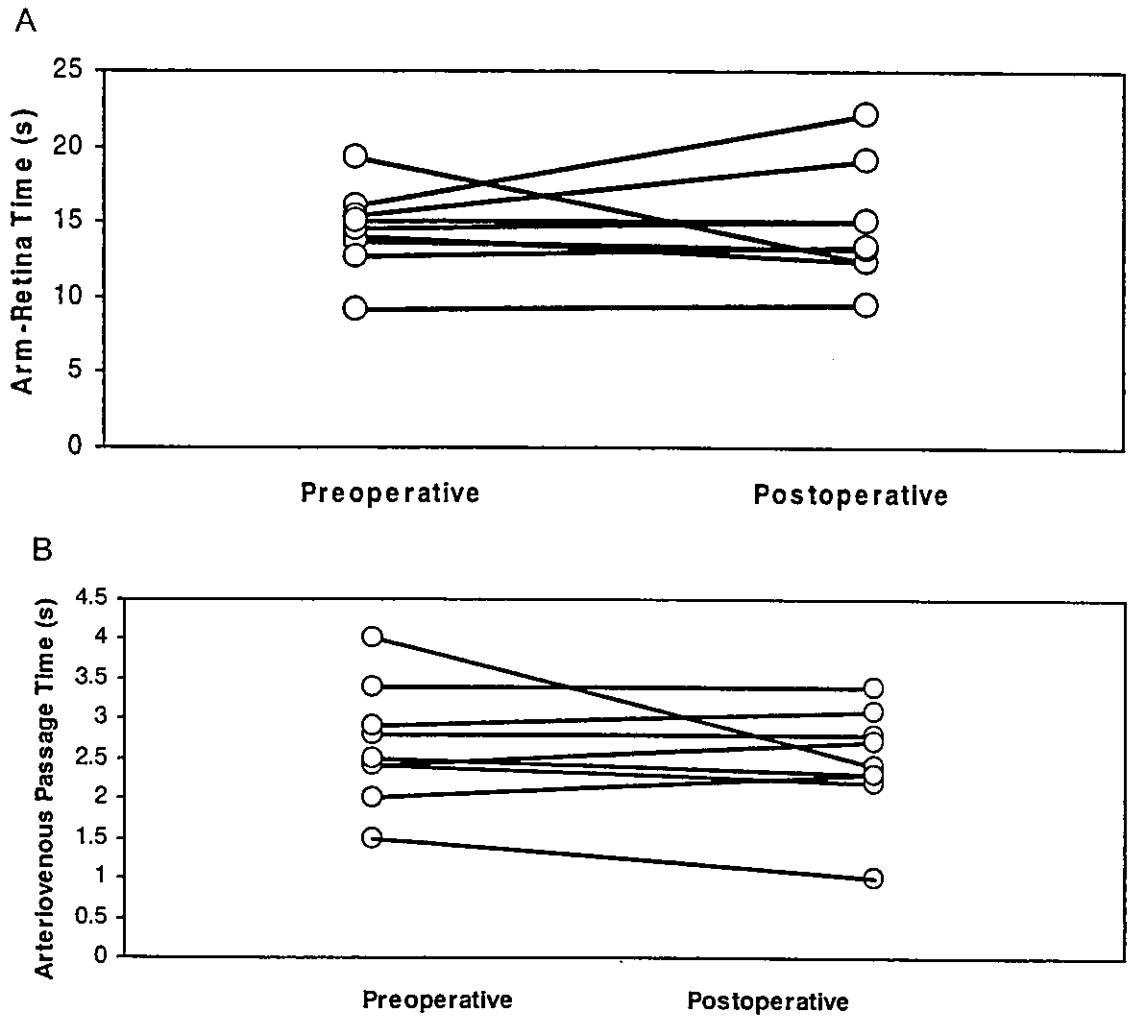

Fig. 1. Graphic illustration of data regarding retinal circulation times before and after surgery in the study group. A, Arm-retina time. B, Arteriovenous passage time.

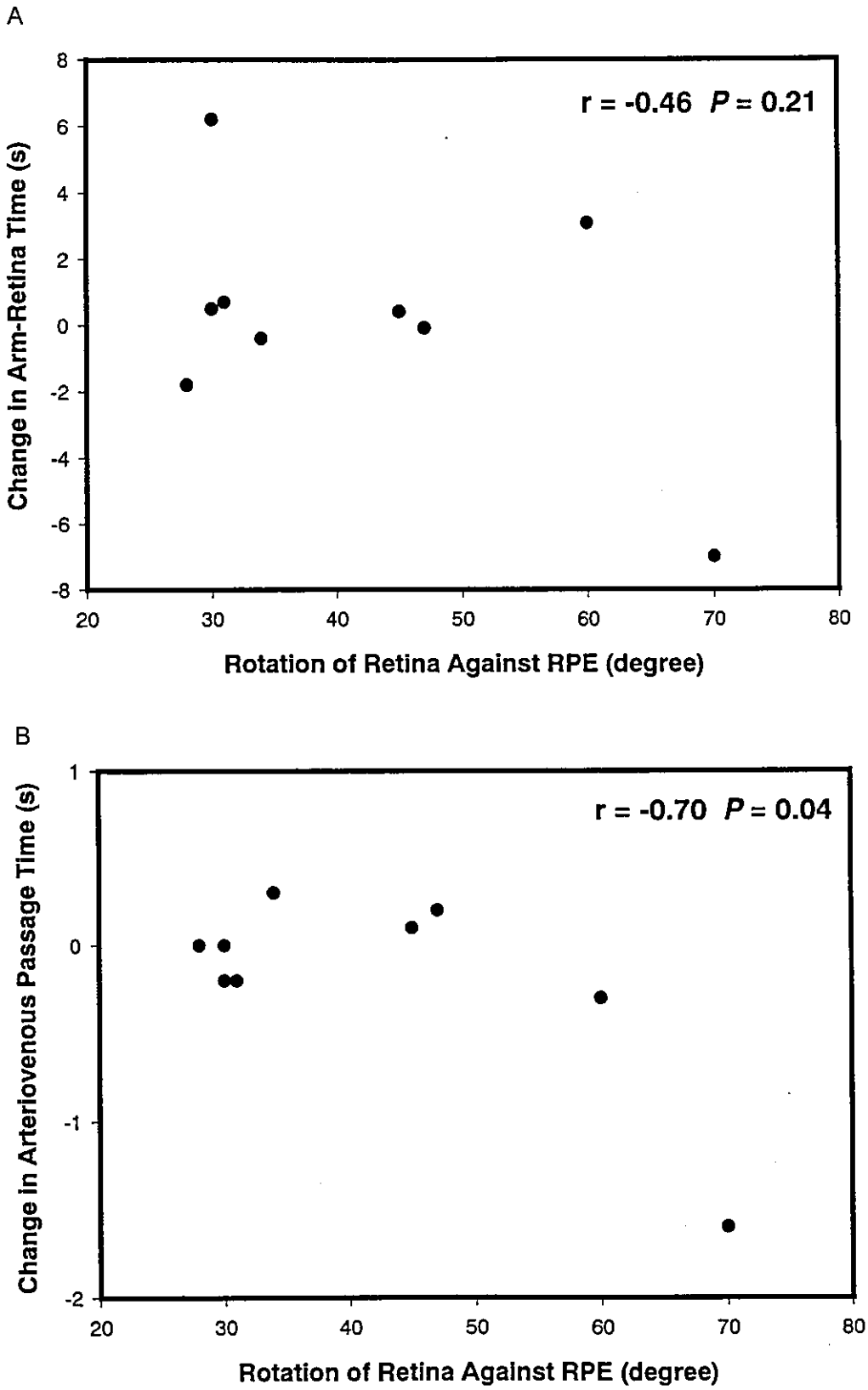

Fig. 2. Changes in retinal circulation times following macular translocation surgery in the study group. A, Changes in arm-retina time. B, Changes in arteriovenous passage time with rotation of the retina about the optic disk following surgery.

Discussion

Ocular perfusion defects have been well known in patients with AMD. Studies have described statistically significant reduced blood flow and increased vascular resistance in retinal[4] and choroidal perfusion[5] in patients with AMD compared with controls.

Blood supply of the neural layer of the human retina is maintained directly by four branch retinal arteries derived from the central retinal artery, and the retinal circulation is independent of the choroidal vasculature. Although differing in their distribution, the retinal circulation and choroidal circulation are in close proximity anatomically. This fact, coupled with the overwhelming volume of the choroidal circulation, necessitates specific techniques for measuring the retinal circulation.[9] It is possible to generate quantitative information specific to retinal blood flow from fluorescein angiograms, although this information is mostly used for qualitative studies. The evaluation of fluorescein angiography by means of digital picture analysis provides reproducible data in the assessment of retinal hemodynamics. From the analysis of fluorescein intensity curves, useful parameters, such as the arm-retina time and arteriovenous passage time, can be computed to quantify the retinal macrocirculation in normal and diseased eyes.[6,7,10,11]

Considering the intraindividual variation for the circulation times (27%, arm-retina time; 16%, arteriovenous passage time),[10] a control group of subjects with the same severity of AMD as the study group subjects was also evaluated in the current study. To the best of our knowledge, there has been no previous report regarding the retinal circulation times derived from scanning laser fluorescein angiography for patients with exudative AMD. By using the same technique as the current study, another study reported a shorter arm-retina time (12.4 ± 2.4 seconds) for normal subjects of similar age (62 ± 10 years).[10] Another study found a shorter half-maximal arteriovenous passage time (1.83 ± 0.50 seconds) for healthy subjects who were relatively younger (45.1 ± 17.2 years) but had a similar sex ratio (24 males and 13 females).[7] Decreased blood flow as well as increased resistance in the central retinal artery[4] is consistent with prolonged retinal circulation times in patients with AMD.

The retinal circulation has autoregulation capacity, which is due to alteration in resistance to blood flow. The goal of autoregulation is to maintain a relatively constant blood flow and nutrient supply in spite of changes in perfusion pressure.[9,12]

The quantitative state of the retinal circulation has also been determined after retinal interventions.[8,13] Prolongation of arteriovenous passage times was reported for silicone oil-filled eyes at 3 to 5 days after vitrectomy. Both the silicone oil itself and the operative trauma were proposed as the possible causes of the adverse effect on the retinal blood flow during the early postoperative period.[13] Our results showed that, after removal of silicone oil, macular translocation with 360° retinotomy had no unfavorable effect on retinal circulation times in patients with exudative AMD.

To date, no optimal rotational degree has been determined for translocation surgery. A larger degree of rotations is essential in patients with very large choroidal neovascular membranes, but the visual outcome could be poor in such cases.[2] The current study clarified the significant negative correlation between retinal rotation and retinal arteriovenous passage time. This seems to be inconsistent with unaltered preoperative and postoperative arteriovenous passage times. However, retinal rotations up to approximately 50° generally did not result in deviant arteriovenous passage time differences (Figure 2B). Arm-retina time results also supported this impression in most cases (Figure 2A). This study was a nonrandomized preliminary study that included relatively few patients. An increased number of subjects might alter the significance, particularly in eyes with larger rotations.

In conclusion, it is possible to estimate roughly the effect of macular translocation surgery on the retinal circulation by using a minimally invasive method, scanning laser fluorescein angiography. Retinal displacement about the optic disk did not alter the retinal macrocirculation significantly in the long term. The high autoregulatory capacity of retinal vessels is probably the main contributory factor to the results.

Key words: age-related macular degeneration, arm-retina time, arteriovenous passage time, fluorescein angiogram, macular translocation, scanning laser ophthalmoscope.

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Retinal Changes After Macular Translocation With 360-Degree Retinotomy in Monkey Eyes

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• PURPOSE: To determine the morphologic and functional changes of the fovea and retina of monkey eyes after macular translocation with 360-degree retinotomy.
• DESIGN: Experimental study.
• METHODS: The retinas of eight monkey eyes were surgically translocated with a 360-degree retinotomy with procedures similar to those used on human eyes. At 1, 2, and 3 months after the surgery, the six eyes that had successful surgery were studied by light and transmission electron microscopy, terminal deoxynucleotidyl transferase (TdT)-dNTP terminal nick-end labeling (TUNEL) assay, and immunohistochemistry with peanut agglutinin (PNA) lectin and glial fibrillary acidic protein (GFAP). Retinal physiology was assessed by scotopic and photopic electroretinograms (ERGs).
• RESULTS: The fovea was successfully translocated approximately 30 to 40 degrees superiorly in six eyes. The translocated macula and fovea had a normal layered architecture with no TUNEL-positive cells, minimal misalignment of the outer segments, and strong immunoreactivity to GFAP. The mean amplitudes of the scotopic and photopic b-waves were significantly reduced at 1 month after the surgery, and there was only a slight recovery at 3 months. No significant changes were observed in the mean implicit times after the surgery.
• CONCLUSION: These findings indicate that macular translocation surgery with 360-degree retinotomy results in minimal morphologic alterations but significant depression of electrophysiologic function. (Am J Ophthalmol 2004;137:1034–1041. © 2004 by Elsevier Inc. All rights reserved.)

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MACULAR TRANSLOCATION SURGERY WITH 360-degree retinotomy, one surgical approach to treat subfoveal diseases, was first introduced by Machemer and Steinhorst in 1993.[1] De Juan and associates[2] developed a limited macular translocation surgical procedure of scleral shortening. Currently, these two surgical techniques are performed, and although both have been reported to improve the visual function in the short term, the long-term effectiveness has not been evaluated.[1–11]

Macular translocation surgery with 360-degree retinotomy involves detaching the entire neurosensory retina from the retinal pigment epithelium, and freeing the retina by a 360-degree peripheral retinotomy. The retina is then rotated to relocate the fovea onto healthier retinal pigment epithelium. During the operation, the retina undergoes considerable mechanical and ischemic stress, and thus there is great potential for morphologic and physiologic alterations even though the central visual function has been reported to be improved in many clinical case series.[1–11]

The effects of macular translocation on retinal morphology and physiology have also been examined in animals. We have found that scleral shortening in dog eyes resulted in retinal folds and significant damage to the retina within the folds.[12] We have also shown that calcium- and magnesium-free BSS Plus solution facilitated the artificial retinal detachment for macular translocation surgery.[13] The purpose of this study was to determine whether macular translocation surgery with 360-degree retinotomy alters the morphology and physiology of the retina and fovea. To accomplish this, we performed surgery on eight monkey eyes with procedures similar to those used in human eyes and examined the retina by histologic, immunohistochemical, and electrophysiologic methods.

METHODS

• MACULAR TRANSLOCATION SURGICAL PROCEDURES: One eye each from eight female *Macaca fascicularis* monkeys weighing 2.5 to 3.5 kg whose ages were 2 to

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3 years was used. All experimental procedures on the monkeys were performed to conform to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

The monkeys were initially anesthetized by an intramuscular injection of ketamine (0.5 ml, 5 mg/kg) and xylazine (0.25 ml, 10 mg/kg), and surgical anesthesia was maintained with intraperitoneal pentobarbital (1.25 ml, 10 mg/kg). Then, 0.25 ml pentobarbital was injected intraperitoneally every hour to maintain the general anesthesia.

The pupil was fully dilated with topical 0.5% tropicamide and 0.5% phenylephrine, and preoperative fundus photographs and fluorescein angiograms (Topcon, Tokyo, Japan) were obtained.

For the macular translocation surgery, the conjunctiva was incised with microscissors for 360 degrees, and the sclera was exposed under an operating microscope. The three ports for the standard pars plana vitrectomy were created 2.5 mm from the limbus at 2, 8, and 10 o'clock. After lensectomy and removal of the posterior lens capsules, core vitrectomy was performed. A posterior vitreous detachment was created with a Grizzard needle (Eagle Laboratories, Rancho Cocamonga, CA) with 400 mm Hg of aspiration. After peripheral vitrectomy, the sensory retina was intentionally detached from the retinal pigment epithelium by injecting irrigating solution (BSS Plus; Alcon Surgical, Fort Worth, Texas) into the subretinal space in the posterior pole with a 42-gauge polyimide cannula. Three or four injections were usually necessary to produce a total retinal detachment. During the operation, a retinal manipulator was used to detach peripheral residual attachments of the sensory retina from the retinal pigment epithelium because of an incomplete retinal detachment in all eyes. A 360-degree of retinotomy was performed close to the ora serrata with a vitreous cutter or microscissors.

While injecting perfluorocarbon liquid, the detached and freed retina was rotated with a diamond-dusted membrane scraper and reattached with the fovea positioned superior to its former position. Laser photocoagulation was applied near the edges of the retinotomy to fix the retina and to seal the retinotomy sites. Finally, perfluorocarbon liquid was replaced by silicone oil, the sclerotomy sites were closed, and the conjunctiva was sutured.

After the operation, dexamethasone was injected into the subconjunctival space, and antibiotic ointment was placed in the cul-de-sac and injected intramuscularly. Silicone oil was removed in a second operation 4 weeks after the first surgery.

Fundus examination, fundus photography, and fluorescein angiography were performed before, and 1, 2, and 3 months after the surgery.

The animals were sacrificed by an overdose of intravenous pentobarbital under deep anesthesia. Six eyes without marked postoperative complications were enucleated for further histologic investigation (one eye at 1 month, one eye at 2 months, four eyes at 3 months after surgery). In addition, two unoperated eyes were examined as controls.

• HISTOCHEMICAL PROCEDURES: The enucleated eyes were fixed overnight in 4% paraformaldehyde and 0.1% glutaraldehyde in 0.1 mol/l phosphate buffered solution (PBS) at 4°C. The anterior segment was removed, and the macular area including the fovea was cut into smaller pieces. Some of the tissues were processed for standard histology, and the others for immunohistochemical and terminal deoxynucleotidyl transferase (TdT)-dNTP terminal nick-end labeling (TUNEL) assay.[12]

For standard histology, the tissues were dehydrated through a graded series of ethanol, and placed in two changes of propylene oxide for 15 minutes. They were infiltrated overnight in a 1:1 solution of propylene oxide and epoxy resin (Quetol 812; Nisshin EM, Tokyo, Japan). The pieces were then embedded in 100% Quetol 812, and 1-μm sections were cut and stained with 0.5% toluidine blue and 0.25% sodium borate. The sections were examined and photographed under a light microscope (Olympus, Tokyo, Japan). Ultrathin sections were cut, examined, and photographed under a transmission electron microscope (Hitachi, Tokyo, Japan).

The other pieces were immersed in 30% sucrose in 0.1 mol/l PBS at 4°C overnight and embedded in optimal cutting temperature compound (OCT; Miles, Elkhart, Indiana). Cryosections of 10-μm thickness were cut and processed for TUNEL assay and immunohistochemistry.

• TUNEL ASSAY Cryosections of the operated eyes were processed to detect DNA fragmentation in the retina by the TdT-mediated dUTP nick-end labeling (TUNEL) method with a peroxidase kit (ApopTag; Oncor, Gaithersburg, Maryland) according to the manufacturer's instructions. Briefly, residues of digoxygenin-nucleotide were catalytically added by TdT to the 3'-OH ends of double- or single-strand DNA. The labeled products were made visible by diaminobenzidine (DAB)-enhanced commercial methods (HistoMark Orange; Kirkegaard & Perry; Gaithersburg, Maryland), which resulted in reddish-orange positive staining. The sections were counterstained with 1% methyl green. Positive and negative controls of TUNEL assay were performed simultaneously using retinal sections of the operated eyes. Positive controls were pretreated with 0.4 μg/ml deoxyribonuclease 1 (Sigma Chemical, St. Louis, Missouri) solution for 10 minutes at room temperature before the incubation with digoxygenin-nucleotides. Negative controls were obtained by incubation without active TdT.

• IMMUNOHISTOCHEMISTRY: Cryosections of the operated and unoperated eyes were stained with peanut agglutinin (PNA) lectin (Honen, Tokyo, Japan) or antihuman glial fibrillary acidic protein (GFAP) antibody (ICN Pharmaceuticals, Aurora, Ohio). After the sections were rehydrated in 0.1 mol/l PBS, they were incubated with

fluorescein isothionate (FITC)-conjugated PNA lectin (1:500 diluted in 0.1 mol/l PBS) for 1 hour at 37°C. After sections were rinsed in 0.1 mol/l PBS several times, they were mounted and examined with an epifluorescence microscope (Zeiss, Tokyo, Japan).

For GFAP staining, the sections were incubated with anti-GFAP antibody (1:50 diluted in 0.1 mol/l PBS) for 1 hour at 37°C. After rinsing in 0.1 mol/l PBS, they were incubated with FITC-conjugated antirabbit IgG antibody (Jackson ImmunoResearch, West Grove, Pennsylvania) for 1 hour at 37°C. They were examined with an epifluorescence microscope (Ziess, Tokyo, Japan).

• ELECTRORETINOGRAPHY: Retinal function was assessed by full-field, dark-adapted (scotopic) and light-adapted (photopic) electroretinograms ([ERGs] Neuropack 2, Model MEB-7202; Nihon Kohden, Tokyo, Japan) that were recorded before, and at 1, 2, and 3 months (four eyes each) after the surgery. The recordings were performed according to the standards of the International Society for Clinical Electrophysiology of Vision (ISCEV).[14]

Under general anesthesia, the pupil was dilated with 0.5% tropicamide and 0.5% phenylephrine hydrochloride. A contact lens electrode with LEDs as a light source (Tomey, Nagoya, Japan) was placed on the anesthetized cornea (0.4% oxybuprocaine hydrochloride). The reference and ground electrodes were attached to the two ears. After 60 minutes of dark-adaptation, the scotopic (rod) ERGs, elicited by a blue stimulus at an intensity of 0.01 cd.sec/m^2, were recorded. Then, the scotopic rod-cone ERGs, elicited by a white stimulus of 200 cd.sec/m^2 were recorded. After 15 minutes of light adaptation, the photopic (cone) ERGs and the 30-Hz flicker ERGs that were elicited with a white stimulus intensity of 3 cd.sec/m^2 and 10 cd.sec/m^2, respectively, on a white background of 25 cd/m^2 luminance were recorded.

Three responses were averaged for both the scotopic ERGs (at 1-minute intervals) and the photopic ERGs (at 30-second intervals) for each eye. The amplitudes and implicit times of the b-waves were expressed as the percentages of the preoperative values.

• STATISTICAL ANALYSIS: Paired-sample *t* tests were used to compare the data. A *P* value of less than .05 was considered statistically significant.

RESULTS

• RETINAL TRANSLOCATION SURGERY: Macular translocation surgery was performed successfully on the eight eyes. The retina remained reattached after the silicone oil was removed, and the fovea was successfully relocated superiorly approximately 30 to 40 degrees. Two of eight eyes developed proliferative and retinal detachment after the silicone oil was removed. These two eyes were excluded from further investigation.

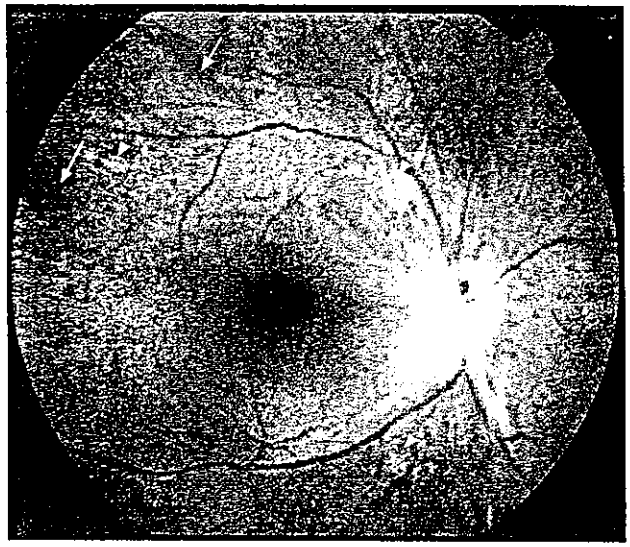

FIGURE 1. Fundus photograph of a monkey eye at 3 months after macular translocation surgery. Pigmentation (arrows) and depigmentation (arrowheads) of RPE were seen in the fundus.

Pigmentation and depigmentation of retinal pigment epithelium were observed by ophthalmoscopy (Figure 1) in association with hypofluorescence and hyperfluorescence during fluorescein angiography (Figure 2) postoperatively in all six eyes. No other specific fluorescein angiography changes were detected in all six eyes.

• LIGHT MICROSCOPY: The macula including the relocated fovea of six eyes was examined by light microscopy at 1 (one eye), 2 (one eye), and 3 (four eyes) months postoperatively. The sensory retina in the macular area was relatively well preserved with no marked misalignment of the outer segments of the photoreceptors. The retinal pigment epithelium was juxtaposed against the outer segments. A mild retinal edema was observed in the outer plexiform layer in the perifoveal area. The fovea had a concave shape but was mildly distorted (Figure 3).

• TRANSMISSION ELECTRON MICROSCOPY: Examination of the macula including the relocated fovea of the four eyes at 3 months showed that the inner and outer segments of the photoreceptors were essentially intact (Figure 4). Some swollen mitochondria were seen in the inner segments of photoreceptors and in the retinal pigment epithelium (arrows). Some debris of outer segments was observed between outer segments and retinal pigment epithelium microvilli (asterisks). Phagosomes were present in the retinal pigment epithelium (arrowheads). The outer limiting membrane was intact.

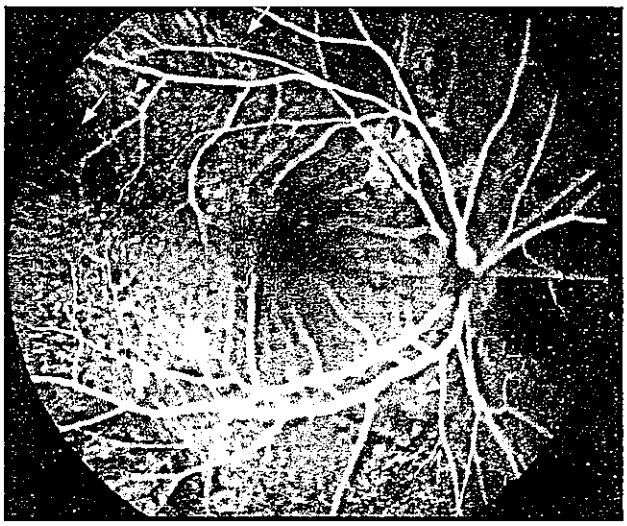

FIGURE 2. Photograph of fluorescein angiogram of a monkey eye at 3 months after macular translocation surgery. Postoperative fluorescein angiogram showed hypofluorescence (arrows) and hyperfluorescence (arrowheads) which corresponded to the pigmentation and depigmentation in the fundus.

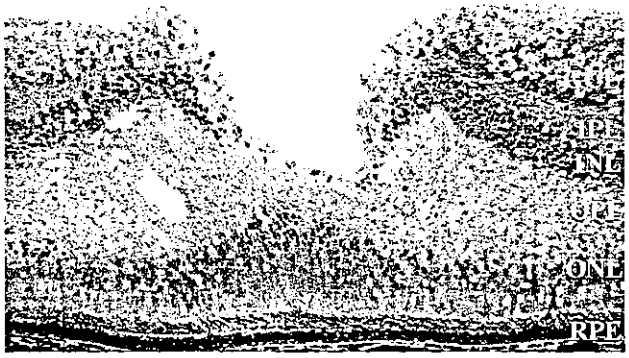

FIGURE 3. Photomicrograph of the fovea of the monkey retina 3 months postoperatively. Fovea showed a foveal depression, and the retina appeared relatively normal. The fovea was juxtaposed against the RPE and mildly distorted. The retina showed a mild retinal edema in the perifoveal outer plexiform layer (arrows). GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; RPE, retinal pigmented epithelium. (×400)

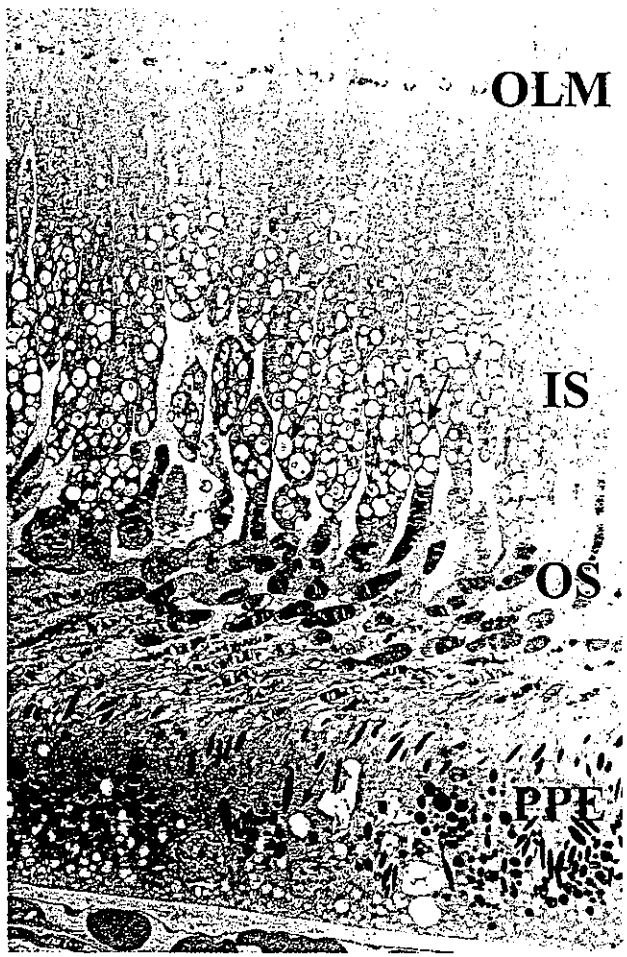

FIGURE 4. Transmission electron micrograph of the same foveal area as shown in Figure 3. The RPE, outer and inner segments of the photoreceptor cells, and outer limiting membrane were seen. The inner and outer segments of the photoreceptors appeared relatively intact. The apical microvilli of the RPE cells interdigitated with the outer segments. Some swollen mitochondria were observed in the inner segments of photoreceptors and RPE (arrows). Debris of outer segments was observed between outer segments and RPE microvilli (asterisks). Some phagosomes (arrowheads) were observed in the RPE. OLM, outer limiting membrane; IS, inner segments; OS, outer segments; RPE, retinal pigment epithelium. (×1000)

The retinal pigment epithelium cells were preserved, and the apical microvilli of the retinal pigment epithelium cells were interdigitated with the outer segments.

• TUNEL ASSAY: The TUNEL assay was performed at 1 (one eye), 2 (one eye), and 3 (four eyes) months postoperatively to detect apoptosis of the photoreceptor cells. Positive controls showed reddish-orange, TUNEL-positive staining in all nuclei of cells in the retina (Figure 5, A). No TUNEL-positive nuclei were seen in retinal sections from negative controls (data not shown). TUNEL-positive cells were not detected in the retinas of all six eyes after macular translocation surgery (Figure 5, B).

• IMMUNOHISTOCHEMISTRY: Cryosections of the macula of two unoperated eyes and six operated eyes at 1 (one eye), 2 (one eye), and 3 (four eyes) months were stained with FITC-conjugated PNA lectin. In unoperated retinas, the PNA-stained cone matrix sheath extended over the entire inner and outer segments of the photoreceptors

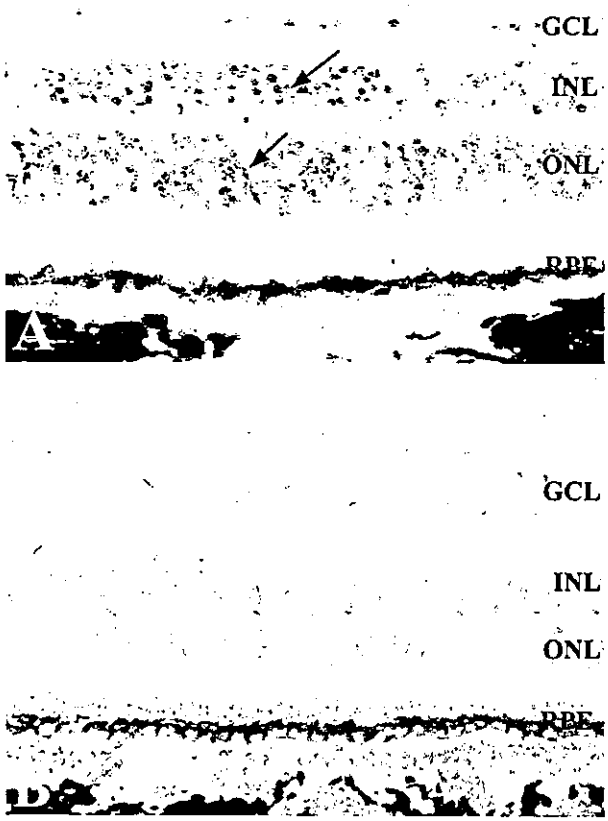

FIGURE 5. Photomicrographs of retinas of an operated monkey eye at 3 months postoperation with TUNEL assay. (A) Positive control retina. All nuclei in the retina were labeled with reddish-orange color (arrows). (B) No TUNEL-positive nuclei were detected in the retina of the operated eye at 3 months after surgery. GCL, ganglion cell layer; INL, inner nuclear layer; ONL, outer nuclear layer; RPE, retinal pigment epithelium. (×200)

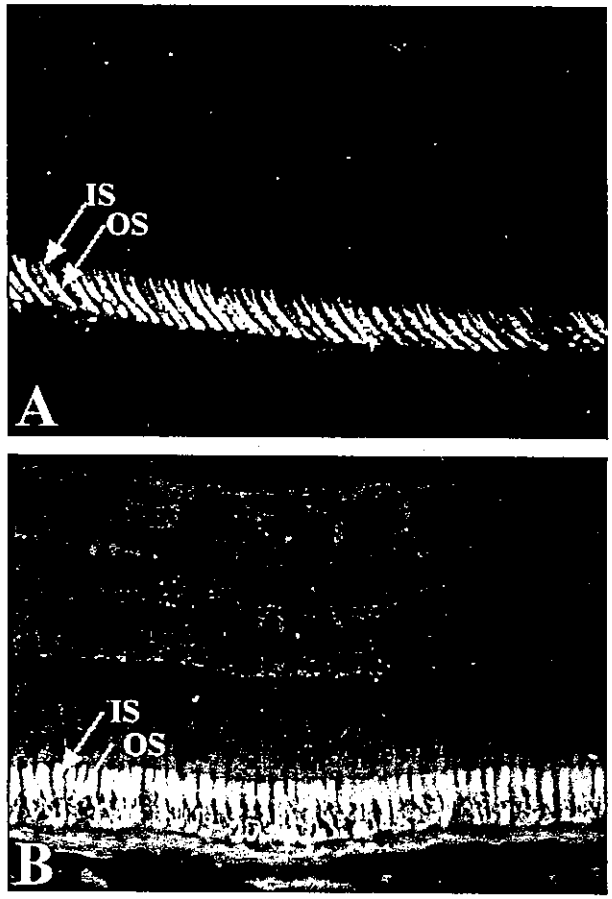

FIGURE 6. Fluorescent photomicrographs of retinas immunolabled with FITC-conjugated PNA lectin. (A) Retina from an unoperated monkey eye. The cone matrix sheath around the inner and outer segments of photoreceptor cells were positively stained. (B) Retina from an operated monkey eye at 3 months after surgery. The staining was similar to that seen in A. Slight disturbance in the arrangement of the outer segments was seen. IS, inner segments; OS, outer segments. (×200)

(Figure 6, A). Peanut agglutinin-positive staining of the cone matrix sheaths was present in the operated retinas at 1, 2, and 3 months after surgery. The alignment of the outer segments was slightly distorted in the operated retinas after surgery (Figure 6, B).

The cryosections were also stained with anti-GFAP antibody. In unoperated eyes, GFAP staining was observed in the Mueller cell endfeet and the processes of astrocytes in the nerve fiber layer (Figure 7, A). At 1 month after surgery, the Mueller cells were strongly positive to GFAP and the staining extended into the inner nuclear layer (Figure 7, B). Similar positive staining for GFAP was observed at 2 and 3 months after surgery (data not shown).

• ELECTRORETINOGRAPHY: Representative scotopic, rod-cone, photopic, and 30-Hz flicker ERGs recorded before and at 3 months after the surgery are shown in Figure 8. The mean amplitudes of the b-wave at 1 month were significantly reduced to 18.2% ± 3.5% (mean ± SD) for the scotopic rod ERGs, to 45.1% ± 3.0% for the rod-cone ERGs, to 23.2% ± 5.2% for the cone ERGs, and to 30.2% ± 3.1% for the 30-Hz flicker ERGs of the preoperative amplitudes ($P < .05$ for all). The amplitudes recovered gradually except the rod-cone ERGs, but at 3 months, they were still significantly reduced at 47.3% ± 4.5% for the scotopic rod ERGs, 38.1 ± 4.2% for the scotopic rod-cone ERGs, 36.1% ± 5.8% for the cone ERGs, and 40.1% ± 6.9% for the 30-Hz flicker ERGs of the preoperative amplitudes ($P < .05$, for all; Figure 9, A).

The mean implicit times of the b-wave were delayed by 28.1% ± 4.1% for the scotopic rod ERGs, by 30.1% ± 3.5% for the scotopic rod-cone ERGs, by 13.1% ± 4.9% for the cone ERGs, and by 1.2% ± 3.1% for the 30-Hz flicker ERGs of the preoperative implicit times at 1 month after the surgery. However, these delays were not statisti-

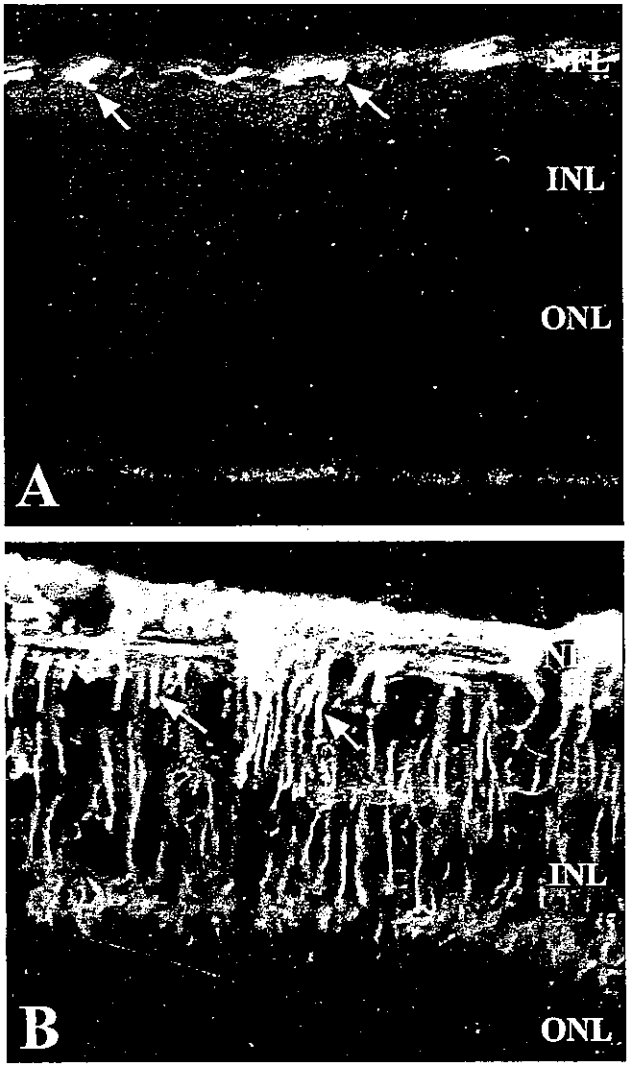

FIGURE 7. Fluorescence photomicrographs of retinas stained with anti-human GFAP antibody. (A) Retina from an unoperated monkey eye. GFAP staining was observed in the Mueller cell endfeet and astrocytes in the nerve fiber layer (arrows). (B) Retina from an operated monkey eye at 3 months after surgery. Strong GFAP staining was observed in the vertical processes of the Mueller cell and in the nerve fiber layer extending into the inner nuclear layer (arrows). NFL, nerve fiber layer; INL, inner nuclear layer; ONL, outer nuclear layer. (×400)

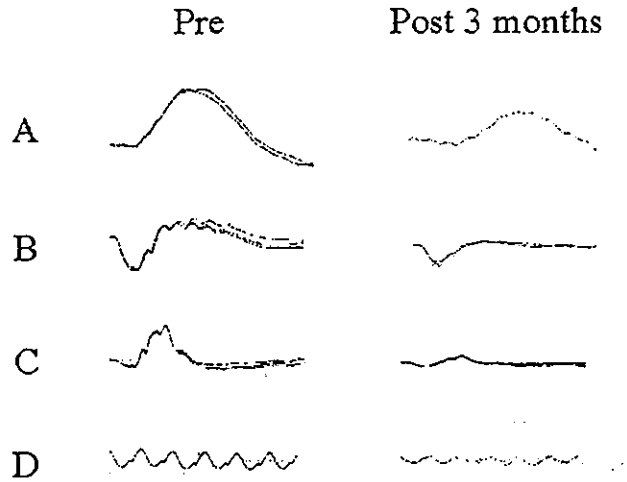

FIGURE 8. Representative scotopic rod ERGs (A), scotopic rod-cone ERGs (B) after dark-adaptation for 60 minutes, and cone ERGs (C) and 30-Hz flicker ERGs (D) after light-adaptation for 15 minutes before and at 3 months after surgery. The b-wave amplitude was reduced markedly at 3 months after surgery.

cally significant ($P > .05$ for all). The implicit time of the ERGs recovered almost to the preoperative values at 2 months after surgery (Figure 9, B).

DISCUSSION

MACULAR TRANSLOCATION SURGERY HAS GENERATED widespread interest among ophthalmologists, and can be considered clinically successful as assessed by the improvement of visual acuity and microperimetric findings.[1-11] In parallel with the clinical studies, laboratory studies on rabbit, pig, and dog eyes that have undergone macular translocation surgery[12,15,16] have shown a variety of complex and characteristic cellular responses in the photoreceptors, retinal pigment epithelium cells, and inner retinal neurons. Simple, short-term retinal detachments did not induce significant photoreceptor degeneration. After longer detachments, reattachment of the retina resulted in rapid regeneration of the photoreceptor outer segments.[17-19] For limited macular translocation, some loss of the vertical alignment of the photoreceptors was detected, and an increase in the interphotoreceptor space recovered with time in pig eyes.[16] In dog eyes, scleral shortening resulted in extensive loss of photoreceptor cells in the retinal folds.[12]

In our macular translocation surgery on monkey eyes, the creation of the intentional retinal detachment is a critical procedure. The adhesive force between the photoreceptor cells and retinal pigment epithelium is different in different species,[20] and several methods have been used to detach the retina with less damage to the retina and retinal pigment epithelium.[13,21,22] The ease of this surgical procedure is directly related to the strength of the adhesion. Detaching the sensory retina off the retinal pigment epithelium in rabbit eyes resulted in a partial loss of the outer segments and microvillus fragments peeled from the retinal pigment epithelium.[13,15] The retinal adhesive force in monkeys is roughly 40% greater than that in rabbits.[20] Because our monkeys were young, the retinal adhesive force was probably stronger in these younger animals than in older monkeys. Thus, we encountered some difficulties

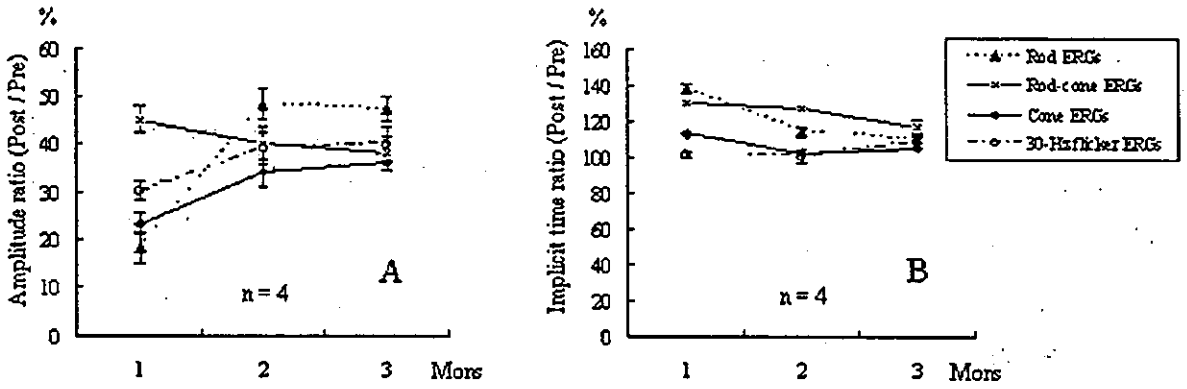

FIGURE 9. The amplitude (A) and the implicit time ratio (B) between post- and pre-operative b-wave for the scotopic rod and the rod-cone ERGs after dark-adaptation at for 60 minutes and for the cone and the 30-Hz flicker ERGs after light-adaptation for 15 minutes at 1, 2, and 3 (n = 4) months postoperatively. The retinal function was reduced significantly at 1 month after surgery, recovered gradually to 36–47% of the preoperative values at 3 months after surgery ($P < .05$, respectively). Values were given as mean ± SD.

during the hydrodissection of the retina from retinal pigment epithelium. Pigments were observed on the photoreceptor surface of retina, and a migration of pigment granules into the vitreous cavity was observed during the retinal hydrodissection and the separation of the residual peripheral retina away from the retinal pigment epithelium. All of these observations clearly indicate damage to the photoreceptors and retinal pigment epithelium cells. The depigmentation and pigmentation observed in the fundus that were correlated with the fluorescence changes demonstrated the postoperative damage to the retinal pigment epithelium. Although the adhesive force of human eyes has not been determined, our surgical observations and experiences on the human and monkey eyes suggest that the retinal adhesive force is weaker in humans than in our young monkeys.

During the macular translocation surgery with 360-degree peripheral retinotomy, the retina was totally detached by hydrodissection and mechanical peeling, although the detached retina was reattached before the end of the surgery. Bereczki and associates[23] showed that the outer retina was not affected by macular translocation surgery in one cadaver eye.

Our results showed that the relocated fovea appeared macroscopically normal, and the histologic appearance of the macula was relatively normal with minimal loss of photoreceptor cells but there was a mild alteration of the morphology of the interface between photoreceptor outer segments and the retinal pigment epithelium. Macular translocation surgery induced expression of GFAP in the Mueller cells. The intraocular manipulations involved in the surgery, including lensectomy, vitrectomy, artificial retinal detachment and then reattachment, and silicon oil tamponade, were probably the cause of the increased GFAP expression.[17,24]

Our histologic observations probably account for the clinical observation of improved visual acuity and microperimetric images in many patients.[1–11] We can conclude from our results on monkey eyes that the histology of the macula is not severely altered after macular translocation surgery with 360-degree retinotomy.

However, the mean amplitudes of the b-wave of the full-field ERGs were significantly reduced to 18% to 45% of the preoperative amplitudes in four eyes at 1 month after the surgery. The ERGs recovered to some degree, but were still significantly lower at 36% to 47% of the preoperative values at 3 months after the surgery. These results are consistent with that of Luke and associates[25] who reported that the mean b-wave amplitude of the scotopic ERG was reduced by 60% to 70%, and the photopic a- and b-wave amplitudes were 27% and 43%, respectively, smaller at 4 weeks after silicone oil removal. Terasaki and associates[26] reported that the mean amplitude of the full-field ERG was reduced by 44% for the rod response, by 24% for the mixed rod-cone b-wave, by 12% for the cone single-flash b-wave, and by 35% for the 30-Hz flicker ERGs, and the mean implicit times were significantly delayed in all eyes with age-related macular degeneration at a mean 5.4 months after operation. Our data, together with the clinical investigations, indicate that retinal function was depressed severely after macular translocation with 360-degree retinotomy.

The two surgical procedures for macular translocation have their advantages and disadvantages. Limited macular translocation surgery has less surgical trauma to the retina, shorter operation time, and improvement of visual acuity with low incidence of proliferate vitreoretinopathy. Macular translocation with 360-degree retinotomy, conversely, can translocate the fovea a larger distance, the site where the fovea will be translocated can be made intraopera-

tively, improved vision can be maintained in the long run, and there is less corneal astigmatism.[27,28] At present, both surgical approaches are needed for treatment of patients with neovascular maculopathy.

In conclusion, macular translocation surgery with 360-degree retinotomy is feasible in terms of postoperative morphologic changes. However, there is considerable depression of physiologic function, and methods to reduce damage to the entire retina and retinal pigment epithelium cells during macular translocation surgery should be developed to make this surgery less traumatic.

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