けでなく総人口の減少も反映した結果となっている。なお、この将来予測は眼科医療の水準が現状のままという前提であることに注意したい。日本の眼科医療が予防，早期発見，治療法の開発など様々な面で進歩すれば，このような視覚障害の有病率，有病者数の増加を抑えることができるはずである。

おわりに

本邦の視覚障害の疫学，将来予測について述べた。視覚障害の有病率は高齢者で高く，視覚障害の主要原因は加齢性眼疾患である。今後当分の間，社会の高齢化に伴い，視覚障害を有する高齢者の数は増加していくことが推定される。視覚は日常生活機能の維持に非常に重要な要素である。今後，視覚障害による個人の疾病負担，社会の疾病負担は増加することが予想され，眼科医療の重要性は大きくなるものと推測される。

我々眼科医の責務の第一は，視覚障害の原因になる疾患の予防，早期発見，治療法の開発により一層努めることであると思われる。それとともに，効用分析など他領域の医療とも比較可能な広い指標を用いて眼科医療の重要性を医学界全体や社会に広く示していくことも重要と考えられた。

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Evaluation of Scleral Buckling for Stage 4A Retinopathy of Prematurity by Fluorescein Angiography

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• PURPOSE: To determine the early efficacy of scleral buckling for active neovascularization by fundus fluorescein angiography (FA) in eyes with stage 4A retinopathy of prematurity.

• DESIGN: A retrospective, nonrandomized, observational case series.

• METHODS: Patients who underwent scleral buckling for stage 4A ROP at the National Center for Child Health and Development, Tokyo, Japan, from October 2007 through November 2008 were included. Preoperative and postoperative FA and fundus photographs obtained with a wide-field digital pediatric imaging system were reviewed. Three patients (5 eyes; gestational ages at birth, 23 to 25 weeks; birth weights, 574 to 811 g) with zone II stage 4A ROP who underwent postoperative FA, 2 weeks or less after scleral buckling (range, 7 to 12 days; postmenstrual ages at postoperative FA, 41 to 45 weeks) were evaluated. Patients who underwent postoperative FA 2 weeks or more after scleral buckling were excluded.

• RESULTS: Despite fluorescein leakage from fibrovascular tissue in all eyes before surgery, markedly decreased leakage occurred only between 7 to 12 days after surgery. The retinas were reattached completely in all eyes after surgery.

• CONCLUSIONS: Scleral buckling may prevent progression of retinal detachment in stage 4A ROP by reducing the tractional force and stabilizing the neovascular activity of the fibrovascular tissue. (Am J Ophthalmol 2009;148: 544–550. © 2009 by Elsevier Inc. All rights reserved.)

RETINOPATHY OF PREMATURITY (ROP) SOMETIMES progresses to retinal detachment (RD) despite application of early dense photocoagulation. Surgery is considered at the next treatment. Scleral buckling[1–7] or lens-sparing vitrectomy[8–14] has been performed with good surgical outcomes in eyes with stage 4A ROP, with the exception of those with aggressive posterior ROP. Scleral buckling or lens-sparing vitrectomy cannot stop the progression of RDs in eyes with aggressive posterior ROP because fibrovascular tissue rapidly reaches the posterior lens surface, extends toward the vitreous base, and generates higher contractile forces.[15] Scleral buckling has been performed in less advanced cases of stage 4A ROP, and the mechanism of action has been reported to be relief of the vitreoretinal traction.[6,14,16,17] However, it is unknown whether scleral buckling itself contributes to stabilization of the neovascular activity.

With an advanced digital camera that obtains panoramic images of the neonatal fundus, fundus fluorescein angiography (FA) was performed to assess the retinal vasculature of infants with many peripheral retinal diseases. FA enables easy visualization of the retinal vasculature and aids in early diagnosis and prompt management of patients with ROP.[18] FA findings in ROP have included arteriovenous shunting at the junction of the vascular and avascular retina, a neovascular tuft posterior to the ridge, and a capillary-free zone behind the ridge or capillary-free zone along both veins and arteries.[19–21] Of those seen on FA, the most important sign of activity is fluorescein dye leakage resulting from the neovascularization. We performed preoperative and postoperative FA in eyes with zone II stage 4A ROP with active neovascularization to assess the efficacy of scleral buckling for neovascular activity.

METHODS

WE PERFORMED A RETROSPECTIVE REVIEW OF THE CASE notes of all surgeries for eyes with stage 4 ROP that had developed along classical stages 1 through 3 without any sign of aggressive posterior ROP, performed by one surgeon (N.A.) between October 2007 and November 2008 at the National Center for Child Health and Development, Tokyo, Japan. All patients previously had undergone bilateral peripheral photocoagulation at other clinics. However, the primary treatment did not stop progression of the fibrovascular tissue proliferation and RD, and the patients were referred to us for the next surgery. In the patients who required surgery, lens-sparing vitrectomy generally was performed as a first procedure. However, when fibrovascular tissue developed in the periphery or extended to the vitreous base, the lens was removed to resect the vitreous gel around the fibrovascular tissue and vitreous base. A few eyes underwent scleral buckling for lens preservation.

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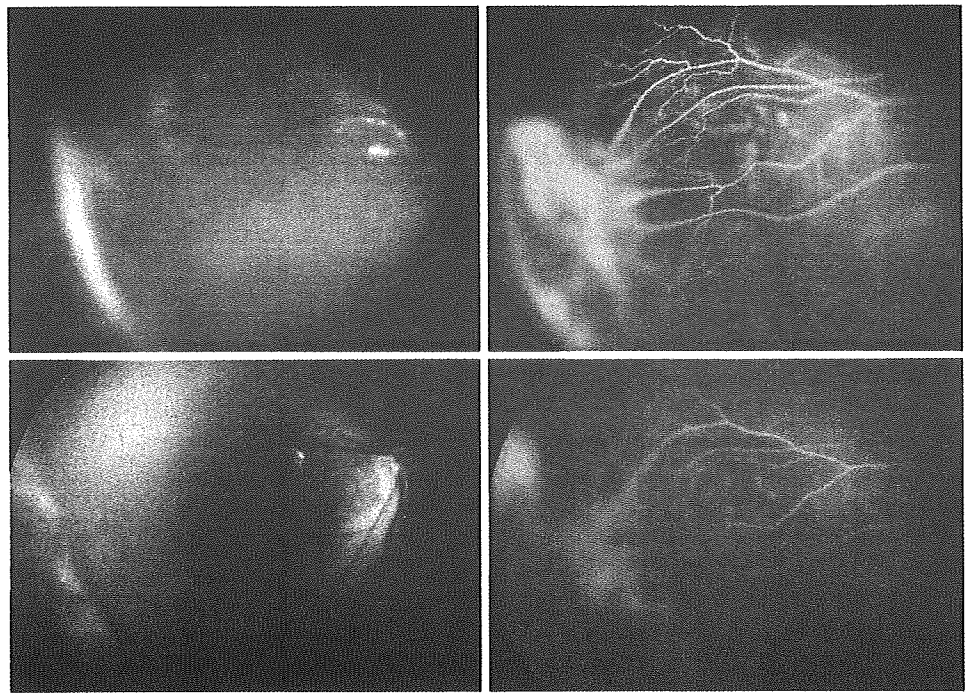

FIGURE 1. Fundus photography and fluorescein angiography (FA) images from Case 1 carried out before and after surgery in both eyes with stage 4A retinopathy of prematurity. (Top left) Fundus photograph obtained before scleral buckling at postmenstrual age 42 weeks in the right eye showing expanded fibrovascular tissue at the temporal junction between the vascular and avascular retina. (Top right) FA image obtained before scleral buckling showing marked fluorescein leakage from the fibrovascular tissue at the junction. (Bottom left) Fundus photograph obtained after scleral buckling showing that the progression of the retinal detachment (RD) stopped after surgery. (Bottom right) FA image obtained after treatment showing markedly decreased fluorescein leakage from the fibrovascular tissue. The findings in the right eye are clearer than those in the left eye and are representative of the 2 eyes.

A scleral buckling procedure without simultaneous vitreous surgery was performed at a postmenstrual age of 41 to 45 weeks by placing a 2.0-mm-diameter silicone sponge on each eye (Mira Inc, Waltham, Massachusetts, USA). The sponge was secured with a 5-0 Dacron scleral suture (Alcon Laboratories, Fort Worth, Texas, USA) in each quadrant, and the ends of the sponge were sutured end to end with the same suture at the superior nasal region. The aqueous tap also was performed if necessary, but drainage of subretinal fluid was not.

Fluorescein angiography examination was performed before and after scleral buckling using the RetCam120 (Massie Research Laboratories Inc, Pleasanton, California, USA). The pupils were dilated using 0.5% phenylephrine and 0.5% tropicamide eye drops instilled 3 times at 10-minute intervals 1 hour before the procedure. A neonatal lid speculum and Scopisol Solution for Eyes (Senju Pharmaceutical Co, Ltd, Osaka, Japan) were used to maintain the cornea–camera interface. The RetCam120 obtained color fundus images and FA images using a blue excitation light source and the yellow filters in the system. FA was performed after administration of an intravenous bolus dose of 0.1 ml/kg 10% sodium fluorescein dye followed by an isotonic saline flush. Images of the posterior pole, peripheral retina, and fibrovascular tissue were recorded at 2-second intervals during all phases of the angiogram until 5 minutes from the injection of fluorescein dye. Dye leakage from the fibrovascular tissue was evaluated in the preoperative and postoperative images in which the recording time was approximately the same. To eliminate the natural course of cicatrization, eyes that underwent FA 2 weeks or less after scleral buckling were evaluated in this study. Five eyes of 3 consecutive infants (2 girls and 1 boy; gestational age range at birth, 23 to 25 weeks; birth weight range, 574 to 811 g) with stage 4A ROP were included. The patients were followed up for 4 to 18 months after surgery. The surgical outcomes at the latest follow-up examinations were determined by binocular ophthalmoscopy and photography.

To evaluate the preoperative and postoperative fluorescein leakage objectively, semi-automated computer-assisted image analyses were performed using ImageJ version 1.41 (Wayne Rasband; National Institutes of Health, Bethesda, Maryland, USA). The relative area of fluorescein leakage was outlined using the freehand tool, and the relative mean signal intensity of the area was quantified using ImageJ densitometry. The outlined area was fixed between preoperative and postoperative images. The illumination knob was fixed with maximum range throughout the FA examinations.

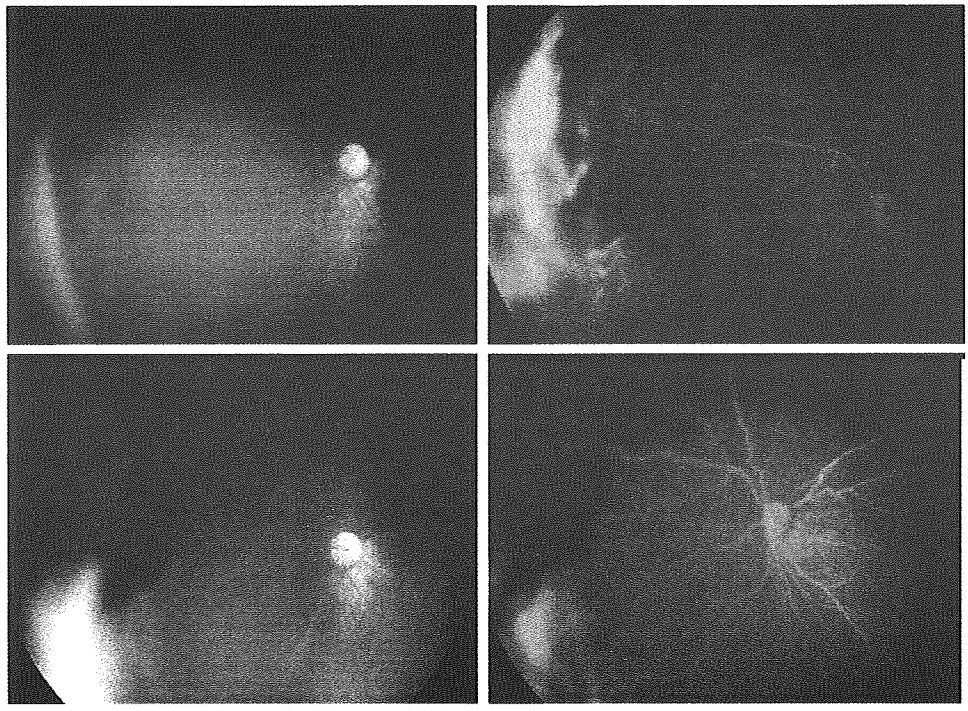

FIGURE 2. Fundus photography and FA images from Case 2 obtained before and after surgery in both eyes with stage 4A retinopathy of prematurity. (Top left) Fundus photograph obtained before scleral buckling in the left eye at postmenstrual age 41 weeks showing expanded fibrovascular tissue and that the retinal vessels stopped in zone II. (Top right) FA image obtained before scleral buckling was performed showing moderate fluorescein leakage from the nasal fibrovascular tissue. (Bottom left) Fundus photograph obtained after scleral buckling showing that the progression of the RD stopped after surgery. (Bottom right) FA image obtained after treatment showing markedly decreased fluorescein leakage from the fibrovascular tissue. The findings in the left eye are clearer than those in the right eye and are representative of the 2 eyes.

RESULTS

• CASE 1: A 25-week-gestation female infant weighing 811 g was delivered vaginally with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. She also had respiratory distress syndrome requiring mechanical ventilation, patent ductus arteriosus treated with one course of ibuprofen, posthemorrhagic hydrocephalus treated with an implant of an Ommaya reservoir, and sepsis treated with antibiotics.

Bilateral ROP screening at the postmenstrual age of 32 weeks identified immature development of retinal vessels that stopped in zone II. During the next 2 weeks, the clinical condition deteriorated to stage 3 with plus disease bilaterally, and argon laser photocoagulation was applied to the avascular retina. The vascular activity was stabilized transiently, but it reactivated. The fibrovascular tissue grew circumferentially, and a regional tractional retinal detachment (RD) developed in both eyes 7 weeks after photocoagulation.

The patient was referred to us and scleral buckling was performed bilaterally at the postmenstrual age of 42 weeks. The fundus examination before scleral buckling showed expanded fibrovascular tissue nearly 4 clock hours in size at the temporal junction between the vascular and avascular retina, and no apparent skip lesions in photocoagulation were seen in either eye (Figure 1). FA performed just before the intervention showed marked fluorescein leakage from the fibrovascular tissue. The progression of the RD stopped after surgery in both eyes. FA performed 7 days after surgery showed markedly decreased fluorescein leakage. Mean signal intensity of the outlined area (72,464 pixels) decreased from 69.7 to 40.6 in right eye after surgery. The retina was reattached, and the fovea was well formed at the correct retinal position at the last follow-up examination.

• CASE 2: A 24-week-gestation male infant weighing 656 g was delivered vaginally with Apgar scores of 5 and 7 at 1 and 5 minutes, respectively. He had respiratory distress syndrome requiring mechanical ventilation.

Bilateral ROP screening at the postmenstrual age of 30 weeks identified immature development of retinal vessels that stopped in zone II and a demarcation line at the junction of the vascular and avascular retina. During the next 3 weeks, the clinical situation deteriorated to stage 3 with plus disease bilaterally, and argon laser photocoagulation was applied to the avascular retina over the course of 4 weeks. The vascular activity stabilized transiently but later reactivated. The fibrovascular tissue grew circumferentially, and a tractional RD developed gradually after the

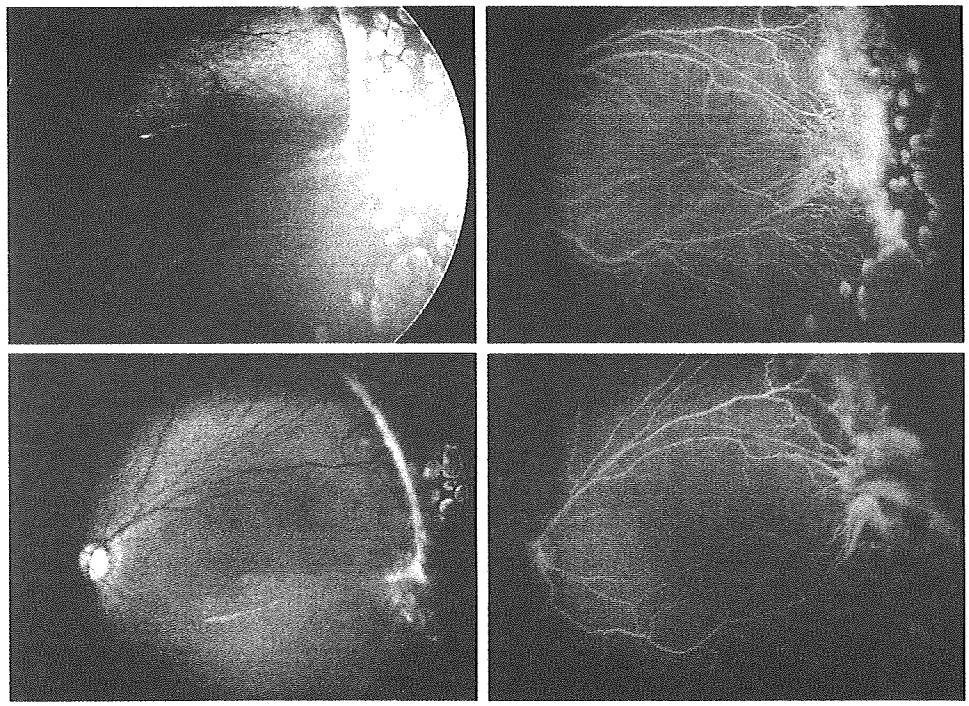

FIGURE 3. Fundus photography and FA images from Case 3 obtained before and after surgery in the left eye with stage 4A retinopathy of prematurity. (Top left) Fundus photograph obtained before scleral buckling in the left eye at postmenstrual age 45 weeks showing that the retinal vessels stopped in zone II and showing expanded fibrovascular tissue at the temporal junction between the vascular and avascular retina. Skip lesions are present. (Top right) FA image obtained before scleral buckling showing marked fluorescein leakage from the temporal fibrovascular tissue. (Bottom left) Fundus photograph obtained after scleral buckling showing that the progression of the RD stopped after surgery. (Bottom right) FA image obtained after treatment showing markedly decreased fluorescein leakage from the fibrovascular tissue.

last session of photocoagulation at the postmenstrual age of 37 weeks.

The patient was referred to us and scleral buckling was performed bilaterally at the postmenstrual age of 41 weeks. The fundus examination before scleral buckling showed expanded fibrovascular tissue 5 clock hours in size at the junction of the vascular and avascular retina on the temporal inferior side of the right eye and for nearly 5 clock hours nasally in the left eye (Figure 2). No apparent skip lesions in photocoagulation were seen in either eye. FA performed just before the intervention showed fluorescein leakage from the fibrovascular tissue. Progression of the RD stopped in both eyes after surgery, and FA performed 12 days after surgery showed markedly decreased fluorescein leakage. Because there seemed to be some mask effect by blood after scleral buckling in the right eye, the mean signal intensity of fluorescein leakage was measured except the area covered with blood. The mean signal intensity of the outlined area (16,595 pixels) decreased 79.5 to 28.2. The retina reattached, and the fovea was well formed at the correct retinal position at the last follow-up examination.

• CASE 3: A 23-week-gestation female infant weighing 574 g was delivered by cesarean section with Apgar scores of 5 and 7 at 1 and 5 minutes, respectively. The patient had respiratory distress syndrome requiring mechanical ventilation, patent ductus arteriosus treated with three courses of ibuprofen, subsequent surgical closure, and chronic lung disease without home oxygen therapy.

Bilateral ROP screening at the postmenstrual age of 28 weeks identified immature development of the retinal vessels that stopped in zone II. During the next 10 weeks, the clinical condition deteriorated to stage 3 with plus disease bilaterally, and argon laser photocoagulation was applied during a number of sessions to the avascular retina. The vascular activity stabilized transiently but later reactivated. The fibrovascular tissue grew circumferentially in both eyes after the last photocoagulation session at the postmenstrual age of 40 weeks. A tractional and serous RD developed in the right eye, and a regional tractional RD developed in the left eye.

Because of the rapid progression of bilateral RD, the patient was referred to us, and scleral buckling to both eyes was performed immediately at the postmenstrual age of 45 weeks. Although some skip lesions were present bilaterally, additional laser photocoagulation was not performed because of the risk of retinal tear after operation. The fundus examination before scleral buckling showed expanded fibrovascular tissue nearly 5 clock hours in size at the

TABLE. Characteristics of Eyes Undergoing Fluorescein Angiography before and after Scleral Buckling for Stage 4A Retinopathy of Prematurity

Patient	Gender	GA (wks)	BW (g)	Eye	Zone	Stage	Extent of FT (clock hours)	PMA of Ablation (wks)	PMA at SB (wks)	Preoperative Dye Leakage from FT	PMA at FA (wks)	Postoperative Dye Leakage from FT	Follow-up (mos)	Retinal Attachment	Foveal Formation (final)	SCF
1	F	25	811	Right	II	4A	4	34	42	Severe	43	Decrease[a]	7	Y	Y	Y
				Left	II	4A	4	34	42	Severe	43	None	7	Y	Y	Y
2	M	24	656	Right	II	4A	5	33 to 38	41	Moderate	44	Decrease[a]	17	Y	Y	Y
				Left	II	4A	5	33 to 38	41	Moderate	44	Decrease[a]	17	Y	Y	Y
3	F	23	574	Right	II	4A	5	38 to 40	45	Severe	47	Decrease	2	Y	Y	Y

BW = birth weight; F = female; FA = fluorescein angiography; FT = fibrovascular tissue; GA = gestational age; M = male; mos = months; PMA = postmenstrual age; POD = postoperative day; SB = scleral buckling; SCF = steady central fixation; wks = weeks; Y = yes.
[a]More than 40% decrease of mean signal intensity of dye leakage.

junction of the vascular and avascular retina temporally in both eyes (Figure 3). A serous RD in the right eye was diagnosed based on the presence of exudates in the posterior pole and a bullous RD involving the macula with no retinal tear. FA performed just before the intervention detected marked fluorescein leakage from the fibrovascular tissue temporally in both eyes and diffuse fluorescein leakage from the retinal vessels in the right eye. Although serous RD in the right eye was exacerbated after scleral buckling, the progression of the tractional RD in the left eye stopped after surgery. FA performed 8 days after surgery showed marked cessation of fluorescein leakage in the left eye. Mean signal intensity of the outlined area (51,194 pixels) decreased from 84.3 to 49.7 in the left eye after surgery. Retinal reattachment was achieved and the fovea was well formed at the correct retinal position in left eye at the last follow-up examination. Results are summarized in the Table.

DISCUSSION

SCLERAL BUCKLING ORIGINALLY WAS THOUGHT TO ADdress RDs by offsetting the vitreoretinal traction as the buckle indented the globe. The procedure allows the retinal pigment epithelium (RPE) to absorb the subretinal fluid and to support the fixed surface area of the developing retina while the eyeball grows rapidly in infants. Scleral buckling also may prevent death of the immature retinal cells by maintaining contact between the retina and the RPE.[3,6,14,16,17] One study reported that scleral buckling contributes to a notable change in neovascularization, which was identified by funduscopy.[3] In the current series, we found that leakage from the fibrovascular tissue markedly decreased only 7 to 12 days after scleral buckling. This course obviously was different from the natural course of fibrovascular tissue regression, which usually requires 1 month or more, suggesting that scleral buckling itself stabilizes the neovascular activity.

Neovascularization of ROP is induced by several growth factors,[22–25] of which vascular endothelial growth factor (VEGF) is the most important in the development of pathologic neovascularization, which is released from the vascular endothelial cells in hypoxia. A recent in vitro study reported that retinal vascular endothelial cells and the RPE, when stretched, release VEGF.[26–28] Integrin is the major receptor that connects vascular endothelial cells and the extracellular matrix and plays a key role in development of pathologic neovascularization.[29–31] Inhibition of integrin reduced VEGF in a murine model of ROP.[32] Because integrin is the mechanotransduction receptor that transforms mechanical stress into chemical signaling,[33] surgically offsetting the mechanical stress on the retinal vascular endothelial cells may reduce the release VEGF by inhibiting the integrin-mediated mechanotransduction. Vitrectomy may wash out VEGF directly from the vitreous cavity and may remove the vitreous gels that may contain the source of VEGF.[34] In contrast, scleral buckling does not have such effects. Thus, relieving the mechanical stress may decrease VEGF expression in the vascular endothelial cells, which may have contributed to decreased neovascular activity in our series.

Vascular endothelial growth factor expression is regulated primarily by hypoxia.[35] Hypoxia in the retinal outer layers caused by RD increases VEGF expression in the subretinal fluid.[36] In the eyes with stage 4 ROP, elevated VEGF levels also are detected in the subretinal fluid.[37] Retinal reattachment around the scleral buckling region may improve the oxygen supply from the choroid to the retina, contributing to the reduction of VEGF and preventing exacerbation of the neovascular activity.

In ROP and other proliferative retinopathies, the active stage characterized by neovascular formation is followed by the cicatricial stage with formation of contractile connective tissue.[38] A recent report demonstrated that the connective tissue growth factor, which is established as a profibrotic factor in retina,[39,40] in a critical balance with VEGF, drives the angiofibrotic switch and subsequent fibrosis in eyes with

proliferative diabetic retinopathies.[41] Compared with the natural course, pathologic neovascular inactivation in our series was achieved rapidly with subsequent cicatricial phase, which is not explained only by a decrease in the release of growth factors and suggests that scleral buckling also may act as the modulator of angiofibrotic switch.

Good surgical results have been reported after scleral buckling[1–7]; however, it also has some disadvantages, including high myopia resulting from changes in the corneal or lens refractive power or the need for another surgery to divide or remove the buckle to reduce the intrusion and promote ocular growth.[38,42] Recently, lens-sparing vitrectomy has become the surgery of choice for stage 4 ROP, although application is limited to eyes with posterior proliferation. Thus, scleral buckling that allows lens preservation still may be chosen to treat eyes with peripheral proliferation in stage 4 ROP. Although the purpose of the surgery has been primarily to reduce traction,[6,14,16,17] the current small series showed that scleral buckling also can reduce the neovascular activity of peripheral proliferation in progressive stage 4A ROP. Thus, scleral buckling may be considered a treatment option to reduce the neovascular activity in eyes with peripheral proliferation where lens-sparing vitrectomy is difficult to perform, although further prospective studies are needed.

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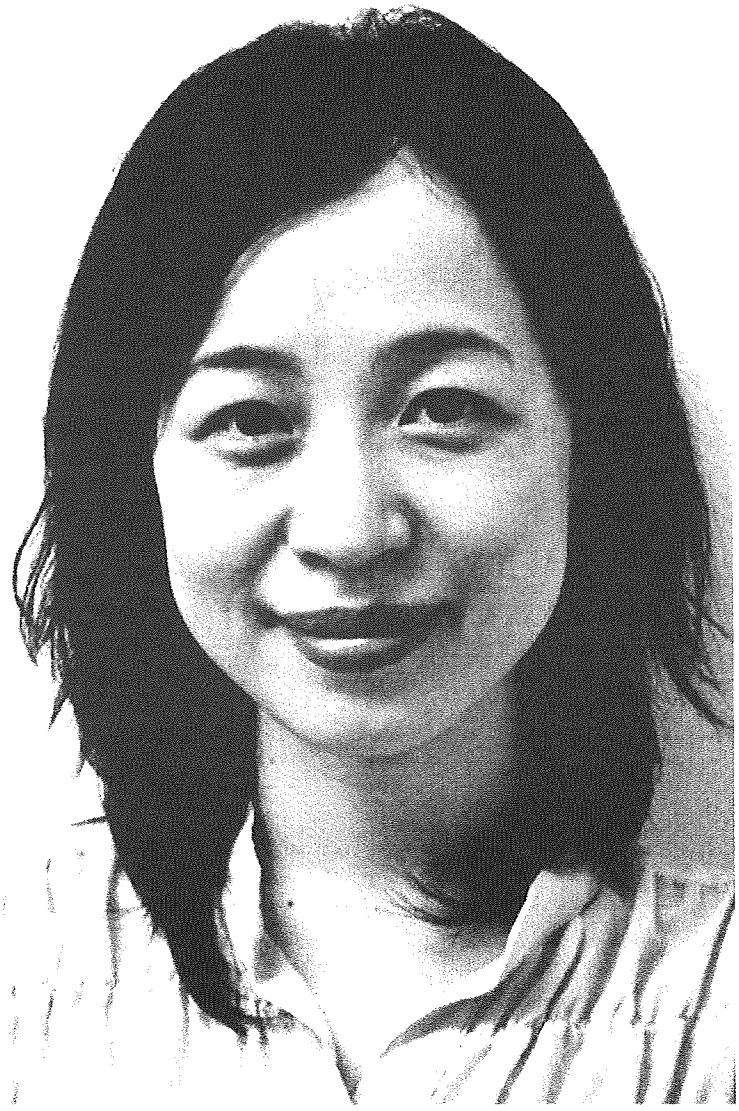

Biosketch

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Vascular Abnormalities in Aggressive Posterior Retinopathy of Prematurity Detected by Fluorescein Angiography

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Purpose: To evaluate fluorescein angiography (FA) in eyes with aggressive posterior retinopathy of prematurity (AP-ROP).

Design: Retrospective, nonrandomized case series.

Participants: Three patients (6 eyes) with AP-ROP.

Methods: Three patients (6 eyes) diagnosed with AP-ROP during ROP screening between July 2007 and July 2008 were included in this study. Fundus photographs and FA were obtained before and after laser and surgical treatment using a wide-field digital pediatric imaging system.

Main Outcome Measures: Fluorescein angiography and fundus photographs.

Results: At the initial stage of AP-ROP, FA showed vascular abnormalities, including capillary nonperfusion throughout the vascularized retina, shunting in the vascularized retina, a circumferential demarcation line, and limited vessel development, which was difficult to identify only by ophthalmoscopy. After treatment, FA showed poorly developed retinal vessels, including 4 small major vessels without an arcade pattern, small macular vessels, an inhomogeneous capillary bed, and absence of a capillary-free zone in the fovea.

Conclusions: Capillary bed loss throughout the vascularized posterior retina is characteristic of AP-ROP and may exacerbate retinopathy.

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Aggressive posterior retinopathy of prematurity (AP-ROP) is a severe, atypical form of ROP characterized by posterior retinal location, rapidly progressive vascular changes, flat neovascularization, hemorrhages, and intraretinal shunting without ridge tissue. Often, AP-ROP results in retinal detachment despite adequate laser ablation without progressing through classic stages 1 to 5.[1–6] Although early recognition and early treatment seem crucial for improving the unfavorable outcome, the initial signs of AP-ROP, including a subtle demarcation line or extraretinal neovascularization before dilatation and tortuosity of the retinal vessels occur, and vascular loops and frizzy vessels that lie at the periphery of vascularized retina and resembles frizzy hair, especially in the superior nasal quadrant, are difficult to recognize ophthalmoscopically.[7]

Previous reports on fluorescein angiography (FA) in classical ROP showed leakage from the fibrovascular tissue, arteriovenous shunting at the junction of the vascularized and unvascularized retina, a neovascular tuft posterior to the ridge, a capillary-free zone behind the ridge, or a capillary-free zone along both veins and arteries.[8–12] However, little has been learned about the FA findings of AP-ROP. We investigated the characteristics of vascular abnormalities in eyes with AP-ROP at the initial stage and after a series of treatments.

Patients and Methods

Three infants (6 eyes) with AP-ROP examined at our institute between July 2007 and July 2008 were included. The patient charts and medical records were reviewed retrospectively. All infants underwent an initial ROP screening at a postmenstrual age of 29 to 31 weeks. Fundus photographs were taken using RetCam (Massie Research Laboratories, Inc., Pleasanton, CA) when the initial signs of ROP were detected by ophthalmoscopy. We also performed FA by RetCam with a blue excitation light source and a yellow-green, barrier-filtered camera after administration of an intravenous bolus dose of 0.1 ml/kg fluorescein followed by a 3.0-ml isotonic saline flush. Fundus photographs and FA were evaluated after laser application or surgery. This study was approved by the ethics committee of the National Center for Child Health and Development.

Results

Case 1

A male infant (age, 22 weeks gestation) weighing 400 g was delivered vaginally with Apgar scores of 5 and 6 at 1 and 5 minutes, respectively. This patient had respiratory distress syndrome requiring mechanical ventilation and 1 dose of surfactant, a patent ductus arteriosus treated with 8 courses of ibuprofen and subsequent surgical closure, and chronic lung disease without home oxygen therapy.

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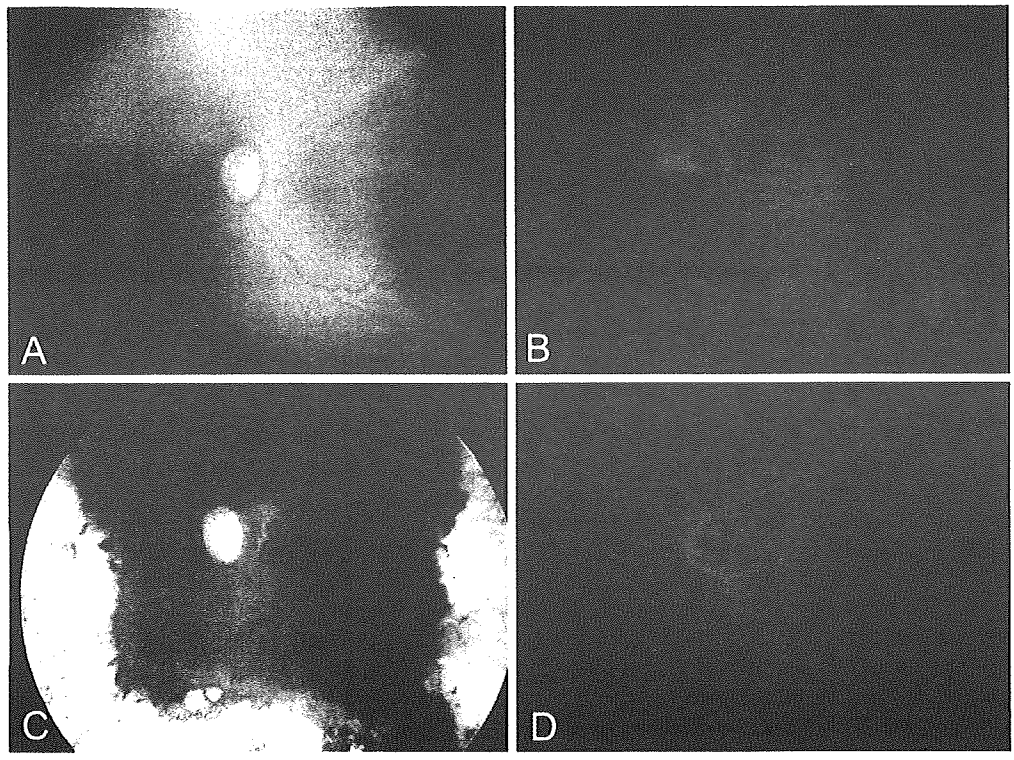

Figure 1. Fundus photographs and fluorescein angiography (FA) of aggressive posterior retinopathy of prematurity in the left eye of patient 1. A, A fundus photograph obtained at the initial stage shows the posterior retinal vessels, a nasal demarcation line, and a hemorrhage at the junction between the vascularized and unvascularized retina. B, At the initial stage, FA shows vessels with 4-lobed topography, capillary nonperfusion around the vascularized retina, vessel proliferation at the junction, and circumferential shunting. C, A fundus photograph obtained after laser treatment shows stabilized vascular proliferation with foveal formation. D, After treatment, FA shows abnormal vessels, such as an inhomogeneous capillary bed, small major vessels without an arcade pattern, and insufficient macular vessels. Because the vitreous cavity was filled with fluorescein after administration, the findings in the left eye, which were clearer than those in the right eye, are representative of the 2 eyes.

Bilateral ROP screening at a postmenstrual age of 30 weeks identified immature development of the retinal vessels that stopped in zone I, a nasal demarcation line, vessel tortuosity around the vessel end, a hemorrhage at the junction, and slight shunting in the vascularized retina (Fig 1A). On FA, there was extension of the major vessels in 4 directions with 4-lobed topography (i.e., vessels develop more temporally than nasally) and capillary nonperfusion and shunting throughout the vascularized retina including the posterior pole, even though a relatively strong choroidal flush, probably owing to immature pigmentation of the retinal pigment epithelium, complicated the identification of capillary nonperfusion. At the junction of the vascularized and unvascularized retina, the branches of the retinal vessels had a brush-like appearance, with capillary nonperfusion and arteriovenous shunting that resulted in a circumferentially continuous demarcation line. Leakage from the neovascular tissue in the junction also was confirmed. In the posterior pole, a cilioretinal artery abnormally passed through the incipient fovea, and few macular vessels or branch vessels, including arterioles and venules from the major vessels, were observed (Fig 1B). The disease activity decreased successfully as the result of laser treatment with foveal formation (Fig 1C), and FA after laser treatment showed stabilized neovascularization, 4 small major vessels especially in the nasal vessels, decreased branch vessels, loss of the arcade pattern, an inhomogeneous capillary bed around the retina, insufficient macular vessels, absence of a capillary-free zone in the fovea, and disappearance of the preexisting vessels that had passed through the fovea (Fig 1D).

Case 2

A female infant (age, 23 weeks gestation) weighing 480 g was delivered vaginally with Apgar scores of 4 and 5 at 1 and 5 minutes, respectively. The patient had respiratory distress syndrome that required mechanical ventilation and 1 dose of surfactant, a patent ductus arteriosus treated with 3 courses of ibuprofen, and chronic lung disease without home oxygen therapy.

Bilateral ROP screening at a postmenstrual age of 30 weeks identified immature development of retinal vessels that stopped in zone I, a few tortuous and dilated vessels, a hemorrhage at the junction of the vascularized and unvascularized retina, and a circumferential vessel at the junction (Fig 2A). On the same day, FA detected vessels extending more in the temporal than nasal quadrant, circumferential vessels, and shunting in the junction resulting in formation of a demarcation line, leakage from the neovascular tissue on the demarcation line, and capillary nonperfusion and shunting throughout the vascularized retina including the posterior pole. Macular vessels and branch vessels including arterioles and venules from major vessels were as hypoplastic as in case 1 (Fig 2B). Despite early laser treatment that was applied densely, fibrovascular proliferation and a regional retinal detachment (stage 4A) occurred in the coagulation scars at 40 weeks. Early vitrectomy with lensectomy was performed at 41 weeks, and the retina was reattached with foveal formation (Fig 2C). After surgery, FA identified an inhomogeneous capillary bed throughout the retina, 4 small and irregular major vessels, decreased branch

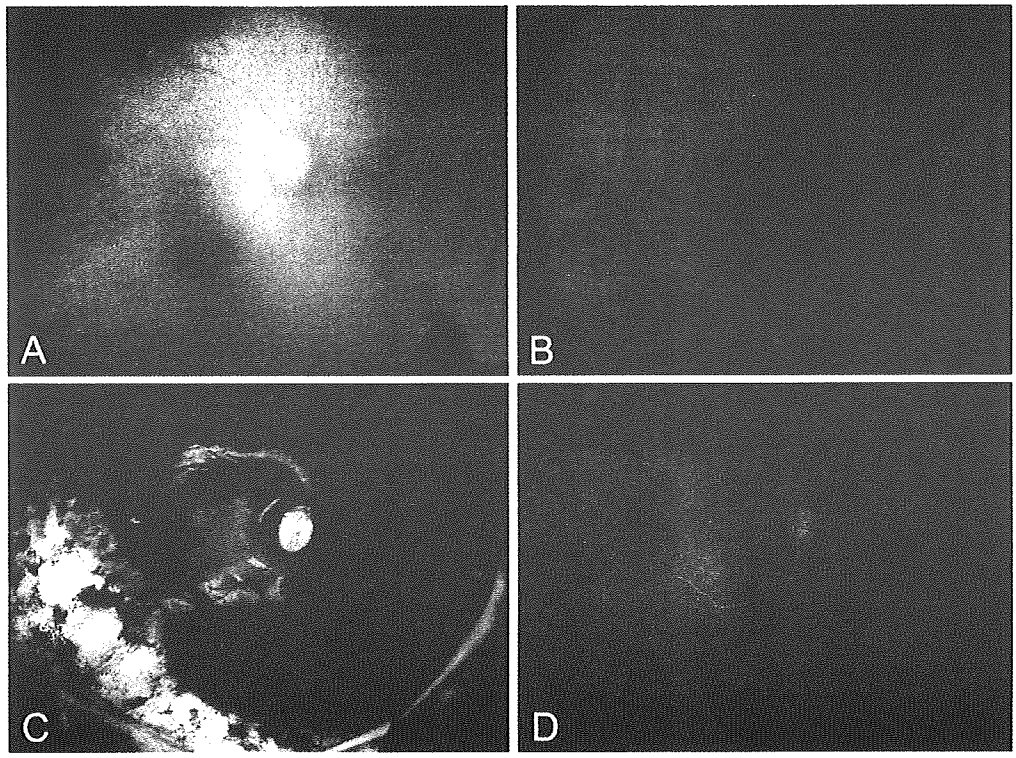

Figure 2. Fundus photographs and fluorescein angiography (FA) of aggressive posterior retinopathy of prematurity in the right eye of patient 2. A, A fundus photograph obtained at the initial stage shows posterior vessels, hemorrhage, and circumferential vessel in the interotemporal junction. B, At the initial stage, FA shows limited vessel extension with circumferential vessels, shunting in the junction, subtle leakage from the neovascular tissue in the demarcation line, capillary nonperfusion around the vascularized retina, and hypoplastic macular vessels. C, Fundus photograph obtained after laser and surgery shows stabilized vascular proliferation with foveal formation and a localized tractional retinal detachment that developed in the laser scars. D, After laser and surgery, FA shows a inhomogeneous capillary bed throughout the retina, tiny and irregularly shaped major vessels, loss of the arcade pattern, insufficient macular vessels, and absence of a capillary-free zone in the fovea.

vessels, loss of the arcade pattern, insufficient macular vessels, and absence of a capillary-free zone in the fovea (Fig 2D).

Case 3

A female infant (age, 27 weeks gestation) weighing 920 g was delivered by Cesarean section with Apgar scores of 1 and 4 at 1 and 5 minutes, respectively. The patient had respiratory distress syndrome requiring mechanical ventilation and 1 dose of surfactant, a patent ductus arteriosus treated with 2 courses of ibuprofen, and sepsis treated with antibiotics.

Bilateral ROP screening at a postmenstrual age of 34 weeks identified immature development of retinal vessels that stopped in zone I, a continual demarcation line, budding from the junction of the vascularized and unvascularized retina, flat neovascularization around the nasal junction, and a hemorrhage at the junction (Fig 3A). On the same day, FA showed vessels extended more in the temporal than nasal quadrant; obvious vessel tortuosity, capillary nonperfusion, and shunting in the entire vascularized retina; few macular vessels and branch vessels including arterioles and venules from the major vessels; and leakage from the flat nasal neovascular tissue and the neovascular tuft behind the junction (Fig 3B). Although the disease activity was stabilized successfully by laser treatment with foveal formation (Fig 3C), FA after a series of laser applications still showed insufficient vasculature, including an inhomogeneous capillary bed in the retina, 4 small major vessels, a decrease in branch vessels, loss of an arcade pattern, and few macular vessels or absence of a capillary-free zone in the fovea; however, there was much better vessel formation than in the other cases (Fig 3D).

Discussion

The major FA findings in the current case series of early-stage AP-ROP are: (1) vessels extending more temporally than nasally that sometimes show 4-lobed topography, (2) a continuous demarcation line composed of shunting and circumferential vessels along the junction of the vascularized and unvascularized retina, (3) shunting in the vascularized retina, (4) tortuous vessels without dilatation clearly detected on FA, (5) leakage from neovascular tissue, (6) few macular vessels and few branch vessels from the major vessels including arterioles and venules, and (7) inhomogeneous capillary bed loss throughout the entire vascularized retina, including the posterior pole. Interestingly, in the current case series of AP-ROP, capillary nonperfusion or arteriovenous shunting was present throughout the vascularized retina, which is in contrast to the capillary nonperfusion present only along the junction of the vascularized and unvascularized retina in classic ROP. Even after the ROP stabilized after a series of laser or surgical treatments, vascular abnormalities remained, including an inhomogeneous capillary bed throughout the vascularized retina, loss

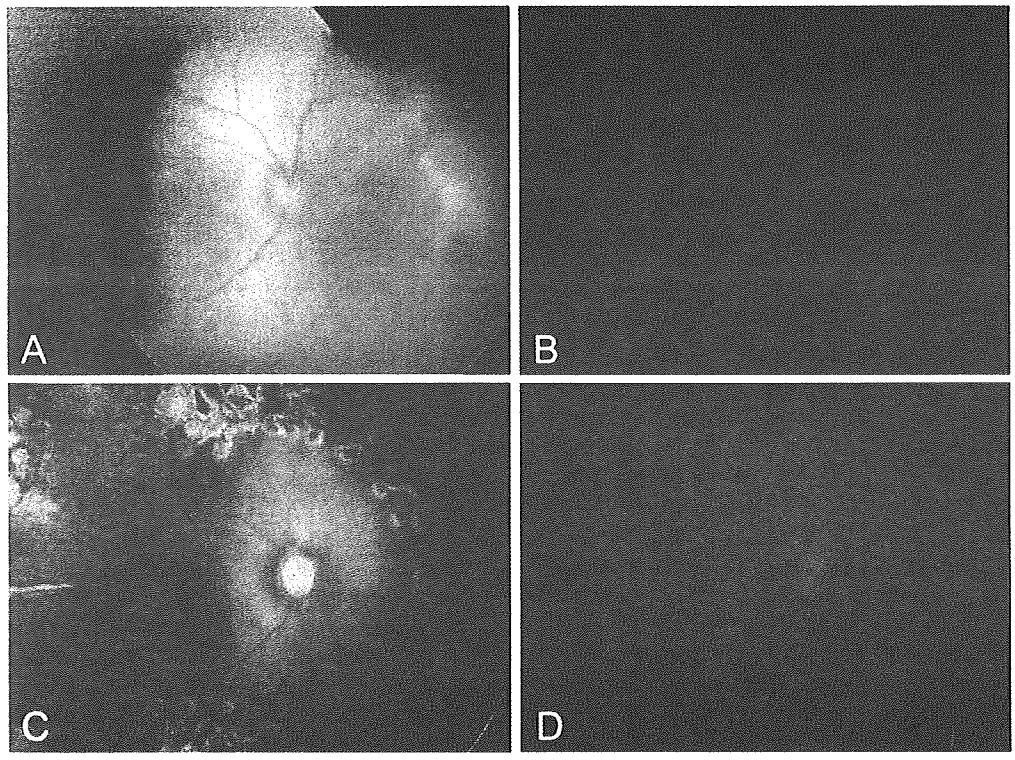

Figure 3. Fundus photographs and fluorescein angiography (FA) of aggressive posterior retinopathy of prematurity in the right eye of patient 3. A. A fundus photograph obtained at the initial stage shows retinal vessels stopped in zone I, a continual demarcation line, budding from the junction, flat neovascularization in the nasal junction, and a hemorrhage at the junction. B. At the initial stage, FA shows vessel tortuosity and capillary nonperfusion around the vascularized retina, shunting in the vascularized retina, few vessels branching toward the fovea, and leakage from the flat nasal neovascular tissue and neovascular tuft behind the junction. C. A fundus photograph obtained after a series of laser treatments shows stabilized vascular proliferation with foveal formation. D. After treatment, FA shows a inhomogeneous capillary bed throughout the vascularized retina, loss of the arcade pattern, insufficient macular vessels, and deficiency of the capillary-free zone in the fovea.

of the arcade pattern, 4 small major vessels, decreased branch vessels, hypoplastic macular vessels, and insufficiency of the capillary-free zone in the fovea.

Recently, a retinal whole-mount preparation method has shown primary retinal vasculature in humans.[13] Retinal vasculature begins to develop from the optic nerve to form the inner vascular plexuses at about 14 weeks gestation as hyaloid vessels regress.[13,14] At 25 weeks' gestation, the inner plexus spreads toward the peripheral retina in a lopsided fashion showing the 4-lobed topography pattern.[13–15] Between 25 and 26 weeks' gestation, the outer vascular plexus begins to sprout from the inner plexus and elongates downward into the outer retina, where a second vascular network is established parallel to the first network.[13,14,16] By 32 weeks' gestation, the inner plexus reaches the peripheral retina, whereas the outer plexus does so after birth.[13] Because most infants with AP-ROP are born prematurely (gestational age ≤25 weeks),[3,5,17] the retinal vasculature has formed the inner plexus posterior to the middle retina, whereas the outer plexus has just started to develop. In our patients who were born at approximately 25 weeks' gestation, the inner vascular plexus may have been established at birth; however, FA showed a noncapillary area of arteriovenous shunting throughout the vascularized retina, probably because of loss of the preexisting inner vascular plexus rather than malformation of the plexus.

Most immature babies have a dramatic change in Pao_2 from 20 to 25 mmHg in utero[18] to about 60 to 100 mmHg after delivery.[19] High-level, long-term oxygen administration disturbs the development of the primary retinal vasculature. Hyperoxia suppresses production of vascular endothelial growth factor from the primary retinal cells and leads to subsequent vascular endothelial cell apoptosis[20–24] and decreased vascular density. In addition, the more immature the vessels, the greater the oxygen toxicity to the vessels.[25,26] Because patients with AP-ROP have immature vessels and often receive long-term, high oxygen therapy, the retinal capillary bed may be lost. Moreover, in a murine model of ROP, vaso-obliteration has been detected mainly in the posterior retina, possibly because the retina around the optic disc and arteries, through which oxygen-rich vessels initially pass, experiences hyperoxia-mediated vascular endothelial growth factor mRNA downregulation and subsequent vascular endothelial cell apoptosis, resulting in a surrounding capillary-free zone.[22] Because most patients with AP-ROP have vessel development posteriorly, the same mechanism may contribute to the severe capillary bed loss around the retina. Meanwhile, because not all patients with AP-ROP have vasculature localized in zone I and not all extremely premature infants develop AP-ROP, other factors, including insulin-like growth factor 1,[27] erythropoi-

etin,[28] vasculogenesis,[15] and genetic factors,[29] may be associated with the disease.

Laser has been applied only to avascular retinas with classical ROP,[4] whereas eyes with AP-ROP often develop retinal detachment despite early, dense laser treatment to the avascular retina.[2–4] In extremely low-birth-weight infants with ROP, Schulenburg and Tsanaktsidis[30] advocated laser application to the vascularized retina, demonstrating the areas of capillary nonperfusion posterior to the demarcation line. Because capillary beds were widely absent in the vascularized retina including the posterior pole, laser application even to the vascular retina may be needed to prevent progression of AP-ROP. Early vitreous surgery with lensectomy successfully stabilized AP-ROP; the vascularized retina was treated preoperatively with sufficient laser ablation 3 to 4 spots posterior to the junction of the vascularized and unvascularized retina.[17]

Interestingly, FA showed that the affected retinal vasculature, including abnormal formation of the major arteries and veins, decreased arterioles and venules, an inhomogeneous capillary bed throughout the retina, hypoplastic macular vessels, and loss of the avascular zone in the fovea and macular vessels are still affected, even after a series of treatments, although this was not well detected on ophthalmoscopy. Thus, once the developing vasculature is damaged, it may never recover. Joshi et al[31] examined 14 eyes with stage 4A ROP preoperatively and detected anatomic macular abnormalities, such as absence of a foveal avascular zone and foveal depression. Although the visual prognosis in AP-ROP improved with early vitreous surgery,[17] because the disease severity is much worse than classic ROP and the development of vasculature was affected in the current study, long-term follow-up of the visual acuity and further investigation of the retinal function are necessary.

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Footnotes and Financial Disclosures

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Effect of Early Vitreous Surgery for Aggressive Posterior Retinopathy of Prematurity Detected by Fundus Fluorescein Angiography

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Objective: To assess the effect of early vitrectomy for aggressive posterior retinopathy of prematurity (APROP) using fundus fluorescein angiography.

Design: Retrospective, observational case series.

Participants: Eleven eyes of 7 patients with APROP that underwent early vitreous surgery.

Methods: All eyes underwent vitrectomy with lensectomy that removed the vitreous gel around the fibrovascular proliferative tissue, but not the proliferative tissue when fibrovascular proliferation and retinal detachment occurred despite retinal photocoagulation. Fundus fluorescein angiography was performed before and after the early vitreous surgery.

Main Outcome Measures: Dye leakage from the fibrovascular tissue, dilation and tortuosity of the retinal vasculature, and shunt vessels were evaluated by fundus fluorescein angiography. The status of the retinal reattachment was assessed postoperatively.

Results: Nine eyes had severe dye leakage from the fibrovascular tissue and 2 eyes had moderate leakage seen by preoperative fluorescein angiography. Severe dilation and tortuosity of the retinal vessels were detected in 10 eyes and shunt vessels in 7 eyes. Six to 12 days after successful surgery, the retina reattached and dilation and tortuosity of the retinal vessels decreased substantially. Dye leakage diminished markedly in all eyes, resolved completely in 7 eyes, and was still apparent slightly in 4. At the final examination, fibrovascular proliferation and retinal detachment did not progress in any eyes; however, 2 eyes had a dragged or folded retina. Follow-up ranged from 6 to 19 months (mean, 9.2).

Conclusions: Early vitrectomy that removes vitreous gel from around the proliferative tissue promptly reduces vascular activity and may limit progression of retinal detachment in APROP.

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The revised International Classification of Retinopathy of Prematurity (ROP)[1] described aggressive posterior retinopathy of prematurity (APROP) and recognized it as an unusual form of ROP that rapidly progresses to a closed funnel of tractional retinal detachment within 1 or 2 weeks despite application of early, dense photocoagulation. The features and pathogenesis of this severe form of ROP have been investigated as type II ROP since 1974 in Japan.[2,3] Identification of the initial signs of APROP and immediate application of dense, extensive laser photocoagulation to the nonvascularized retina and adjacent vascularized retina including the area of the shunting vessels are essential for treating APROP.[2–5] Laser ablation performed early, densely, and repeatedly may transiently stabilize APROP; however, fibrovascular proliferation sometimes recurs in the area of the photocoagulation scars, and the tractional retinal detachment rapidly progresses.[4–6] Recently, we have reported that early vitrectomy with lensectomy for APROP and early photocoagulation prevented progression of retinal detachment.[5] Early vitreous surgery for APROP also was evaluated in another report.[6] The aim of the surgery was not to remove the fibrovascular proliferative tissue, but to remove the surrounding vitreous gel along which the fibrovascular tissue grows. However, the mechanism by which the surgery stabilizes the retinopathy has not been clarified fully.

Fundus fluorescein angiography for ROP, first performed by Flynn et al,[7] is now available with a digital fundus camera, the RetCam 120 (Massie Research Laboratories, Inc., Pleasanton, CA), that can view a wide angle of the fundus including the periphery. With this camera, bedside fluorescein angiography can be performed easily to detect vascular areas of nonperfusion and early neovascularization of active retinopathy.[8,9]

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We conducted the current study to evaluate the preoperative status and the efficacy of early vitreous surgery for APROP using fundus fluorescein angiography with the Retcam 120.

Patients and Methods

This study was approved by the institutional ethics committee; the parents of the patients provided informed consent before the infants were enrolled. Eleven eyes of 7 patients with APROP were studied. All eyes had undergone previous laser ablation at other clinics when the initial signs of APROP[1–3] were identified, and laser was applied repeatedly and densely to the nonvascularized and adjacent vascularized retina. However, when laser treatment could not stop the progression of fibrovascular proliferation and tractional retinal detachment, the patients were referred immediately to our clinic at the National Center for Child Health and Development, Tokyo, Japan.

All eyes underwent early vitrectomy with lensectomy as a second treatment performed by 1 surgeon (NA) in our clinic between December 2006 and March 2008. Three-port vitrectomy was performed using the Accurus 25-Gauge Surgical System (Alcon, Fort Worth, TX) and a small contact lens was designed for premature eyes. The details of the surgery have been described previously[5] and are shown in online Video Clips 1 through 3 (available at http://aaojournal.org). We did not remove the fibrovascular tissue to avoid intraoperative bleeding, but we did remove the surrounding vitreous gel. Fluid–air exchange and endophotocoagulation were unnecessary, because no iatrogenic breaks occurred during the surgery.

Fundus fluorescein angiography was performed within 2 days before the surgery and 6 to 12 days after the surgery. The pupils were dilated using 0.5% phenylephrine and 0.5% tropicamide eye drops instilled 3 times at 10-minute intervals 1 hour before the examination. A neonatal lid speculum and hydroxyethyl cellulose (Scopisol 15; Senju Pharmaceutical Co., Ltd., Osaka, Japan) were used to maintain the cornea–camera interface. The Retcam 120 was used to obtain color fundus photographs and perform fluorescein angiography using a blue excitation light source and the yellow filters in the system. The vital signs were monitored by a neonatologist during the procedure. Fundus fluorescein angiography was performed after administration of an intravenous dose of 0.1 ml/kg of 10% sodium fluorescein dye followed by a saline flush to obtain a bolus dose. Images of the posterior pole, peripheral retina, and fibrovascular tissue were recorded at 2-second intervals during all phases of the angiogram until 5 minutes. Dye leakage from the fibrovascular tissue, dilation and tortuosity of the vasculature, and shunt vessels were evaluated.

The patients were followed for 6 to 19 months (mean, 9.2) postoperatively. Aphakic eyes were corrected with spectacles or contact lenses designed for premature babies about 2 weeks after surgery. The final anatomic outcomes were determined by binocular ophthalmoscopy and photography.

Results

The characteristics of eyes that underwent early vitreous surgery for APROP and the results of fundus fluorescein angiography before and after surgery are shown in Table 1. The patients included 1 boy and 6 girls. The gestational ages at birth ranged from 23 to 28 weeks (mean, 25), and the birth weights ranged from 389 to 1194 g (mean, 734). The ROP extended to all 4 quadrants and underwent laser ablation within zone I in 9 eyes and to posterior zone II in 2 eyes. The extent of the fibrovascular tissue ranged from 6 to 10 clock hours and all eyes had a tractional retinal detachment; the fovea was not involved (stage 4A) in 10 eyes and was involved (stage 4B) in 1 eye. The tip of the fibrovascular tissue was not attached to the vitreous base in any eyes. The postmenstrual ages at the time of vitreous surgery ranged from 35 to 41 weeks (mean, 38). Intraoperative complications did not develop in any eyes.

Preoperative fundus fluorescein angiography showed severe dye leakage (the extent of dye leakage was 100%) from the fibrovascular tissue in 9 eyes and moderate leakage (the extent of leakage was >70%) in 2 eyes. Severe dilation and tortuosity of the vasculature at the posterior pole were seen clearly in 10 eyes and the shunt vessels remained in 7 eyes. Six to 12 days after successful operations, the dye leakage decreased markedly in all eyes, that is, it resolved in 7 eyes (Figs 1 and 2) and was still apparent in 4 eyes (Fig 3). The extent of the fibrovascular tissue with residual dye leakage in the 4 eyes was <50% of the preoperative findings. The dilation and tortuosity of vasculature also decreased in all eyes (Figs 1 to 3). Fluorescein did not cause any adverse effects.

At the final examination, there was no progression of fibrovascular proliferation or retinal detachment in any eyes. Two eyes had a dragged or folded retina (Fig 3).

Discussion

We perform vitrectomy with lensectomy in eyes with APROP as early as possible when fibrovascular tissue extends from the posterior retina to the posterior lens surface and causes a regional retinal detachment (stage 4A) despite sufficient laser ablation. Retinopathy of prematurity rapidly progresses to stage 5 within 1 to 2 weeks, when the growing fibrovascular tissue attaches to the posterior lens surface or the retina and ciliary body beneath the vitreous base. Thus, a wide-field vitrectomy with lensectomy to remove the vitreous gel between the fibrous tissue and vitreous base is needed to prevent progression of APROP.[5] If the tip of the fibrovascular tissue has attached to the vitreous base, the tractional retinal detachment rapidly progresses to involve the fovea. In this case, cutting the fibrovascular tissue and removing the firm adhesion to the vitreous base are difficult without iatrogenic retinal breaks, resulting in retinal folds or a dragged retina as a result of the strong contraction of the residual fibrovascular tissue and no foveal formation.[5]

In the current series, all but 1 eye had stage 4A disease in which the fibrovascular tissue increased to 6 to 10 clock hours without attachment to the vitreous base. The eye with stage 4B also had 6 clock hours of fibrovascular tissue without attachment to the vitreous base. We successfully treated these eyes with vitrectomy and lensectomy to obtain retinal reattachment. Preoperative fundus fluorescein angiography showed extreme vascular activity based on extensive dye leakage from the fibrovascular tissue, dilation and tortuosity of the retinal vasculature at the posterior pole, and atypical shunt vessels. However, only 6 to 12 days after surgery, fluorescein angiography showed markedly decreased vascular activity and stabilized APROP. The dilation and tortuosity of the retinal vessels decreased, and the dye leakage from the fibrovascular tissue decreased substantially. These findings strongly support the effectiveness of early vitrectomy, not only for preventing fibrovascular pro-

Table 1. Characteristics of Eyes Undergoing Fundus Fluorescein Angiography

Patient	Gender	Gestational Age at Birth (wks)	Body Weight at Birth (g)	Eye	Zone	Stage	Extent of FT (clock hours)
1	Female	26	906	Right	I	4A	10
				Left	I	4A	10
2	Male	23	596	Right	I	4A	6
				Left	I	4A	6
3	Female	24	647	Left	I	4B	6
4	Female	28	1194	Left	I	4A	6
5	Female	28	733	Left	I	4A	7
6	Female	23	389	Right	I	4A	7
				Left	I	4A	7
7	Female	24	670	Right	II	4A	7
				Left	II	4A	10

DR = dragging or folds of the retinal; FT = fibrovascular tissue; PMA = postmenstrual age.
*Severe = extent of dye leakage was 100% of the FT; moderate = the extent of dye leakage was >70% of the FT.
†Decrease = the extent of dye leakage decreased by <50% of the preoperative findings.

liferation but also for rapidly reducing the vascular activity in APROP. Consequently, early vitrectomy may limit the progression of tractional retinal detachment. The extent of the residual dye leakage from the fibrovascular tissue may indicate possible regrowth of fibrovascular tissue and recurrence of a tractional retinal detachment. In this series, the extent of the remaining leakage was <50% in all eyes without recurrence.

These results raise some possibilities about the mechanism of the rapid reduction of vascular activity in APROP after vitrectomy. The first factor is that operative removal of the vitreous framework might reduce the tractional

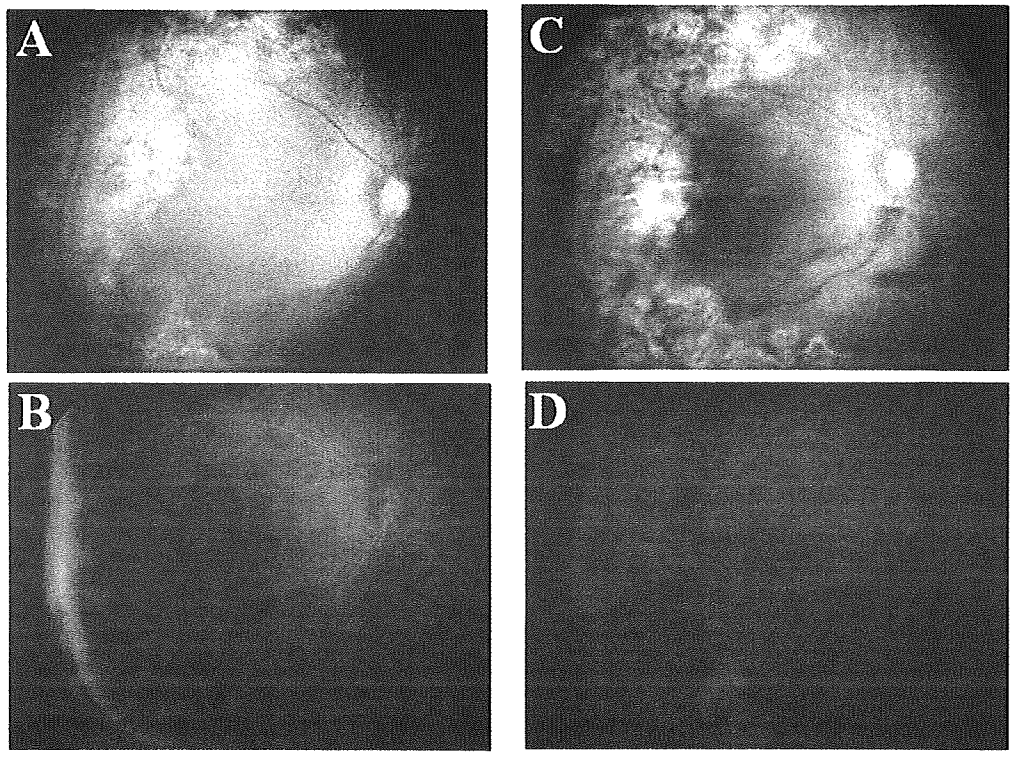

Figure 1. The right eye of patient 6 (gestational age 23 weeks; birth weight, 389 g). **A**, Preoperatively, fibrovascular tissue grows in the photocoagulation scars with a hemorrhage between the 5 and 12 o'clock positions and a regional tractional retinal detachment has developed (stage 4A). **B**, Severe dye leakage from the fibrovascular tissue and dilation and tortuosity of the vasculature at the posterior pole are detected (at approximately 2 minutes and 30 seconds). **C**, Six days postoperatively, the retina has reattached without retinal dragging under residual fibrous tissue. **D**, The dye leakage has almost resolved and less dilation and tortuosity of the vasculature are seen (at approximately 4 minutes to show the most prominent leakage).

(FA) before and after Surgery for Aggressive Posterior Retinopathy of Prematurity

PMA at Vitrectomy (wks)	Preoperative Dye Leakage from FT*	Dilation and Tortuosity of Retinal Vasculature	Postoperative Day of FA	Postoperative Dye Leakage from FT†	Reduced Dilation and Tortuosity of Retinal Vasculature	Retinal Attachment (Final)
36	Severe	Severe	12	None	Yes	Yes
36	Severe	Severe	12	None	Yes	Yes
41	Severe	Severe	6	None	Yes	Yes
41	Severe	Severe	6	None	Yes	Yes
37	Severe	Severe	11	Decrease	Yes	Yes, DR
39	Moderate	Moderate	11	None	Yes	Yes, DR
35	Severe	Severe	7	None	Yes	Yes
38	Severe	Severe	6	None	Yes	Yes
38	Moderate	Severe	6	Decrease	Yes	Yes
38	Severe	Severe	7	Decrease	Yes	Yes
38	Severe	Severe	7	Decrease	Yes	Yes

force of the fibrovascular tissue and suppress the growth of new vessels. Even after scleral buckling, the activity of the fibrovascular tissue seems to be attenuated.[10] Decreased vitreous traction may allow the retinal pigment epithelium pump to absorb subretinal fluid, achieve retinal reattachment, and eliminate the stimulus for neovascularization.[10,11] In vitro and animal studies have shown that traction and stretching of the vascular wall induces changes in the retinal vasculature and may accelerate neovascularization with related integrins and other factors.[12–14] However, scleral buckling has no effect on APROP, which is characterized by extensive, rapidly progressive retinopathy and is similar to florid diabetic retinopathy that requires full panretinal photocoagulation and early vitrectomy to prevent rapid progression of the tractional retinal detachment.[15]

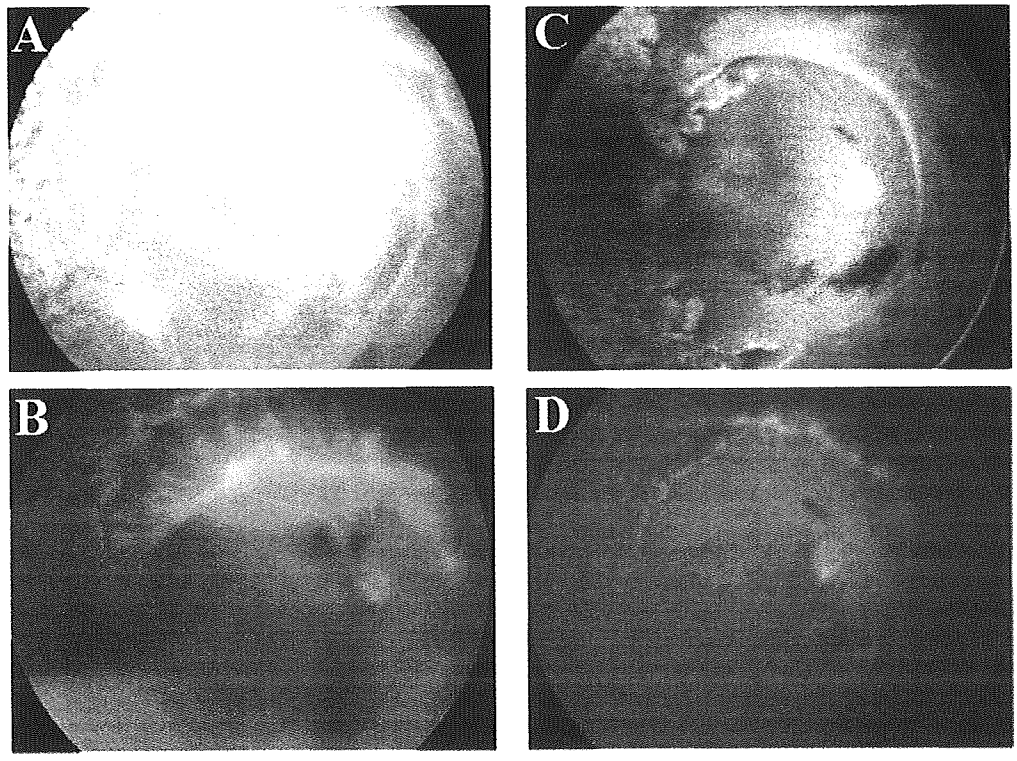

Figure 2. The right eye of patient 1 (gestational age 26 weeks; birth weight, 906 g). A, Preoperatively, extreme fibrovascular tissue grows rapidly in the photocoagulation scars between the 9 and 7 o'clock positions and a tractional retinal detachment has developed (stage 4A). Dilation and tortuosity of the vasculature at the posterior pole, shunt vessels, and retinal and vitreous hemorrhages are seen. B, Severe dye leakage from the fibrovascular tissue is seen (at approximately 2 minutes and 30 seconds). C, Twelve days postoperatively, the retina has reattached without retinal dragging under residual fibrous tissue. D, The dye leakage has almost resolved and the dilation and tortuosity of vasculature have decreased (at approximately 4 minutes).

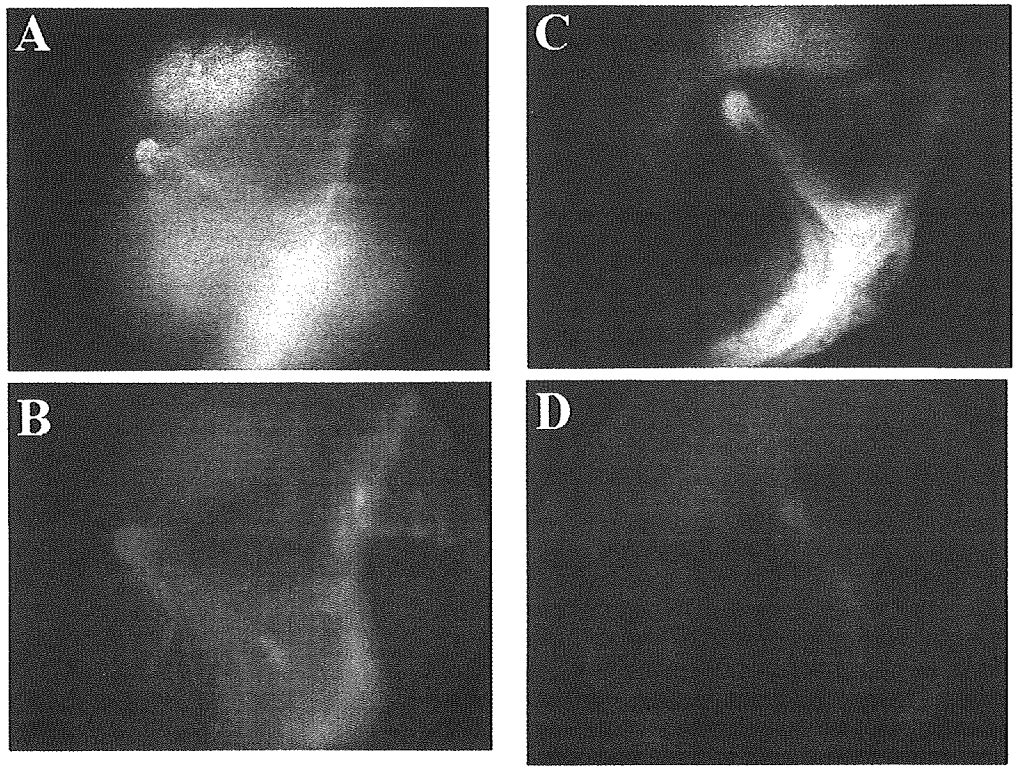

Figure 3. The left eye of patient 3 (gestational age 24 weeks; birth weight, 647 g). A, Preoperatively, fibrovascular tissue grows between the 2 and 8 o'clock positions and a tractional retinal detachment has developed involving the fovea (stage 4B). B, Severe dye leakage from the fibrovascular tissue is seen (at approximately 2 minutes and 30 seconds). C, Eleven days postoperatively, the retina has reattached with residual retinal folds. D, The dye leakage is reduced markedly with slight residual leakage (at approximately 4 minutes).

Vascular endothelial growth factor (VEGF) and other angiogenic factors contribute to the formation of neovascularization in ROP. Vitreous VEGF and stromal cell-derived factor 1α levels increase in eyes with active vascular stage 4 ROP.[16] The second essential role of early vitrectomy for APROP may be that the operation washes out angiogenic factors such as VEGF and stromal cell-derived factor 1α. Vitrectomy also seems to effectively remove the scaffold tissue and extracellular matrix that mediate angiogenesis.[17]

Recently, anti-VEGF treatment has been studied to treat ROP based on the efficacy of other angiogenic disorders such as age-related macular disease, proliferative diabetic retinopathy, and neovascular glaucoma. Intravitreal injection of bevacizumab (Avastin, Genentech, South San Francisco, CA), a recombinant humanized anti-VEGF monoclonal antibody, has been investigated for severe ROP including APROP.[18–20] The drug seems to effectively reduce vascular activity including the tunica vasculosa lentis, dilation and tortuosity of the retinal vessels, and neovascular proliferation with laser photocoagulation in early stage APROP.[18,19] Bevacizumab also may have an effect on stage 4 ROP; however, in eyes with advanced ROP, the drug cannot sufficiently reduce the vascular activity of the fibrous tissue and prevent the rapid progression of the tractional retinal detachment without vitrectomy.[20] Most important, the optimal dose of bevacizumab that preserves the normal neuroretinal development has not been determined in human ROP.[19–22] Severe ischemic retinopathies, including APROP and florid diabetic retinopathy, are followed by marked overproduction of VEGF and other angiogenic factors that lead to abnormal vascularization. Thus, 1 injection of a safe dose of bevacizumab probably cannot prevent rapid progression of the disease. Meanwhile, an intravitreal injection of bevacizumab is problematic for APROP, which is characterized by prominent fibrovascular proliferative tissue, because the drug may cause strong contraction of the fibrous tissue in advanced ROP.[23]

Early vitrectomy has a substantial effect on APROP, presumably by washing out VEGF and other angiogenic factors resulting in prompt declines in vascular activity. The positive effect on the disease may result from the complete removal of the vitreous tractional force and washing out of the VEGF and other angiogenic factors simultaneously. It is uncertain if vitrectomy can convert the active vascular stage to the inactive cicatricial stage via a change in cytokine release or if the APROP may progress spontaneously to cicatrization because of the reduced scaffolding area for the fibrovascular tissue. Further investigation is needed to clarify the mechanism of the rapid conversion of APROP to cicatrization after vitrectomy.

The current study had some limitations in that it was not randomized, controlled, or prospective to clarify whether vitrectomy with lensectomy is more appropriate to treat eyes with stage 4A APROP. Lens preservation is important to promote visual development; however, lensectomy may be necessary when the fibrovascular tissue rapidly grows to