

# ULTRA-WIDE-FIELD IMAGING AND INTRAVENOUS FUNDUS FLUORESCEIN ANGIOGRAPHY IN INFANTS WITH RETINOPATHY OF PREMATURITY

JIANBO MAO, MD, YIRUN SHAO, MD, JIMENG LAO, MD, XUETING YU, MD, YIQI CHEN, MD, CAIYUN ZHANG, MD, HANXIAO LI, MD, LIJUN SHEN, MD

**Purpose:** To determine the feasibility of ultra-wide-field imaging and ultra-wide-field intravenous fundus fluorescein angiography (UWF-IV-FFA) in infants with retinopathy of prematurity (ROP) using Optos 200Tx.

**Methods:** We performed Optos 200Tx capturing on 32 premature infants (14 females) and UWF-IV-FFA with Optos 200Tx on 12 of the 32 infants between April 2017 and July 2018 at the affiliated eye hospital of Wenzhou Medical University and analyzed their fundus images.

**Results:** Ultra-wide-field color images were acquired from 32 infants (64 eyes). UWF-IV-FFA was performed successfully in 12 premature infants (24 eyes). No adverse events were observed. The ultra-wide-field Optos 200Tx color images and UWF-IV-FFA images revealed Stages 1, 2, and 3 ROP and aggressive posterior ROP.

**Conclusion:** Ultra-wide-field imaging and intravenous fundus fluorescein angiography using Optos 200Tx are feasible in infants with ROP, which have the potential to screen, diagnose, and follow-up for ROP.

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Retinopathy of prematurity (ROP) is a vasoproliferative vitreoretinopathy affecting premature infants that is a leading cause of childhood blindness worldwide.<sup>1</sup> Early and accurate diagnosis is significant for early treatment and good prognosis. Binocular indirect ophthalmoscopy (BIO) has been the standard technique for screening ROP in premature infants; however, some facilities lack qualified ophthalmologist examiners, and images are not stored for future reference.<sup>2</sup> Digital imaging using wide-angle digital retinal

photography has been an alternative method for screening ROP.<sup>3</sup> RetCam, which has high reliability and accuracy for detecting referral-warranted ROP, has been widely used in fundus examinations for premature infants. However, it requires apposition to the cornea, the camera weight can decrease the perceived severity of Stage 3 or plus disease, and it has the potential to induce some ocular complications.<sup>4</sup> Chandra et al<sup>5</sup> reported a case of posterior retinal hem-

From the Department of Retina Center, Affiliated Eye Hospital of Wenzhou Medical University, Hangzhou, Zhejiang, China.

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Reprint requests: Lijun Shen, MD, Department of Retina Center, Affiliated Eye Hospital of Wenzhou Medical University, Hangzhou, Zhejiang, China; e-mail: slj@mail.eye.ac.cn

Table 1. Data of 32 Infants Undergoing Ultra-Wide-Field Color Imaging

No. of eyes	64
GA	28.8 w (26–34 w)
CGA	39.7 w (35–48 w)
Sex (male/female)	18/14
Birth weight	1,291.7 g (640–2,250 g)
Weight	3,306.2 g (2,100–5,330 g)
Diagnosis	
Normal	5
AP-ROP	8
Stage 1 ROP	7
Stage 2 ROP	24
Stage 3 ROP	20

Table 2. Data of 12 Infants Undergoing UWF-IV-FFA

No. of eyes	24
GA	28.8 w (27–34 w)
CGA	38.7 w (37–42 w)
Sex (male/female)	5/7
Birth weight	1,330.7 g (995–2,200 g)
Weight	3,359.3 g (2,700–3,825 g)
Diagnosis	
AP-ROP	2
Stage 1 ROP	0
Stage 2 ROP	13
Stage 3 ROP	9

orrhage during RetCam examination. As the infants who have contraindication of cornea contacting, such as infection, early postoperative period etc, noncontact screening is a much better choice.<sup>6,7</sup>

The ultra-wide-field imaging (UWFI) has been widely used in adults but not in infants. Ultra-wide-field imaging showed some advantages for fundus imaging obtained in special conditions, such as fixed small pupil.<sup>8</sup> Pupil is not able to be dilated fully in some infants. Patel et al<sup>6</sup> reported 9 cases obtaining high-quality images of the fundus in ROP subjects with UWFI and proved its potential to monitor ROP progression and document ROP regression after treatment. Fluorescein angiography has shown advantages in evaluating retinal vasculature, which increases the sensitivity for diagnosis of Stage 2 or worse, Stage 3 or worse, pre-plus or worse, and the identification zone compared with color fundus photography alone.<sup>9,10</sup> Combining UWFI and fluorescein angiography may assist the diagnosis of ROP. Fung et al<sup>11</sup> first reported 3 cases of noncontact ultra-wide-field oral fluorescein angiograms in premature infants with Stage 3 ROP. Subsequently, they successfully performed UWF-IV-FFA in 12 infants with ROP or other proliferative retinopathies.<sup>12</sup> They proved the feasibility of ultra-wide-field fluorescein angiography in ROP infants. Thus, there is no study, to the best of our

knowledge, systematically reported ultra-wide-field color images and UWF-IV-FFA images of a variety of ROP diseases before.

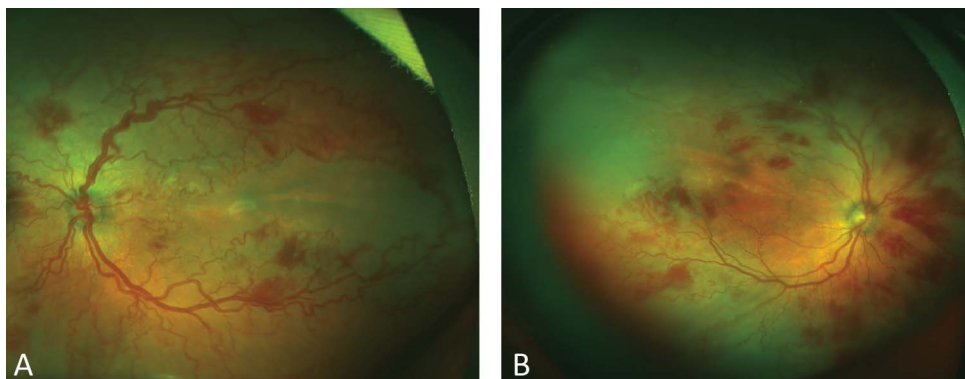
This study reports 32 premature infants with ROP in whom UWFI and UWF-IV-FFA using Optos 200Tx were performed under topical anesthesia at the ophthalmic outpatient department.

## Methods

A total of 32 premature infants (14 females) had their fundus images captured using Optos 200Tx between April 2017 and July 2018 at the affiliated eye hospital of Wenzhou Medical University. All patients were first screened for ROP by our ophthalmologists at the Women's Hospital School of Medicine Zhejiang University. They were then discharged from NICU before the second ROP screening and follow-ups at our hospital following the guidelines for ROP screening in China (2014)<sup>13</sup> according to the 13th Five-Year National Eye Health Plan (2016–2020) published by the general office of the national health and family planning commission of the People's Republic of China on November 9, 2016. The screening criteria include the following: 1) Examinations are recommended for infants with birth weight <2,000 g or with a gestational age (GA) <32 weeks until peripheral retinal vascularization. Examinations are also recommended for infants with severe diseases or long history of supplement of oxygen or with a high risk in ROP in the opinion of the pediatricians. 2) First examination begins at 4 w to 6 w after birth or at a corrected GA (CGA) of 31 w to 32 w. 3) Screening interval: eyes without ROP in Zone I or with Stage 1 or 2 ROP, once a week; eyes with regression ROP in Zone I, screening every 1 week to 2 weeks; eyes with Stage 2 or 3 disease in Zone 2, once a week; Stage 1 disease in Zone II, screening every 1 week to 2 weeks; eyes without ROP

Table 3. Data of Four Infants Follow-up by Optos 200Tx

NO.	Sex	GA	Birth Weight	CGA	Weight	ROP (OD)	ROP (OS)	Therapy
1	Female	29	1,230	36	3,000	Stage 3 in Zone I, plus (+)	Stage 3 in zone I	Anti-VEGF therapy (ou) at 36 w
				37	3,130	Vessels grew to Zone II	Vessels grew to Zone II	
2	Female	33	1,850	37	2,400	Stage 2 in Zone II	Stage 2 in Zone II	Anti-VEGF therapy (ou) at 35 w
				38	2,770	Stage 2 in Zone II	Stage 2 in Zone II	
				41	3,980	Stage 1 in Zone II	Stage 2 in Zone II	
3	Male	27	995	42	3,825	Stage 3 in Zone II	Stage 2 in Zone II	Laser photocoagulation (ou) at 42 w
				46	5,740	After laser photocoagulation	After laser photocoagulation	
4	Female	31	1,550	38	2,980	Stage 3 in Zone II	Stage 3 in Zone II	Anti-VEGF therapy (ou) at 34 w
				39	3,500	Stage 3 in Zone II	Stage 3 in Zone II	



**Fig. 1.** A and B. Male, GA 33 w, corrected age 35 w, with AP-ROP in both eyes. Ultra-wide-field Optos color images demonstrate obvious binocular vascular dilatation and tortuosity with widespread retinal hemorrhages.

or with Stage 1 ROP in Zone II or in Zone III, screening every 2 weeks to 3 weeks. 4) Screening terminate condition: retinal vascularization (nasal quadrant reach ora serrata, temporal quadrant 1PD distant from ora serrata); at a CGA of 45 w, without threshold disease or prethreshold disease, retinal vascularization reaches Zone III; regression of disease. 5) Screening method: screen after mydriasis. Binocular indirect ophthalmoscopy is recommended. Wild-field digital retinal camera is also OK. Examination can be combined with scleral depression, screen at least twice. Inclusion criteria for this study include the following: 1) Infants were diagnosed as monocular or binocular ROP by dilated fundus exam with BIO by Jianbo Mao; 2) in good condition without serious systemic diseases; 3) be able to be in flying baby position; 4) oxygen saturation no less than 95% without supplement of oxygen. Ultra-wide-field Optos color images were evaluated by Jimeng Lao. If the diagnosis is different between Optos images and BIO, the corresponding author will determine the results by BIO. Overall, 12 of the 32 infants who were tentatively diagnosed with ROP Stage 2 or 3 using Optos fundus images or whose nonperfusion condition or the prognosis after treatment was uncertain underwent further ultra-wide-field intravenous fundus fluorescein angiography (UWF-IV-FFA). The infants with hypersensitivity to iodinated contrast media, liver and renal insufficiency, history of asthma (1 infant), serious cardiovascular and cerebrovascular diseases, mydriatic contraindications, oxygen saturation under 95% without supplement of oxygen (3 infants), parents rejection (3 infants), incapability to be in flying baby position (2 infants) were excluded. All the parents were advised of the risks of UWF-IV-FFA and provided signed informed consent forms.

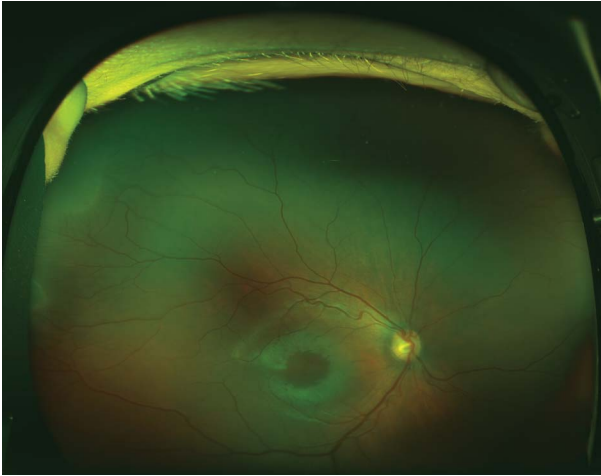
Data of sex, birth weight, weight, GA, CGA, history of supplemental oxygen therapy, Apgar score, and systemic disease were collected through case history and previous medical records.

#### *Optos 200Tx Capturing Technique*

Heart rate, pulse oximetry, respiration, and electrocardiograms of the infants were monitored throughout the procedure. Mydriasis with tropicamide 0.5% and phenylephrine 0.5% eye drops and topical anesthesia with Alcaine (proparacaine hydrochloride 0.5%) were used. The Optos chin underprop was removed. The infants were raised in front of the camera in the “flying baby” position (one arm supporting the chest/chin and the other hand supporting the head).<sup>6</sup> An assistant manually stabilized the infant’s head to keep it stationary. Eyelid speculums were used to open the eyelids and control the eye movements. The photographer and an assistant adjusted the eye, so it was focused on the camera. When the light on the screen turned green, the photographer pressed the shutter button to obtain well-focused images. The eye position was adjusted to get fundus images of different parts of the retina. Three



**Fig. 2.** Female, GA 30 + 1 w, corrected age 36 + 1 w, with Stage 3 Zone 2 ROP.



**Fig. 3.** Male, GA 27 + w, corrected age 42 + w, with Stage 2 Zone 2 ROP in the right eye.

to five ultra-wide-field color images were taken per eye, no more than six totally.

#### *UWF-IV-FFA With Optos 200Tx Technique*

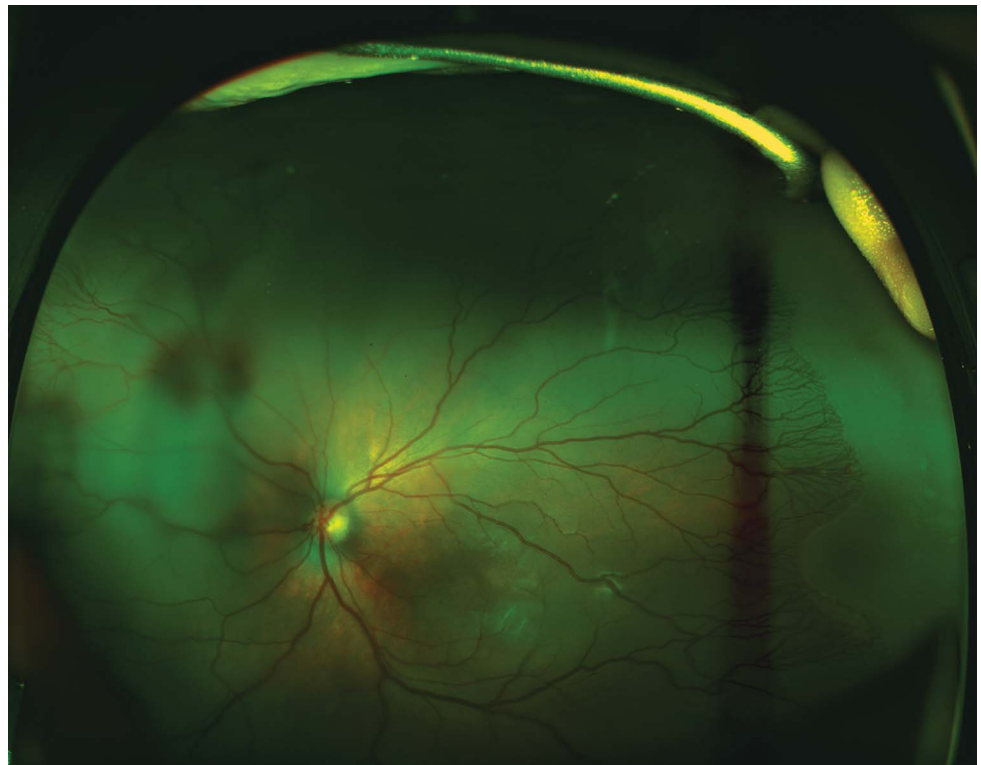
Heart rate, pulse oximetry, respiration, and electrocardiograms of the infants were monitored throughout the procedure. A pediatrician, an anesthesiologist, and

a nurse were present to manage any emergencies. 0.1 mL 0.5% of the fluorescein reagent was successively administered intravenously along with 2 mg dexamethasone to take precautions against anaphylaxis.<sup>14</sup> After confirming the absence of anaphylaxis, a dose of 0.1 mg/kg 10% fluorescein was injected intravenously, and we began to record the time. We then captured the fundus images at different time intervals. Three images were taken in each phase (early phase, metaphase, and late phase) per eye, totaled no more than 15.

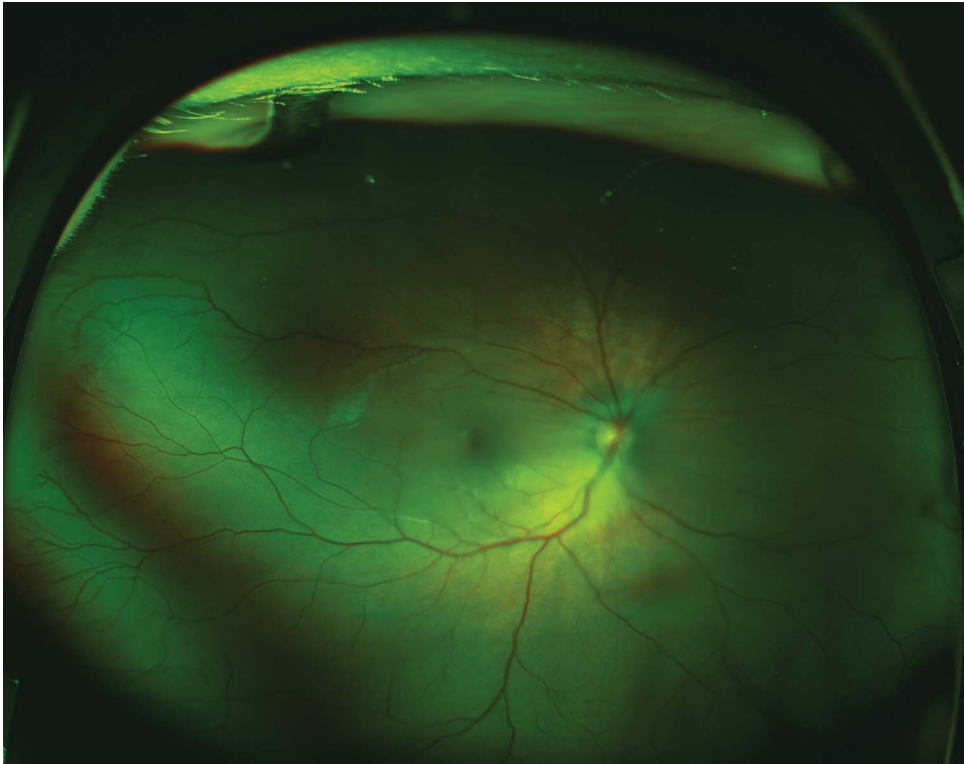
All the images were acquired by a specialized ophthalmologist using Optos 200Tx in an Optos examination room in eye hospital.

### Results

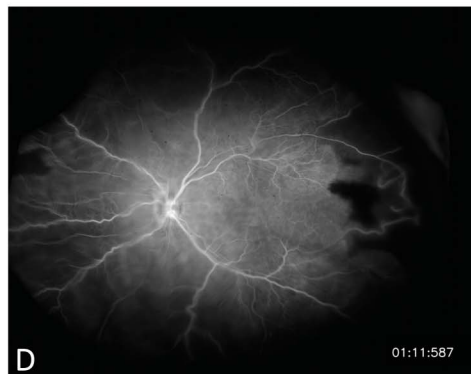
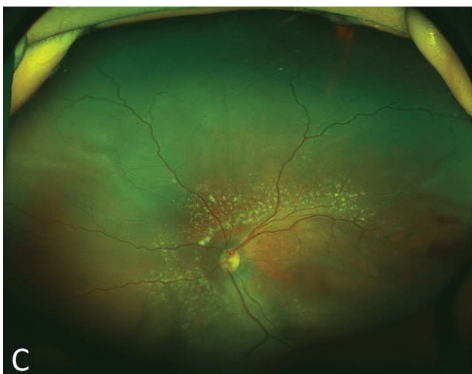
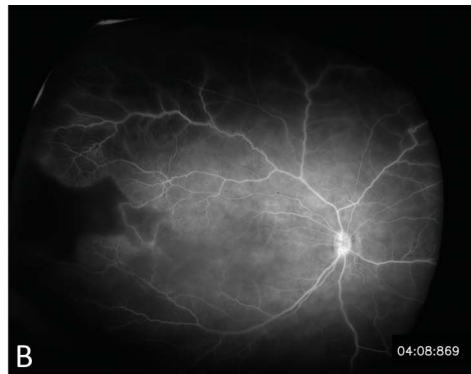
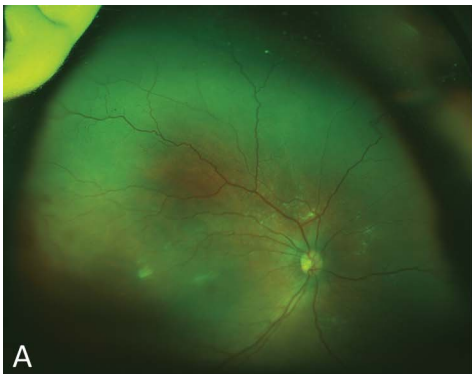
Ultra-wide-field color images were acquired from 32 infants (64 eyes). UWF-IV-FFA was performed successfully in all of the 12 premature infants (24 eyes). As for 32 infants performed UWFI, the average of GA was 28.8 w (26–34 w), the average of CGA was 39.7 w (35–48 w), the average of birth weight was 1,291.7 g (640–2,250 g), and the average of weight was 3,306.2 g (2,100–5,330 g) (Table 1). As for 12 infants performed UWF-IV-FFA, the average of GA was 28.8 w (27–34 w), the average of CGA was 38.7 w (37–42 w), the



**Fig. 4.** Female, GA 26 w, corrected age 44 w, with Stage 1 Zone 2 ROP, demarcation line was showed in the image.

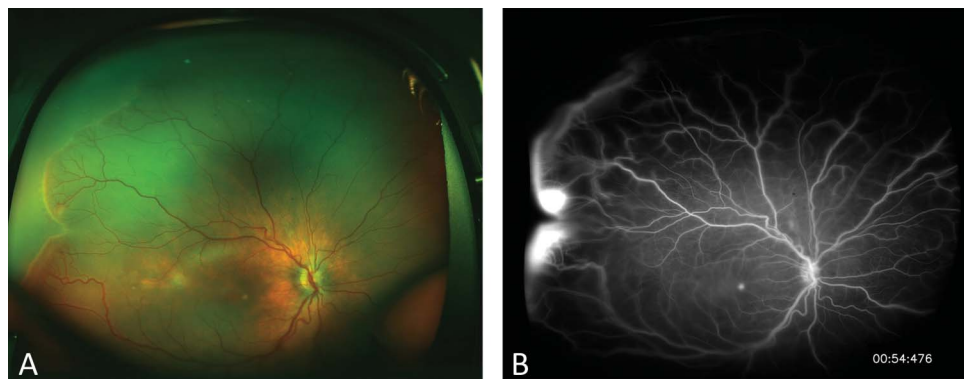


**Fig. 5.** Female, GA 27 w, corrected age 48 w, vascularization of the retina is incomplete but without ROP disease.



**Fig. 6. A–D.** Female, GA 31 + 3 w, corrected age 38 + 6 w, with Stage 3 Zone 2 ROP after IVR in both eyes. The UWF-IV-FFA images showed non-perfusion areas in the retina.

**Fig. 7. A and B.** Female, GA 27 w, corrected age 39 w, with Stage 3 Zone 2 ROP in the right eye. The ultra-wide-field Optos color image revealed the ridge between the vascularized and avascular retina with indistinct neovascularization. The UWF-IV-FFA images demonstrated obvious fluorescein leakage in the neovascular area, which is not shown clearly in the Optos color image.



average of birth weight was 1,330.7 g (995–2,200 g), and the average of weight was 3,359.3 g (2,700–3,825 g) (Table 2).

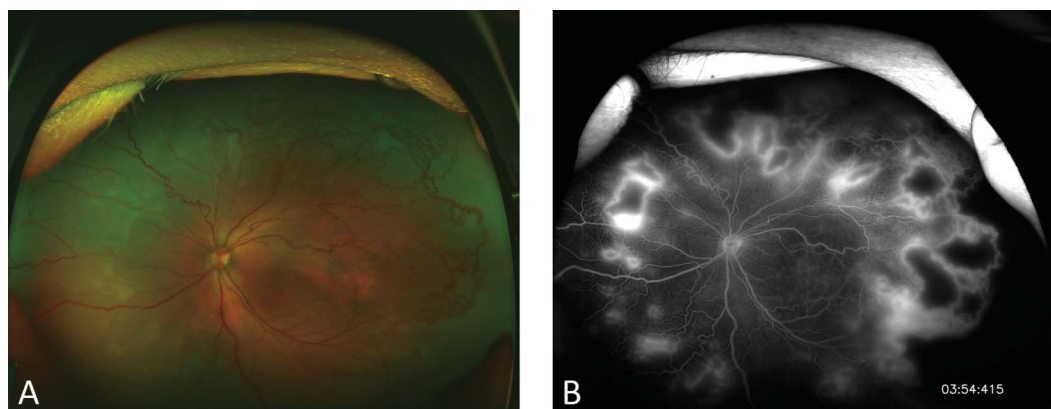
Retinopathy of prematurity stages at the first examination of each infant as recorded in Tables 1 and 2. Four infants had once or twice follow-up by Optos 200Tx in our study; data were recorded in Table 3. There was no case diagnosed different from BIO. Optos 200Tx, and UWF-IV-FFA capturing each took 3–5 minutes. The participants' vital signs were stable during examination. Only slight increase in the heart rate and respiratory rate was found in examination. A few infants presented with decreased oxygen saturation but not less than 90%. No adverse events such as nausea, vomiting, urticaria, cyanosis, hypotension, allergy, or other cardio-cerebrovascular diseases were observed.

The ultra-wide-field Optos 200Tx color images clearly showed nonperfusion areas, demarcation line, ridge, neovascularization, hemorrhage, etc revealed aggressive posterior ROP (AP-ROP) (Figure 1A and B), Stages 3 (Figure 2), 2 (Figure 3), 1 (Figure 4) ROP, and normal (Figure 5). UWF-IV-FFA images showed nonperfusion areas (Figure 6B

and D), neovascularization and fluorescein leakage (Figure 7B), revealed AP-ROP (Figure 8B), Stages 3 (Figure 7B), and 2 (Figure 9) ROP. A case with macular edema was disclosed by UWF-IV-FFA images (Figure 8B). One case follow-up after anti-VEGF therapy was showed in Figure 10A and B.

## Discussion

Optos 200Tx captures a 200° field of view, much wider than the 130° field obtained using RetCam, which shows more details in the peripheral retina; in the context of small pupil, it can capture more peripheral retina. It captures an image (20 Mb) in 0.25 seconds showing more details of the retina without contacting the cornea. It is applicable for regions without RetCam and can be utilized in premature infants with contraindication for contacting the cornea. Binocular indirect ophthalmoscopy is the standard technique for screening ROP; however, it cannot record the images, and the diagnoses were determined by examiners' subjective experience. Scleral depression during examination may impact premature infants, such as inducing oculocardiac reflex.<sup>15</sup> Ultra-wide-



**Fig. 8. A and B.** Female, GA 34 w, corrected age 37 w, with APROP in left eye. The ultra-wide-field Optos color image and UWF-IV-FFA image both demonstrated vascular dilatation and tortuosity. Fluorescein leakage in the macular area in the UWF-IV-FFA image revealed macular edema.



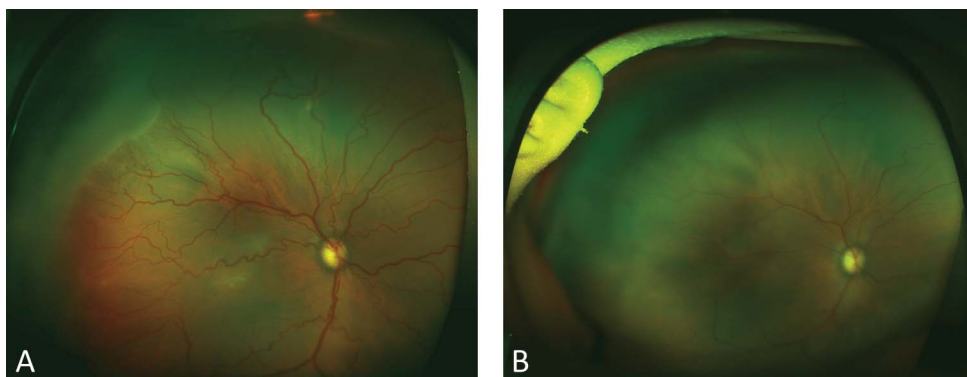
**Fig. 9.** Male, GA 27 + w, corrected age 42+w, with Stage 2 Zone 2 ROP in the left eye.

field imaging avoids the damage of contact and reduces the risk of infection, especially for the infants before or after anti-vascular endothelial growth factor therapy. Although high-resolution color fundus photographs can be obtained from infants to screen ROP, fluorescein angiography is valuable for diagnosis. RetCam FFA is commonly used in infants, whereas UWF-FFA is rarely used in this population although previous studies have reported.

In our study, UWFI was performed in 32 infants with ROP. UWF-IV-FFA was performed in 12 infants who were tentatively diagnosed with ROP Stage 2 or 3 using Optos 200Tx fundus images. The intent was to discover the condition of the nonperfusion area and the prognosis after treatment. All of the infants were administered topical anesthesia to avoid the adverse effects of general anesthesia, such as respiratory obstruction, hypoxemia, arrhythmia, nausea, and hyperthermia. The key to obtaining high-quality images was focusing the camera on the eye. The procedure was executed as follows: First, the chin

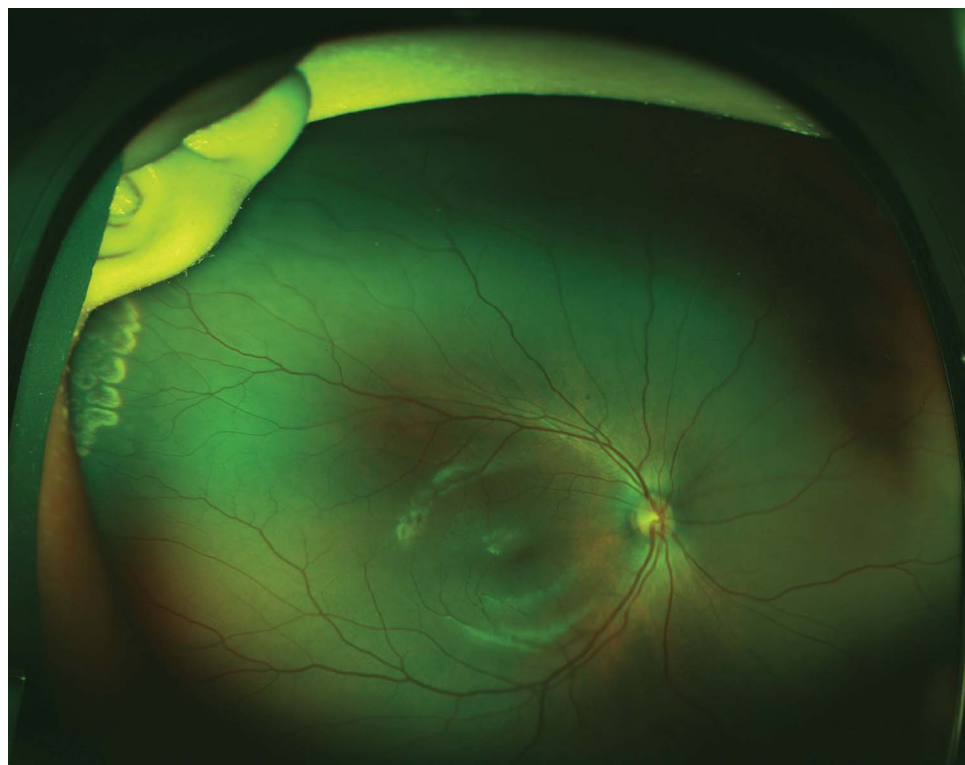
underprop was removed to allow the head to be flexibly adjusted. Second, the assistant manually stabilized the infant's head. Third, the photographer captured the images quickly when the eye was properly positioned. If eye movement was an obstacle, an eye speculum was used to constrain it. The flying baby position may induce cardiorespiratory complications,<sup>11</sup> but only slight increase in the heart rate and respiratory rate was found in examination. A few infants appeared decreasing in oxygen saturation, no less than 90%, and no adverse events occurred in our study. High-quality images were obtained from all 12 premature infants. The feasibility of UWF-IV-FFA for ROP was confirmed.

Characteristics of ROP at different stages were revealed by the Optos 200Tx images. The ultra-wide-field color images showed nonperfusion areas, demarcation line, ridge, neovascularization, hemorrhage, etc. (Figures 1–5, 10, 11) to aid in determination of stage of the disease. There were also some follow-up cases. For example, the alleviation of vascular dilatation and tortuosity and the vessels continued to grow to the peripheral retina after intravitreal injections of ranibizumab (Figure 10A and B). Laser spots could also be easily distinguished in the ultra-wide-field color images (Figure 11). The FFA images showed the junction between the vascularized and avascular retina and the vessel characteristic of much more clearly than the color image; thus, neovascularization is easily distinguish to determine the stage of ROP and make more accurate treatment (Figure 7A and B). The previous report using optical coherence tomography found that infants with ROP may also have cystoid macular edema.<sup>16,17</sup> We also discovered a case (Figure 8B) with macular edema during UWF-IV-FFA that was not revealed by the ultra-wide-field fundus images. Hand-held optical coherence tomography eliminating the use of fluorescein is safer in infants; however, motion artifact are common which limit this facility.<sup>17</sup>



**Fig. 10.** A and B. Female, GA 29 w, corrected age 36 w, with Stage 3 Zone 2 ROP plus disease in the right eye (A); 6 days after intravitreal ranibizumab injection (IVR) vessels grew to peripheral retina (B).

**Fig. 11.** Female, GA 32 + 6 w, corrected age 43 w. laser spots after laser photocoagulation could easily be distinguished on the UWF-IV-FFA image.



In conclusion, Optos 200Tx color images show Stage 1, 2, 3 ROP, plus disease, and avascular area. Optos 200Tx fluorescein angiography should be considered for premature infants with ROP. UWF-IV-FFA images show nonperfusion areas, neovascularization, and fluorescein leakage. Ultra-wide-field imaging and intravenous fundus fluorescein angiography have the potential to screen, diagnose, and follow-up for ROP. The safety of Optos 200Tx performing in infants remains to be proven; we will develop further study in this aspect.

**Key words:** fluorescein fundus angiography, retinopathy of prematurity, Optos 200Tx.

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