Brief Report

Arm-mounted optical coherence tomography angiography in extremely low birth weight neonates with retinopathy of prematurity

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ARTICLE INFO

ABSTRACT

Purpose: To assess the feasibility of imaging extremely low birth weight infants, defined as infants born weighing less than 1000 g or before 27 weeks of gestational age, with an arm-mounted optical coherence tomography angiography (OCTA) device.

Methods: Cross-sectional case series conducted at a single site in-patient academic center. Subjects included infants who had been born premature and met ROP screening criteria. Birth history such as gestational age and birth weight were collected. Subjects were imaged with OCTA in a supine position during ROP screening and treatment. Segmental errors were manually corrected and FAZ area was calculated from the superficial and deep capillary plexus (SCP, DCP) layers. Main outcomes measures were foveal avascular zone (FAZ) area, ROP stage and treatment.

Results: Seven ELBW infants were included with an average gestational age of 25 weeks (range = 23-4/7 to 26 weeks) and average postmenstrual age of 54.7 weeks (range = 43–80 weeks) at the time of imaging. Average birth weight was 615 g (range 500–680 grams). Thirteen eyes had ROP treatment including primary laser, anti-vascular endothelial growth factor injection with delayed laser, and scleral buckle. Six infants were imaged under general anesthesia and one infant was imaged without sedation. Average FAZ area was 0.17 mm^2 (range = 0.03 mm^2–0.37 mm^2) in the SCP and 0.04 mm^2 (range 0 mm^2–0.09 mm^2) in the DCP. FAZ area correlated positively to the ratio of outer retinal layer thickness to inner retinal layer thickness at the foveal center in the SCP and DCP (r^2 = 0.48, p = 0.02; r^2 = 0.46, p = 0.02) and negatively with inner retinal layer thickness in the SCP (r^2 = 0.56, p = 0.008).

Conclusions and Importance: Arm-mounted OCTA was feasible in ELBW infants and provided information about the developing fovea. Measurement of FAZ area and retinal thickness using this modality may be used to study the effects of ELBW, peripheral ROP and ROP treatment on foveal development.

1. Introduction

Retinopathy of prematurity (ROP) is a leading cause of childhood blindness and continues to rise around the world, with preterm infants surviving at increasingly lower birth weights and earlier gestational ages.[1] Extremely low birth weight (ELBW) infants, defined as infants born before 27 weeks of gestational age or weighing less than 1000 g at birth, are increasing and this unique population is at highest risk of developing ROP.[2] Traditional ROP treatment was laser photocoagulation to avascular peripheral retina; however, the use of anti-vascular endothelial growth factor (anti-VEGF) for ROP with delayed peripheral laser has become widely applied for posterior ROP.[3]

Preterm birth results in foveal changes as well.[4–7] The foveal avascular zone (FAZ) in full-term infants normally develops by centrifugal migration of inner retinal layers. Preterm neonates are known to have retained inner retinal layers when imaged with handheld optical coherence tomography (OCT).[8] In school-aged preterm children, an associated finding of reduced or absent FAZ has been demonstrated with optical coherence tomography angiography (OCTA).[4,6] To our knowledge, our study is the first report using an arm-mounted OCTA device in neonates to study FAZ area associated with prematurity.

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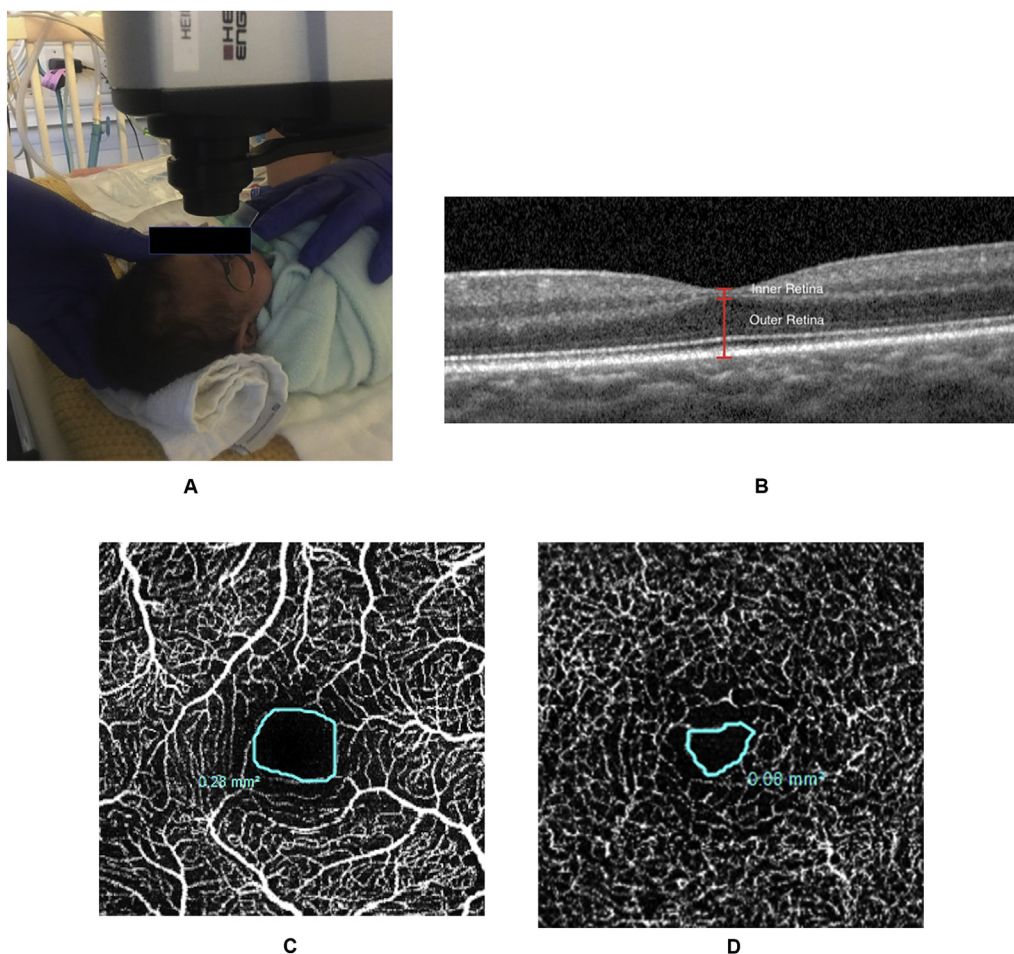**Fig. 1.** (A) Photograph demonstrating non-contact image acquisition. (B) OCT demonstrating measurement of the inner and outer retina at the foveal center. (C) OCTA of the SCP and (D) DCP with measurement of FAZ area.

2. Methods

This study was an observational case series performed at UCLA Ronald Reagan Medical Center. Institutional review board approval was obtained and tenets of the Declaration of Helsinki were followed. Parents of children who had an examination for ROP were invited to participate, and informed consent was obtained. ROP staging and treatment recommendations followed ICROP, ETROP, and BEAT-ROP guidelines.[1]

Subjects were imaged in the neonatal intensive care unit (NICU) or operating room with or without sedation in a supine position. A ROP speculum kit was used to keep the eyelids open and position the eye (Moria, Bourbon l'Archambault, France). Ocular lubrication was applied to maintain a clear ocular surface. A non-contact arm-mounted spectral domain OCT with integrated OCTA software was used for imaging (Spectralis HRA + OCT with Flex module, Heidelberg Engineering, Heidelberg, Germany). The camera was aligned through the pupil without contact (Fig. 1A). Images were acquired at 512 A-scans/B-scan and 512 B-scans/volume with scan sizes of 10°×10°.

Gender, gestational age (GA), birth weight (BW), and postmenstrual age (PMA) were collected at the time of imaging. Images were reviewed on the Heidelberg Eye Explorer using the HRA/Spectralis Viewing Module. The inner and outer retina were measured at the foveal center using the outer plexiform layer as the boundary between inner and outer retina, and their ratio was calculated (Fig. 1B).[10] Superficial capillary plexus (SCP) and deep capillary plexus (DCP) were automatically segmented and then manually adjusted. FAZ area was measured using the caliper tool, as previously described by two

independent graders (N.K. and J.H.) and averaged (Fig. 1C and D).[6] When the FAZ could not be discerned, it was assigned an area of zero.

Statistical analysis was completed using GraphPad Prism 8 (San Diego, CA). A coefficient of determination (r-square) was calculated and a p-value < 0.05 was considered statistically significant. Intergrader reliability was assessed using the intraclass correlation coefficient.

3. Results

Images were obtained in 13 eyes from 7 infants. Six infants were male (86%). ROP stage and treatment are shown in Table 1. Average GA at birth was 25 weeks (range = 23-6/7 to 26-0/7 weeks); average PMA at the time of imaging was 54.7 weeks (range = 43–80 weeks). Average BW was 615 g (range = 547–680 grams). Six infants were imaged under general anesthesia and one infant was imaged without sedation. Seven eyes were imaged without treatment and six infants were imaged after treatment (laser or anti-VEGF).

When considering all infants, average FAZ area was 0.17 mm^2 (range = 0.03 mm^2 -0.37 mm^2) in the SCP and 0.04 mm^2 (range = 0 mm^2–0.09 mm^2) in the DCP (Table 1). There was no correlation between FAZ area and GA (SCP p = 0.44, DCP p = 0.66), PMA (SCP p = 0.37, DCP p = 0.67), or BW (SCP p = 0.73, DCP p = 0.83). There was a positive correlation between FAZ area in both the SCP and DCP and the ratio of the outer to inner retinal layer thickness ($r^2 = 0.48$, p = 0.02; $r^2 = 0.46$, p = 0.02). The FAZ area in the SCP corresponded to a thinner inner retina ($r^2 = 0.55$, p = 0.008) (Figs. 2 and 3). There was no correlation between FAZ area in the DCP and the

Table 1
Infant characteristics and quantitative measurements of foveal avascular zone.

	GA (weeks+days)	PMA Primary Treatment (weeks)	PMA Imaging (weeks)	BW (grams)	ROP Stage	Laterality	Treatment	Timing of Imaging	FAZ SCP	FAZ DCP	Outer/Inner	Outer	Inner
1	23 + 4	44	44	625	Zone 2, stage 2	OD[a]	Laser	Before laser	0.04	0	1.7	120	70
					Zone 2, stage 2	OS[a]	Laser		0.08	0	1.5	115	75
2	23 + 5	37	49	670	Zone 2, stage 3, plus	OD	Anti-VEGF + delayed laser	After anti-VEGF	0.29	0.09	4.7	211	45
					Zone 2, stage 3, plus	OS	Anti-VEGF + delayed laser		0.37	0.08	5	199	40
3	24 + 5	35	56	500	Zone 2, stage 3	OD	Anti-VEGF + delayed laser	After anti-VEGF	0.23	0.07	2.1	156	75
					Zone 2, stage 3	OS	Anti-VEGF + delayed laser		0.26	0	2.1	150	73
4	25 + 1	43	43	680	Zone 2, stage 3, preplus	OD[b]	Laser	Before laser	0.13	n/a	n/a	n/a	n/a
					Zone 2, stage 3, preplus	OS[b]	Laser		0.34	n/a	n/a	n/a	n/a
5	25 + 2	55	55	680	Zone 3, stage 1	OD[a]	Laser	Before laser	0.035	0.02	2.1	169	80
					Zone 3, stage 1	OS[a]	Laser	After laser	0.03	0.01	1.8	164	90
6	26	38	56	547	Zone 2 s/p laser	OD	Laser	After laser	0.04	0.05	1.7	144	86
					Zone 2, stage 1	OS	None		0.34	0.09	2.4	173	73
7	26	39	80	600	Zone 2, stage 3, plus	OD[c]	Anti-VEGF x2, Laser, SB	After all treatments	n/a	n/a	n/a	n/a	n/a
					Zone 2, stage 3, plus	OS	Laser		0.03	0.045	2.5	252	102

GA = gestational age, PMA = postmenstrual age, BW = birth weight, ROP = retinopathy of prematurity, SB = scleral buckle.
FAZ = foveal avascular zone, SCP = superficial capillary plexus, DCP = deep capillary plexus.

[a] Treatment was performed for persistent Stage 1 ROP beyond 52 weeks GA.
[b] Eyes had cystoid macular edema and was excluded from measurement of the inner and outer retinal layer thickness.
[c] Rhegmatogenous retinal detachment developed from peripheral atrophic hole after laser which was treated with scleral buckle. Eye was excluded from further analysis due to profound macula atrophy.

inner retinal thickness (p = 0.16). There was no correlation in FAZ area in the DCP or SCP with outer retinal thickness (SCP p = 0.5, DCP p = 0.07).

A thicker outer retina corresponded with older PMA (r^2 = 0.49, p = 0.02). In addition, a thicker inner retina corresponded to a higher GA (r^2 = 0.51, p = 0.01) and higher PMA (r^2 = 0.41, p = 0.03). There was no correlation between inner retinal thickness and BW (p = 0.44). There was no correlation between outer retinal thickness and GA (p = 0.36) or BW (p = 0.50).

Given the possible effects of treatment, we analyzed infants without treatment (n = 5 eyes from 3 infants), and FAZ area in the DCP retained significance in positive correlation with the ratio of outer to inner retinal layer thickness (r^2 = 0.81, p = 0.04) although FAZ area in the SCP did not correlate with the ratio of outer to inner retinal layer thickness (r^2 p = 0.51, p = 0.18). In this cohort without treatment, outer retinal layer thickness correlated to PMA (r2 = 0.84, p = 0.03) and GA (r2 = 0.96, p = 0.003) but not to BW (p = 0.98).

Intraclass correlation coefficient for FAZ area was 0.99 (95% confidence interval 0.973–0.998) in the SCP and 0.94 (95% confidence interval 0.904–0.997) in the DCP.

4. Discussion

The current study evaluated FAZ area using an arm-mounted OCTA device in infants with ROP in the NICU or operating room setting with and without anesthesia. To our knowledge, this represents the first report using the Heidelberg arm-mounted OCTA in preterm infants. There are two other reports of neonatal OCTA imaging in preterm infants which use different devices.[11,12] One feasibility study used macular OCTA in four preterm infants using a prototype handheld device (Axsun Technologies).[11] This study demonstrated feasibility, but did not report any measurements or specific findings on OCTA. A second report of OCTA in a preterm neonate reported flat neovascularization at the border of peripherally treated retina. The infant was swaddled at 35 weeks PMA and imaged with a desktop Avanti RTVue XR (Optovue Inc, Fremont, CA).[12]

All subjects in our study were ELBW infants who underwent ROP treatment in at least one eye. The presence of thickened inner retinal layers on B-scan OCT corresponded with smaller or absent FAZ which is consistent with previous studies in ex-premature school-aged children imaged with desktop devices.[4,13,14] In our study, subject 6 only had one eye treated with laser photocoagulation and this eye had a poorly developed fovea compared to the contralateral untreated eye. This finding leads to the question of whether laser can cause arrest of foveal maturation. In addition, subject 3 was treated with anti-VEGF and had a more developed FAZ. Studies of children comparing anti-VEGF to laser treatment have demonstrated that eyes treated with anti-VEGF had more mature foveal development as determined by desktop OCTA.[15] In the subset of nontreatment eyes, most of these differences were still present. Given that OCTA images are best acquired in sedated infants, the images obtained in this study were from neonates who were sedated for clinical indications and it is therefore difficult to standardize timing of OCTA image collection and/or obtain pretreatment images.

A recent study used the same arm-mounted OCTA device in infants born at term GA and demonstrated greater average FAZ (0.56 ± 0.082 mm^2) compared with ROP infants in our study (0.169 ± 0.14 mm^2).[9] This difference was present despite the other study using total retinal thickness when calculating FAZ area, which may lead to decreased FAZ area due to artifacts present in the DCP layer. However, our study highlights that there are differences in the development of the FAZ in infants born preterm versus those born at term. Moreover, the relationship of the FAZ and inner and outer retinal layer thickness may be affected by factors such as GA as well as PMA.

Limitations of this report include lack of paired pre- and post-treatment images, variation in treatment course and PMA at time of imaging, and including images taken before or after treatment in a
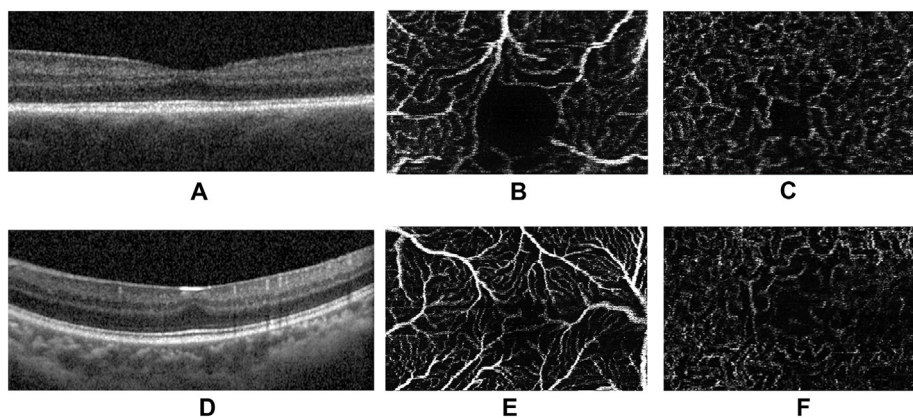
Fig. 2. Patient 6 OS: (A) OCT demonstrating minimal retained inner retinal layers (B) OCTA with distinct FAZ in the SCP and (C) DCP. Patient 7 OS. (D) OCT demonstrating significant retained inner retinal layers (E) OCTA with indistinct FAZ in the SCP and (F) DCP.

small cohort of neonates which makes our study underpowered to draw conclusions about the dynamics of FAZ size. However, this study still contains new information in the field of pediatric retina and indicates that the device could be very useful to investigate foveal development in ELBW infants.

Additional studies in more infants would allow more subgroup analysis to assess the role of OCTA in studying the effects of ELBW, peripheral ROP, and ROP treatment on foveal development. Although one of our images was obtained without sedation, images obtained under general anesthesia resulted in better image quality and less motion artifact.

5. Conclusions

The current study establishes the feasibility of using an arm-mounted OCTA device to image ELBW neonates and increases our knowledge of foveal development. Future studies can also address the question of if and how laser and anti-VEGF treatment for peripheral ROP affects foveal maturation by imaging before and after treatment.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Declaration of competing interest

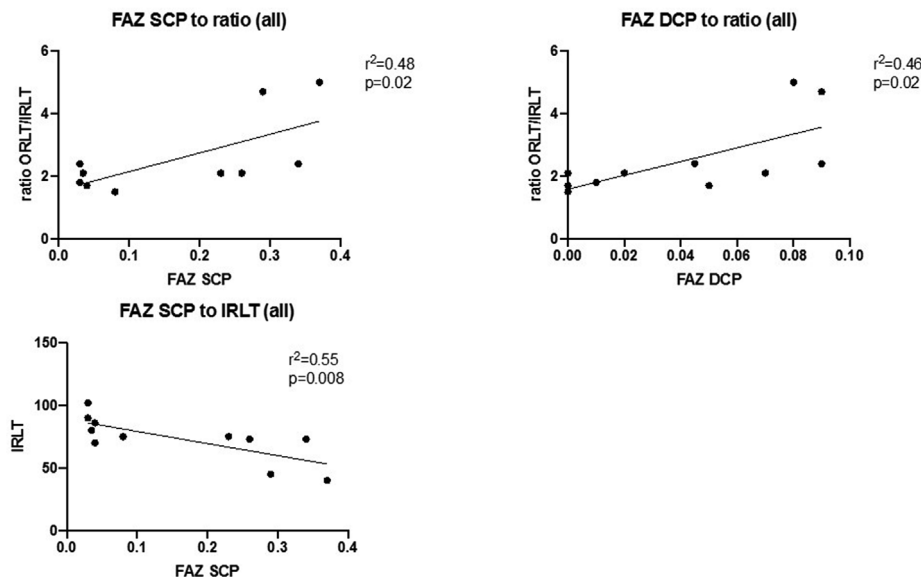None of the authors have any financial disclosures.

Fig. 3. Significant correlations when comparing foveal avascular zone (FAZ) in superficial capillary plexus (SCP) and deep capillary plexus (DCP) to inner retinal layer thickness (IRLT) and ratio of outer to inner retinal layer thickness (ORLT/IRLT).

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