



Comparison between wide-angle OCT angiography and ultra-wide field fluorescein angiography for detecting non-perfusion areas and retinal neovascularization in eyes with diabetic retinopathy

Osamu Sawada¹ · Yusuke Ichiyama¹ · Syunpei Obata¹ · Yuka Ito¹ · Masashi Kakinoki¹ · Tomoko Sawada¹ · Yoshitsugu Saishin¹ · Masahito Ohji¹

Received: 8 January 2018 / Revised: 8 April 2018 / Accepted: 16 April 2018 / Published online: 30 April 2018
© Springer-Verlag GmbH Germany, part of Springer Nature 2018

Abstract

Purpose To compare the ability of wide-angle optical coherence tomography angiography (OCTA) with that of ultra-wide field fluorescein angiography (UWFFA) to detect non-perfusion areas (NPAs) or retinal neovascularization (NV) in eyes with diabetic retinopathy (DR).

Methods Patients with DR underwent UWFFA using the Optos® panoramic 200Tx imaging system and wide-angle OCTA with 12 × 12 mm fields of five visual fixations using the PLEX Elite 9000®. We compared the abilities of UWFFA and OCTA to detect NPAs and NV.

Results Fifty-eight eyes of 33 patients (mean age, 60.0 years old; female/male, 16/17) with DR were evaluated. NPAs were detected in 47 out of 58 eyes using UWFFA and in 48 eyes using OCTA. NVs were detected in 25 out of the 58 eyes using UWFFA and in 26 eyes using OCTA. The sensitivity for detection of NPA using OCTA was 0.98, and the specificity was 0.82. The sensitivity for detection of NV was 1.0, and the specificity was 0.97.

Conclusion The wide-angle OCTA seems to be clinically useful for the detection of NPAs or NV.

Keywords Diabetic retinopathy · Fluorescein angiography · Non-perfusion area · Ocular coherence tomography angiography · Retinal neovascularization

Diabetic retinopathy (DR) is a leading cause of visual impairment in developed countries [1]. DR is essentially a microangiopathy that causes capillary occlusion, vascular hyperpermeability, and neovascularization (NV) in the retina [2]. It is crucial to detect non-perfusion areas (NPAs) or retinal NV in order to evaluate DR progression and decide on courses of treatment [2].

Fluorescein angiography (FA) is an established examination to determine the presence of NPA or NV in the retina.

However, FA is an invasive examination, is unrepeatable on the same day or in the short term, and can cause complications. Severe life-threatening reactions such as anaphylaxis, cardiac arrest, and bronchospasm are extremely rare but do occur. Death is also estimated to occur with a frequency of 1 in 220,000 [3]. A noninvasive examination is desired to replace FA. The predominant candidate is optical coherence tomography angiography (OCTA), a noninvasive novel imaging technique that uses decorrelation between resampled images to detect flow and construct two- and three-dimensional images of blood flow within the eye. Ordinary OCTA can identify NPA and NV in the retina but is limited by its small field of view, which is significantly smaller (3 × 3 mm or 6 × 6 mm) than the standard photographic field [4–7].

The commercially available OCTA platform known as the swept-source (SS) OCT PLEX Elite 9000® (Carl Zeiss Meditec, Dublin, CA) uses a swept-source, tunable laser centered at 1060 nm and operating at a scan speed of 100,000 A-scans per second with an axial resolution of 6.3 μm. This device utilizes optical micro angiography complex (OMAGc)

The authors have no proprietary interest in any aspect of this study.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00417-018-3992-y>) contains supplementary material, which is available to authorized users.

✉ Osamu Sawada
osawada@belle.shiga-med.ac.jp

¹ Department of Ophthalmology, Shiga University of Medical Science, Seta Tukinowacho, Otsu, Shiga 520-2192, Japan

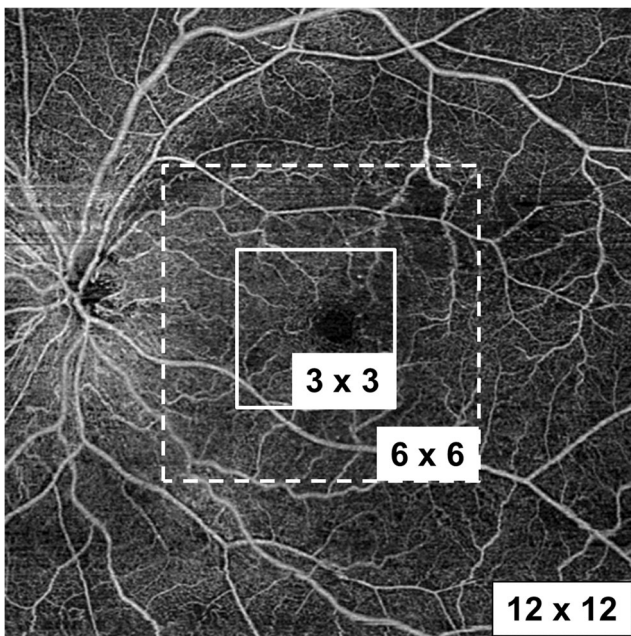
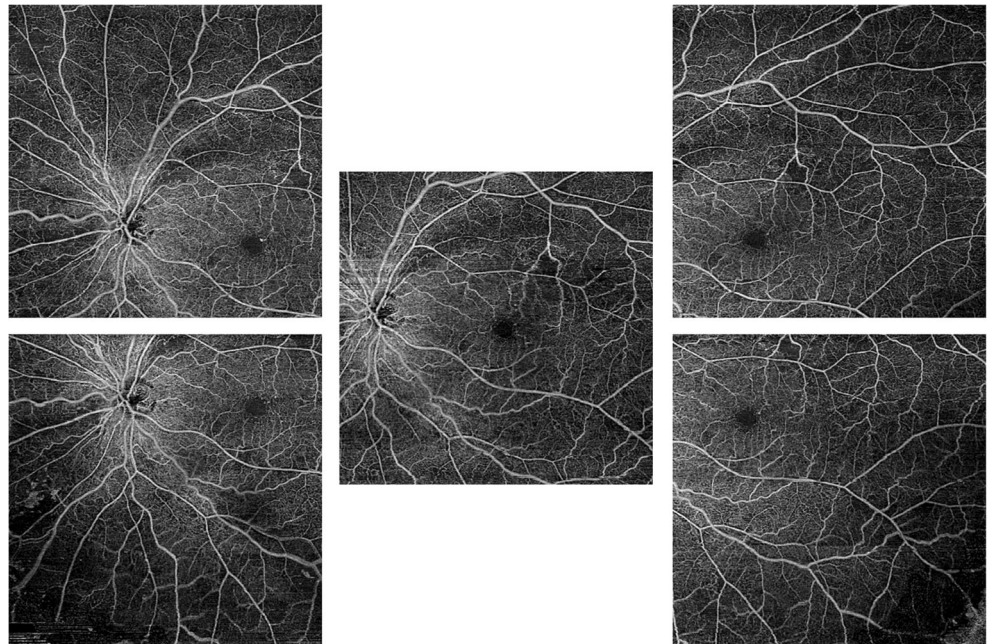


Fig. 1 The wide OCTA, PLEX Elite 9000® image. The field of view is 12×12 mm and includes the optic disc and its major arteries and veins. The 3×3 mm and 6×6 mm fields of view are enclosed by a solid-line square and dashed-line square, respectively

algorithms to visualize microvasculature and wider OCTA scan protocols (i.e., 9×9 mm and 12×12 mm OCTA scan protocols). The OCTA can take 12×12 mm fields (Fig. 1) and get the wider images by five changes of visual fixation (Fig. 2).

In the present study, we compared the ability of the wide-angle OCTA, PLEX Elite 9000® system with that of the ultra-wide field (UWF) FA, Optos 200Tx® system (Optos, PLC,

Fig. 2 Central and four additional OCTA images. The combining of nasal inferior, nasal superior, temporal inferior, and temporal superior images widens the field of detection



Dunfermline, Scotland) to detect NPAs or NV in patients with DR. We selected the ultra-wide field FA, Optos 200Tx® platform as the representative FA instrument because it is frequently used for UWF color imaging and UWFFA of nearly the entire retina (up to 200°) including the peripheral retina, which is captured simultaneously without the need for eye refixation [8]. This study explored whether the noninvasive wide-angle OCTA could clinically substitute UWFFA for detecting NPAs or NV in patients with DR.

Methods

Study participants Participants were patients with diabetic retinopathy (age ≥ 20 years, type 1 or type 2 diabetes mellitus) who received fluorescein angiography after they underwent a comprehensive ophthalmic examination. They provided written informed consent in accord with procedures approved by the Institutional Review Board of Shiga University of Medical Science and the tenets of the Declaration of Helsinki. This prospective cross-sectional study evaluating imaging instrument performance was carried out at Shiga University of Medical School Hospital from August, 2016 to September, 2017, and its protocol was approved by the Institutional Review Board of Shiga University of Medical Science.

UWFFA The participants underwent non-steered UWFFA using the Optos Optomap Panoramic 200Tx imaging system (Optos, PLC, Dunfermline, Scotland). FA was performed according to a standard protocol after intravenous injection of 5 ml of 10% sodium fluorescein into one antecubital vein. Images were digitally captured and reviewed using the review

software (V2 Vantage, Optos, Dunfermline, UK), and subsequently compressed into high-quality Joint Photographic coding Experts Group (JPEG) files. The images were transferred to Adobe® Photoshop® software (Adobe Systems, Inc., San Jose, CA). Proliferative DR (PDR) was defined by the presence of NV on UWFFA images.

Wide-angle OCTA Three-dimensional OCTA scans of 12×12 mm regions were acquired using the swept-source OCT PLEX Elite 9000® instrument (Carl Zeiss Meditec, Dublin, CA). Five OCTA scans were obtained (one at each of five fixation points including center, nasal inferior, nasal superior, temporal inferior, and temporal superior) to obtain a wider field of view (Fig. 2). All scans consisted of 500 A-scans per B-scan, repeated twice at each of 500 B-scan positions.

Detection of NPA or NV We determined the presence of NPA or NV on the basis of FA in each eye. We also judged the

presence of NPA or NV on the basis of all five OCTA images with masking distinction of patients. In all five OCTA images, the retina slab, one of preset slabs of angiography analysis in the PLEX Elite 9000® system, was examined for the presence of NPA. The slab showed the whole retinal vasculature between the inner limiting membrane (ILM) and $70 \mu\text{m}$ above the retinal pigment epithelium (RPE). The OCTA image of the retina slab vasculature resembled the FA image (Fig. 3). The retina slab and vitreoretinal interface (VRI) slab, both preset slabs used in angiography analysis, were respectively used to identify NV in all five OCTA images. The VRI slab demonstrated the growth of blood vessels into vitreous, which is characteristic of NV. The B-scan of the VRI slab was also used to confirm NV (Fig. 4). We calculated the sensitivity and specificity of NPA or NV detection, assuming the accuracy of UWFFA diagnosis.

Locations of the NVs detected by UWFFA We generated the composite panoramic image using Adobe® Photoshop®

Fig. 3 Representative case 1: a 55-year-old male. **a** Central, nasal superior, nasal inferior, temporal superior, and temporal inferior OCTA images. NPA was detected at all five fixation positions using the retina slab of OCTA. NV appears in the upper part of the primary retinal artery and vein (dashed, ellipsoid). **b** UWFFA image. Both UWFFA and OCTA images show the same NPA and NV, but the UWFFA image is wider

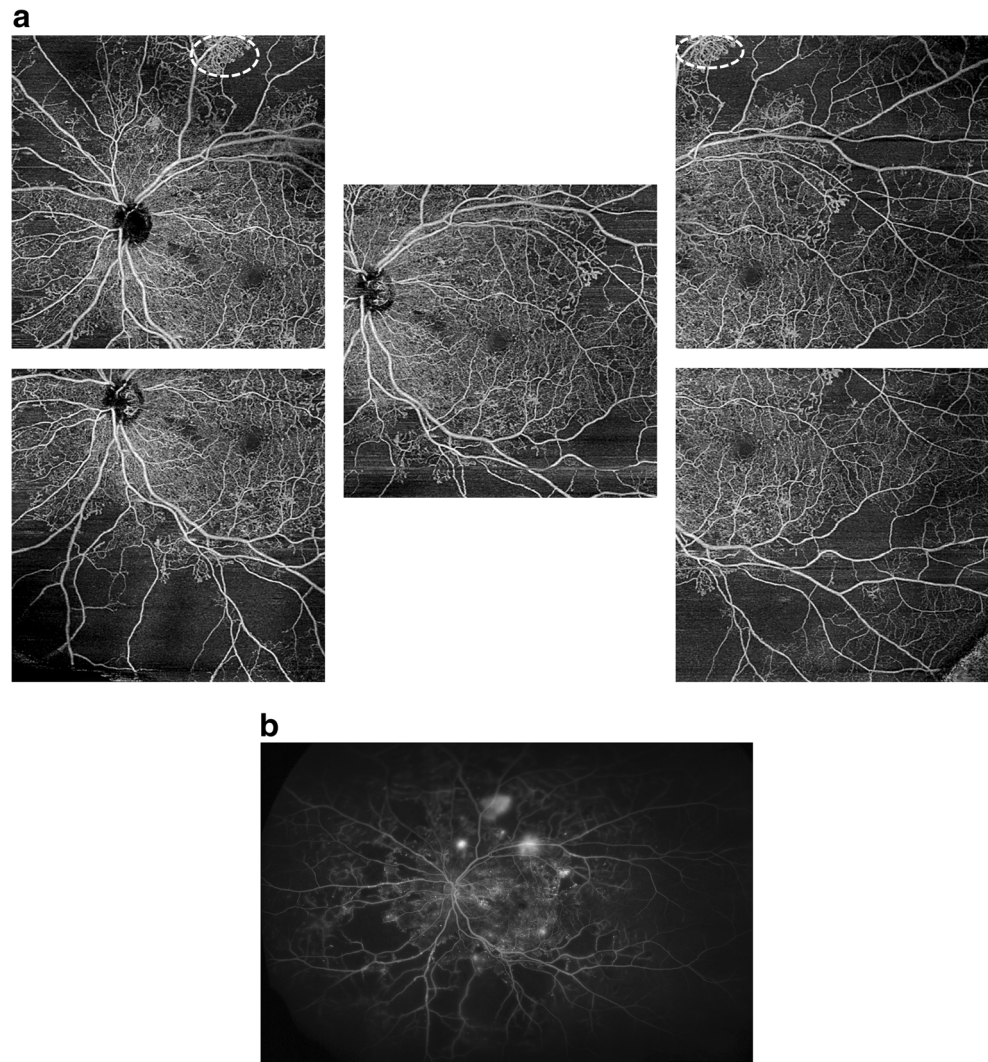
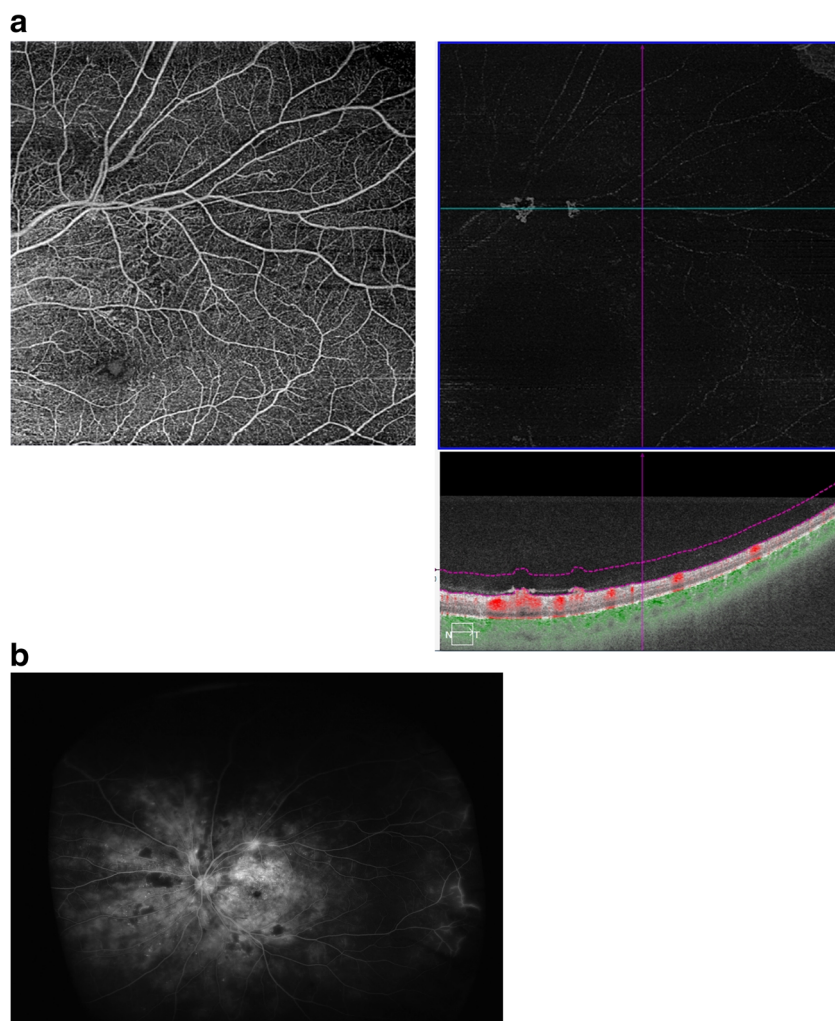


Fig. 4 Representative case 2: a 49-year-old male. **a** Retina slab (left), VRI slab (right top), and B-scan of the VRI slab (right bottom). VRI slab image shows the lesion above the retina and B-scan shows blood flow (red) through the lesion in the vitreous, NV. **b** UWFFA image. NV is located at the same point in both the OCTA and UWFFA images



software (Adobe Systems, Inc., San Jose, CA) from five OCTA images (the center, nasal inferior, nasal superior, temporal inferior, and temporal superior positions) in each eye, and then superimposed the panoramic OCTA image on the UWFFA image using Adobe® Photoshop® software in each eye (Fig. 5). The UWFFA images were compared before and after superimposition, and the positions of NV detected by UWFFA were recorded. We counted the number of cases in which NVs were detected only inside the panoramic OCTA area, only outside the panoramic OCTA area, or both inside and outside the panoramic OCTA area.

Results

Fifty-eight eyes of 33 patients with diabetic retinopathy were imaged for the study. The patients' characteristics are described in Table 1.

Detection of NPA NPA was detected in 46 out of 58 eyes by both UWFFA and OCTA. Assuming accurate detection of

NPAs by UWFFA, we detected true-positive, false-positive, false-negative, and true-negative NPAs in 46, 2, 1, and 9 eyes by OCTA. The sensitivity and specificity of NPA detection by OCTA was 0.98 and 0.82, respectively (Table 2).

Detection of NV NV was detected in 25 eyes by UWFFA, in 19 eyes by OCTA using the retina slab, and 26 eyes in VRI slab. We judged the presence of NV on the basis of the combination of the retina and VRI slabs. Assuming accurate detection of NV areas by UWFFA, we detected true-positive, false-positive, false-negative, and true-negative NV in 25, 1, 0, and 32 eyes by OCTA of the combination of retina and VRI slabs. The sensitivity and specificity of NV detection was 1.0 and 0.97, respectively (Table 3).

Locations of the NVs detected by UWFFA We superimposed the four arteries and four veins of the optic disc in the panoramic OCTA image on that of the UWFFA image. NV was detected by UWFFA only within the panoramic OCTA area, both in and out of the panoramic OCTA area, and only outside

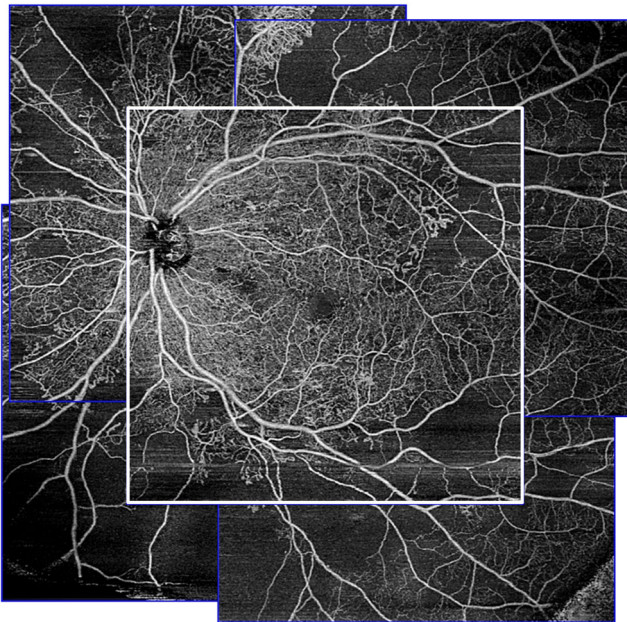


Fig. 5 Comparison between the areas of single image and the composite panoramic OCTA image. The field of the composite panoramic image was approximately 2.4 times larger than that of the single image. The white square shows the area of the single-center image

Table 1 Clinical characteristics of patients

Number of eyes	58 eyes of 33 patients
Mean age	60.0 ± 13.2 (28–88)
Female/male	16/17
Non-PDR/PDR	31 eyes/27 eyes

the panoramic OCTA area in 9, 16, and 0 eyes, respectively (Table 4).

Discussion

This study compared the clinical usefulness of wide OCTA images for NPA or NV detection with that of UWFFA images. To our knowledge, this is the first report to directly compare these two imaging methods. Compared to NPA detection by UWFFA, detection by wide OCTA had a sensitivity of 0.98, indicating that OCTA might be useful for NPA detection. But wide OCTA had not so high specificity (0.82). The reason

Table 2 Detection of NPA by OCTA comparing with UWFFA

	UWFFA, NPA(+)	UWFFA, NPA(-)
OCTA, NPA(+)	46 eyes	2 eyes
OCTA, NPA(-)	1 eye	9 eyes

The sensitivity for detection of NPA by OCTA was 0.98 and the specificity was 0.82

Table 3 Detection of NV by OCTA comparing with UWFFA

	UWFFA, NV(+)	UWFFA, NV(-)
OCTA, NV(+)	25 eyes	1 eyes
OCTA, NV(-)	0 eye	32 eye

The sensitivity for detection of NV by OCTA was 1.0 and the specificity was 0.97

could be the low rate of early DR without NPAs. In this cross-sectional study group, we imaged eyes suspected of, but not known to have, NPAs and NV areas. Invasive FA is unwarranted for patients with early DR. The image using the retina slab can show the definite NV while it sometimes might be difficult to tell NV from intraretinal microvascular abnormality (IRMA) on the image of the retina slab. Therefore, we used the VRI slab as well to judge the presence of NV. VRI slab could show vessel growth into the vitreous. We confirmed the presence of NV by viewing B-scans showing blood flow through the lesion. Compared to UWFFA detection of NV, wide OCTA had a sensitivity of 1.0 and specificity of 0.97.

Out of 25 eyes with NV detected by UWFFA, NVs were detected only within the panoramic OCTA image area in 9 eyes, both inside and outside the panoramic OCTA image area in 16 eyes, and only outside the panoramic OCTA image area in no eye. Despite the limited number of cases in this study, it can be said that NV detected only by UWFFA, but not by OCTA, is rare. Obviously, field of view in UWFFA is wider comparing with that the complex view of five fixations using the wide-angle OCTA; however, the complex view of the five fixations might be clinically enough useful because most NVs in PDR cases are observed within the mid periphery of the retina where are covered by OCTA images. [9]

Previous studies in eyes with diabetic retinopathy have shown that OCTA detects NPA and NV to nearly the same extent as FA [5–7]. But the field of view for conventional OCTA, which is 3 mm × 3 mm or 6 mm × 6 mm, is relatively restricted compared with that for FA. The OCTA, PLEX Elite 9000 system employed in the present study widens the field of

Table 4 Locations of NVs detected by UWFFA

	NV(+) within the area of the panoramic OCTA image	NV(-) within the area of the panoramic OCTA image
NV(+) out of the area of the panoramic OCTA image	16 eyes	0 eye
NV(-) out of the area of the panoramic OCTA image	9 eyes	33 eyes

In all the cases detected by UWFFA, NVs were detected in the area of the composed panoramic OCTA image

view to 12 mm × 12 mm. The additional OCTA images at four fixation positions of the visual field (nasal inferior, nasal superior, temporal inferior, and temporal superior) made possible approximately 2.4 times enlargement of the single-center OCTA field-of-view. The width of the field of view for the panoramic OCTA image was approximately nine times that of a 6 mm × 6 mm conventional OCTA image.

OCTA has other limitations. FA can show the decrease in leakage after treatments such as panretinal photocoagulation (PRP) and anti-VEGF therapy for PDR. Unlike FA, OCTA cannot detect a change in the amount of leakage from NVs. Nevertheless, Ishibazawa et al. was able to show a significant decrease in the vessel area of NV on the optic disc and NV elsewhere following PRP using OCTA [10], and we also could follow the change in NV extent using wide OCTA after treatment.

From the present study, we conclude that wide OCTA (12 × 12 mm) can be clinically useful for NPA or NV detection although wide OCTA images cover a smaller area than UWFFA images.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Early Treatment Diabetic Retinopathy Study Group (1991) Early treatment diabetic retinopathy study design and baseline patient characteristics. ETDRS report number 7. *Ophthalmology* 98:741–756
2. Antonetti DA, Klein R, Gardner TW (2012) Diabetic retinopathy. *N Engl J Med* 366:1227–1239
3. LA Y, KT R, LJ T et al (1986) Fluorescein angiography complication survey. *Ophthalmology* 93:611–617
4. Hwang TS, Jia Y, Gao SS et al (2015) Optical coherence tomography angiography features of diabetic retinopathy. *Retina* 35:2371–2376
5. Salz DA, de Carlo TE, Adhi M et al (2016) Select features of diabetic retinopathy on swept-source optical coherence tomographic angiography compared with fluorescein angiography and normal eyes. *JAMA Ophthalmol* 134:644–650
6. Ishibazawa A, Nagaoka T, Takahashi A et al (2015) Optical coherence tomography angiography in diabetic retinopathy: a prospective pilot study. *Am J Ophthalmol* 160:35–44 e31
7. Matsunaga DR, Yi JJ, De Koo LO, Ameri H, Puliafito CA, Kashani AH (2015) Optical coherence tomography angiography of diabetic retinopathy in human subjects. *Ophthalmic Surg Lasers Imaging* 46:796–805
8. Wessel MM, Aaker GD, Parlitsis G, Cho M, D'Amico DJ, Kiss S (2012) Ultra-wide-field angiography improves the detection and classification of diabetic retinopathy. *Retina* 32:785–791
9. Spaide RF (2011) Peripheral areas of nonperfusion in treated central retinal vein occlusion as imaged by wide-field fluorescein angiography. *Retina* 31:829–837
10. Ishibazawa A, Nagaoka T, Yokota H et al (2016) Characteristics of retinal neovascularization in proliferative diabetic retinopathy imaged by optical coherence tomography angiography. *Invest Ophthalmol Vis Sci* 57:6247–6255