Comparison of indocyanine green angiography and optical coherence tomographic angiography in polypoidal choroidal vasculopathy

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CLINICAL STUDY

Abstract

Purpose   To compare optical coherence tomographic angiography (OCTA) and indocyanine green angiography (ICGA) images for detecting polypoidal lesions (PLs) and branching vascular networks (BVNs), and to measure the polypoidal areas (PAs) in patients with polypoidal choroidal vasculopathy (PCV).

Methods   All patients underwent ICGA, optical coherence tomography (OCT), and OCTA. We compared the detection sensitivity for PL and BVN, as evaluated by the ICGA and OCTA images. Furthermore, PA measured by ICGA was divided into two groups: one in which the area could be measured by OCTA ($ICGA^+OCTA^+$) and the other in which the area could not be measured by OCTA ($ICGA^+OCTA^-$).

Results   Twenty-one consecutive eyes of 21 patients (mean age, 73.8 ± 9.8 years) were included. ICGA detected PL in all eyes (100%), whereas OCTA detected PL in 16 eyes (75.2%); ICGA detected BVN in 15 eyes (71.4%), whereas OCTA detected BVN in 20 eyes (95.2%). The mean PA in $ICGA^+OCTA^+$ and $ICGA^+OCTA^-$ was 0.24 ± 0.04 and 0.14 ± 0.01 mm^2, respectively; a significant difference was observed between $ICGA^+OCTA^+$ PA and $ICGA^+OCTA^-$ PA ($P < 0.0001$). In addition, the mean PA in the $ICGA^+OCTA^+$ group measured by ICGA and OCTA was 0.24 ± 0.04 was 0.19 ± 0.04 mm^2, respectively; these values were significantly different ($P = 0.0046$).

Conclusions   OCTA might detect more BVNs and fewer PLs compared with ICGA, and PL detected by OCTA might be smaller than those detected by ICGA.

Introduction

Polypoidal choroidal vasculopathy (PCV) involves choroidal neovascularisation (CNV) characterised by polypoidal lesions (PLs) with or without branching vascular networks (BVNs) under the retinal pigment epithelium (RPE).[1–3] Microscopic fundus examination, optical coherence tomography (OCT), fluorescein angiography (FA), and indocyanine green angiography (ICGA) are useful for diagnosing eyes with PCV.[4–11] FA and ICGA are invasive techniques that require intravenous dye injection, and hepatic, renal, or allergic complications can arise.[12] In terms of severe reactions, cases of hypotensive shock and death have been reported.[13] Therefore, patients with a history of allergies or hepatic or renal dysfunction are not suited for angiographic examination.

New imaging technologies have recently been developed, which provide new insights into the visualisation of normal and pathologic vascularisation. The development of spectral-domain OCT instruments with increased scanning speeds and high-speed swept-source OCT instruments has enabled the use of optical coherence tomographic angiography (OCTA).[14–17] OCTA, which can noninvasively detect blood flow, provide three-dimensional reconstruction of the perfused microvasculature within the retina and choroid, and identify distinct characteristics of the capillary networks located within the different layers of the retina

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and choroid; thus, it is a useful tool for diagnosing many ocular diseases. Images of PL and BVN in eyes with PCV, and the detection abilities of OCTA and ICGA for detecting PCV have been compared;[18] however, to the best of our knowledge, the accuracy of OCTA and ICGA in assessing PL has not yet been reported. The purpose of this study was to compare the accuracy of OCTA and ICGA images for detecting PL and BVN, and for measuring the polypoidal area (PA) in PCV.

Materials and methods

Patients

This study was approved by the Institutional Review Board of the Nagoya University Graduate School of Medicine. Informed consent was obtained from all patients, and all research and data collection complied with the tenets of the Declaration of Helsinki. We enrolled consecutive 21 cases of eyes with naive PCV seen at our department between March 2015 and August 2015. PCV was diagnosed based on early subretinal ICGA hyperfluorescence (appearing in a 3×3 mm area centred on the fovea within the first 5 min of dye injection) and at least one of the following diagnostic criteria according to the EVEREST study.[19] All patients underwent a complete ophthalmic examination including best-corrected visual acuity (BCVA), anterior segment examination and dilated fundus biomicroscopy, colour fundus photos by CF-60

DSi (Canon, Tokyo, Japan), FA and ICGA by HRA II (Heidelberg Engineering, Heidelberg, Germany), and OCT image by Heidelberg Spectralis (Heidelberg, Germany). Patients who had eye of >25 and <22 mm axial length, PL outside of the scanning area, any other confounding retinal pathology such as diabetic retinopathy or pathologic myopia, previously had been treated with photodynamic therapy, intravitreal injection therapy, transpupil thermal laser, vitrectomy, or previously had any corneal disease or cataract making any images unclear, were excluded from the study.

Optical coherence tomographic microangiography

OCTA was measured by RTvue XR Avanti (Optovue Inc., Fremont, CA, USA) and was used to obtain OCT angiograms as previously described.[16] This instrument has an A-scan rate of 70 000 scans per second using a light source centred at 840 nm and a bandwidth of 50 nm; the resolution is 5 mm axially, with a 15 mm beam width. Each B scan contained 316 A-scans, and two consecutive B-scans (M-B frames) were captured at a fixed position before proceeding to the next sampling location. The volumes were registered and the B-scan images were compared to calculate the decorrelation in the images; the decorrelation was viewed as the maximal projection image of blood flow. Because the retina is a laminar structure with a corresponding stratification of blood supply, segmentation of the retina in specific layers

Table 1 Detection of PL and BVN, and PA by ICGA and OCTA

Case	Age (years)	Right or left	Visual acuity	ICGA			OCTA			
				PL	BVN	PA	PL	BVN	PA	
1	51	L	3/20	+	+	0.49	+	+	0.46	Figure 1
2	62	L	20/20	+	+	0.14	+	+	0.09	
3	65	R	5/20	+	+	0.19	+	+	0.19	
4	72	R	20/20	+	+	0.18	+	+	0.08	
5	73	L	12/20	+	+	0.21	+	+	0.08	
6	76	R	16/20	+	+	0.16	+	+	0.12	
7	77	L	20/20	+	+	0.22	+	+	0.28	
8	78	L	16/20	+	+	0.13	+	+	0.09	
9	83	R	12/20	+	+	0.11	+	+	0.09	
10	88	R	16/20	+	+	0.1	+	+	0.05	
11	66	R	12/20	+	−	0.21	+	+	0.14	Figure 2
12	73	L	12/20	+	−	0.2	+	+	0.19	
13	76	L	20/20	+	−	0.36	+	+	0.25	
14	77	L	8/20	+	−	0.58	+	+	0.63	
15	86	L	16/20	+	−	0.11	+	+	0.1	
16	68	L	10/20	+	+	0.2	−	+		Figure 3
17	66	L	16/20	+	+	0.14	−	+		
18	67	L	25/20	+	+	0.08	−	+		
19	77	L	16/20	+	+	0.1	−	+		
20	85	R	4/20	+	+	0.18	−	+		
21	90	L	5/20	+	−	0.35	+	−	0.18	

allows simple *en face* visualisation of the corresponding vascular supply in that layer.

Evaluation of PA

We investigated how PA detected by ICGA could be depicted by OCTA, and we measured PA from the paired images. To measure PA from ICGA, we used ICGA images at about 60 s after intravenous dye injection. We traced the border of the area that included the hyperfluorescent lesion (representing PL) in the ICGA image and measured the pixels of PL using NAVIS bundled software (Nidek Co. Ltd., Aichi, Japan). The area of one pixel in the ICGA images was calculated as $0.0004\ mm^2$, and all areas were converted from pixels to the area (mm^2). We used $3 \times 3\ mm^2$ OCTA images in the outer retinal layer to measure PA by OCTA. We traced the border between the areas containing the abnormal

capillaries in the same position as the hyperfluorescent lesion on the ICGA images, and measured the pixels using the same method. The area of one pixel in the OCTA images was calculated as $0.000075\ mm^2$, and all areas were converted from pixels to the area (mm^2). The detection of PL and BVN in the paired images and measures of PA were performed by two observers (KT and KK), who were both masked to the patients' clinical status.

Outcomes and statistical analyses

The detection rates of PL and BVN, and the PA were compared. The area data are shown as the mean ± SEM. The one-sided Wilcoxon signed-rank test was used to analyse the outcomes statistically. A probability of $P < 0.05$ was considered statistically significant.
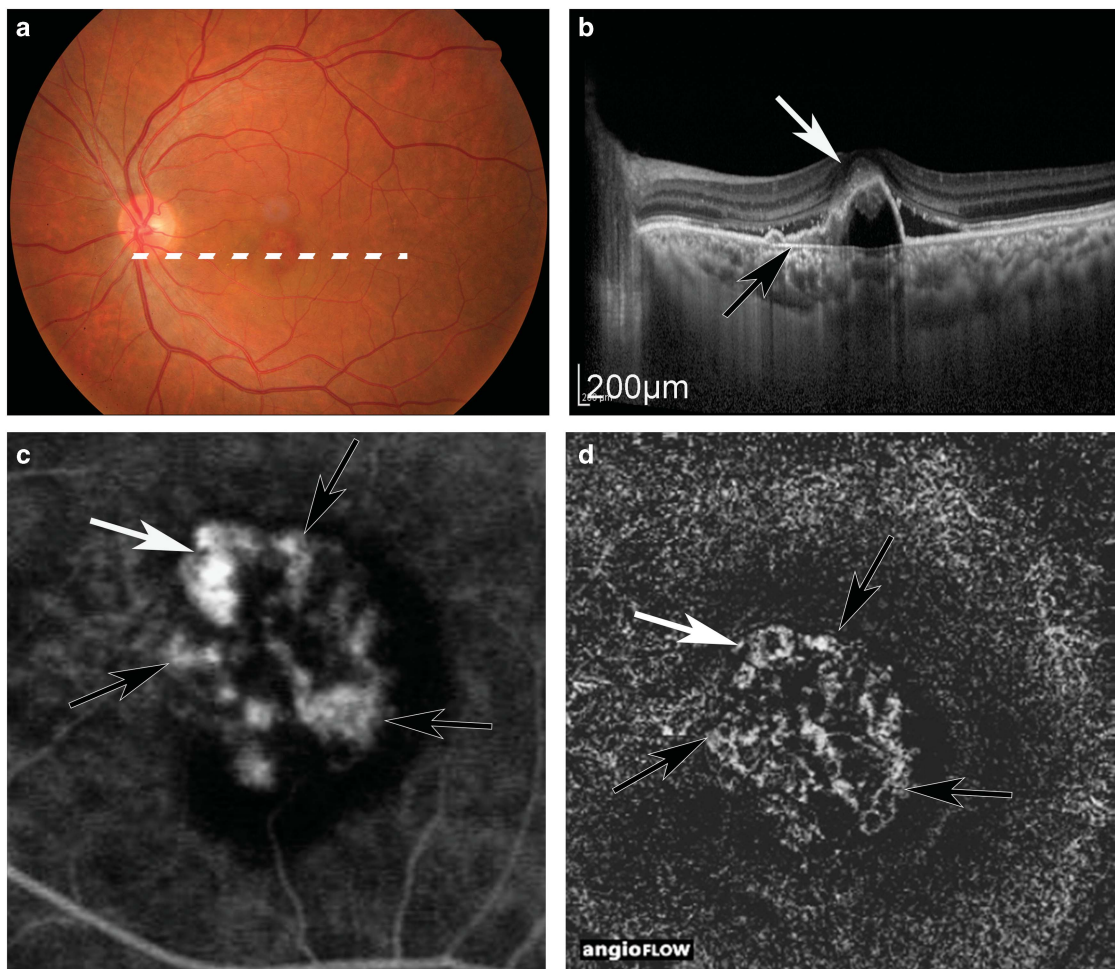
Figure 1 Case 1, in which both ICGA and OCTA could detect PL and BVN. Colour fundus (a), OCT image (b), ICGA image (c), and OCTA image (d). White arrow: PL. Black arrow: BVN. PL and BVN were detected at the same position in ICGA and OCTA, and PAs were 0.49 mm² in ICGA and 0.46 mm² in OCTA.

## Results

Patient characteristics

Twenty-one eyes of 21 patients (15 males and 6 females, all Japanese, Table 1) with PCV were included in the study. They ranged in age from 51 to 90 years, with a mean age of 73.8 ± 9.8 years. The BCVAs ranged from 3/20 to 25/20. The biomicroscopic fundus examinations revealed an orange-red lesion and/or subretinal haemorrhage. OCT showed highly reflective RPE detachments, serous retinal detachment, or macular oedema at the posterior pole, particularly in the macular region in all patients.

### *Sensitivity of PL and BVN detection by ICGA and OCTA*

Detection of PL and BVN by ICGA and OCTA were shown in Table 1. Both ICGA and OCTA detected both PL and BVN in 10 eyes (Case # 1–10). ICGA detected only PL but not BVN, whereas OCTA detected both PL and BVN in five eyes (Case # 11–15). ICGA detected both PL and BVN, whereas OCTA detected only BVN but not PL in five eyes (Case # 16–20). Both ICGA and OCTA detected PL but not BVN in one eye (Case # 21).

The eye in which both ICGA and OCTA detected PL and BVN was from Case 1; the BCVA was 3/20 and the PAs were 0.49 mm^2 in ICGA and 0.46 mm^2 in OCTA (Figure 1). The eye in which ICGA detected only PL, although OCTA detected both of PL and BVN, was from Case 11. The BCVA was 12/20, and the PAs were 0.20 mm^2 in ICGA and 0.19 mm^2 in OCTA (Figure 2). In Case 16, ICGA detected both of PL and BVN, but OCTA detected only BVN. The BCVA was 10/20 and the PA was 0.20 in ICGA (Figure 3). The detection percentages of PL and BVN in ICGA and OCTA are shown in Figure 4a.
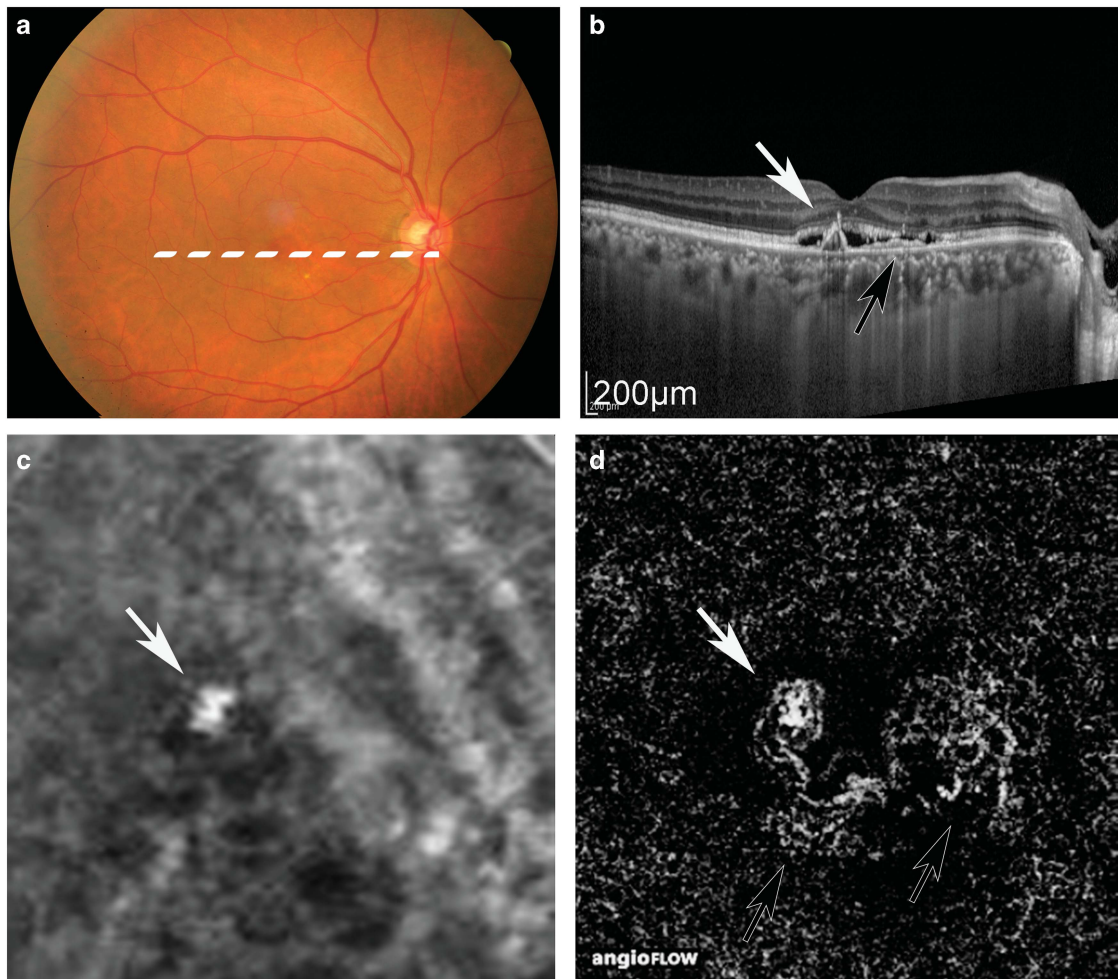
Figure 2 Case 11, in which ICGA could detect only PL, although OCTA detected PL and BVN. Colour fundus (a), OCT image (b), ICGA image (c), and OCTA image (d). White arrow: PL. Black arrow: BVN. In the ICGA image, BVN was unclear, although it appeared clearly in the OCTA images. The PAs were 0.20 mm^2 in ICGA and 0.19 mm^2 in OCTA.
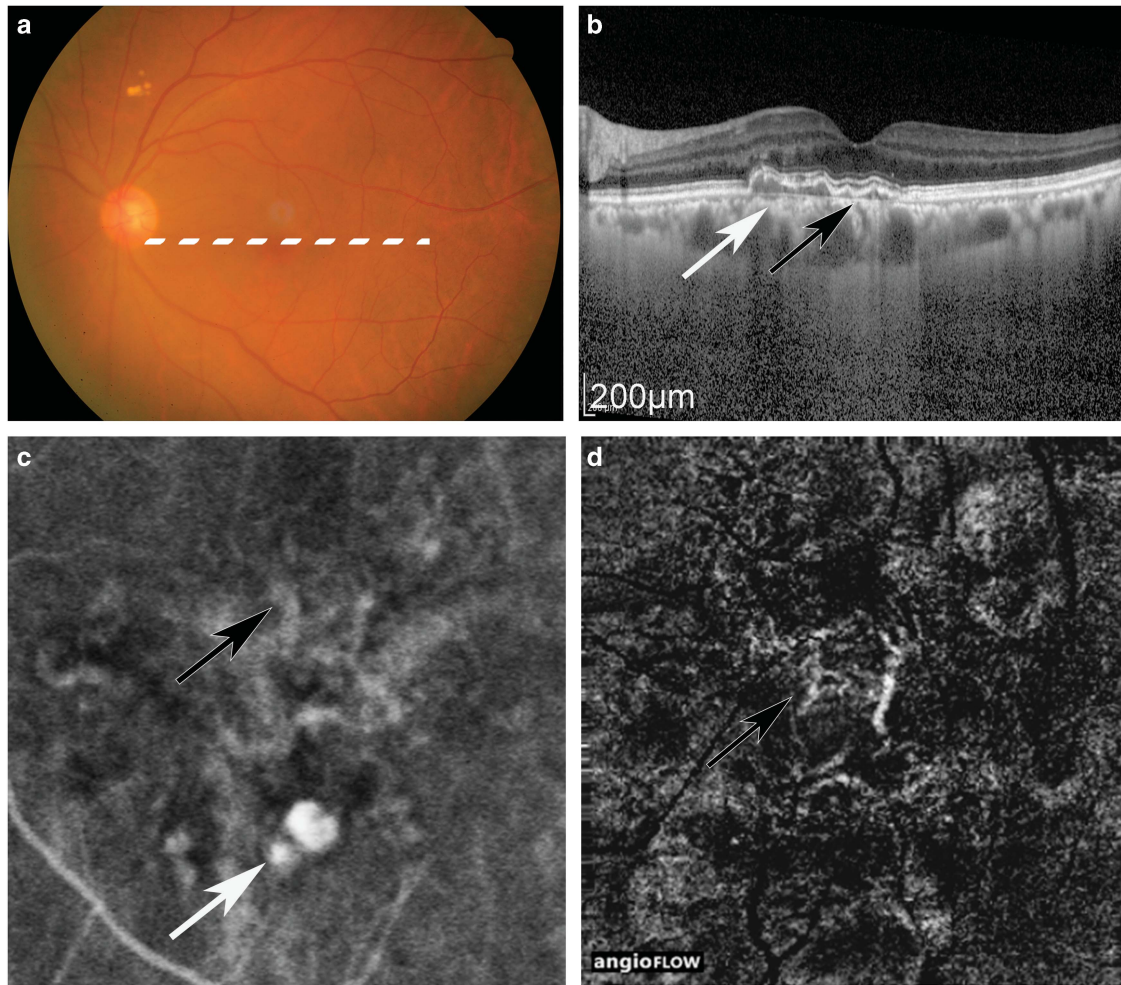
Figure 3 Case 16, in which ICGA, but not OCTA, detected PL. Colour fundus (a), OCT image (b), ICGA image (c), and OCTA image (d). White arrow: PL. Black arrow: BVN. BVN was detected by ICGA and OCTA, and was observed with highly bright vascularity, although PL was shown in dark spot in OCTA. The PA was 0.20 mm^2 in ICGA.

ICGA detected PL in all eyes (100%) and BVN in 15 eyes (71.4%), whereas OCTA detected PL in 16 eyes (76.2%) and BVN in 20 eyes (95.2%).

PA in ICGA and OCTA

We compared the differences in PA size between the cases detected by both ICGA and OCTA (ICGA$^+$OCTA$^+$), and those detected by ICGA, but not by OCTA (ICGA$^+$OCTA$^-$). Figure 4b shows the mean PA as measured by the ICGA images in all eyes, as well as that in ICGA$^+$OCTA$^+$ and ICGA$^+$OCTA$^-$. The mean PAs were 0.21 ± 0.03 mm^2 in all eyes, 0.24 ± 0.04 mm^2 in ICGA$^+$OCTA$^+$ eyes, and 0.14 ± 0.01 mm^2 in ICGA$^+$OCTA$^-$ eyes. Significant differences were found between the mean PA in ICGA$^+$OCTA$^+$ and ICGA$^+$OCTA$^-$ ($P < 0.001$). We also compared the values of PA in ICGA$^+$OCTA$^+$ as

measured by both ICGA and OCTA. Figure 4c shows the mean PA measured from the ICGA and OCTA images in all 16 eyes. The mean PA was 0.24 ± 0.04 mm^2 in ICGA and 0.19 ± 0.04 mm^2 in OCTA. The mean PA measured by ICGA was significantly larger than that measured by OCTA ($P = 0.0046$). Figure 4d shows the correlation of the PA in each eye measured by both ICGA and OCTA. Of 16 eyes, the PA in 14 eyes (87.5%) was smaller in OCTA than in ICGA, and the PA in two eyes (12.5%) was larger than in ICGA.

Discussion

This study showed that OCTA could detect PL and BVN, and that its detection sensitivity was lower for PL and higher for BVN than detection by ICGA. Smaller areas of PL were not detected by OCTA, and the
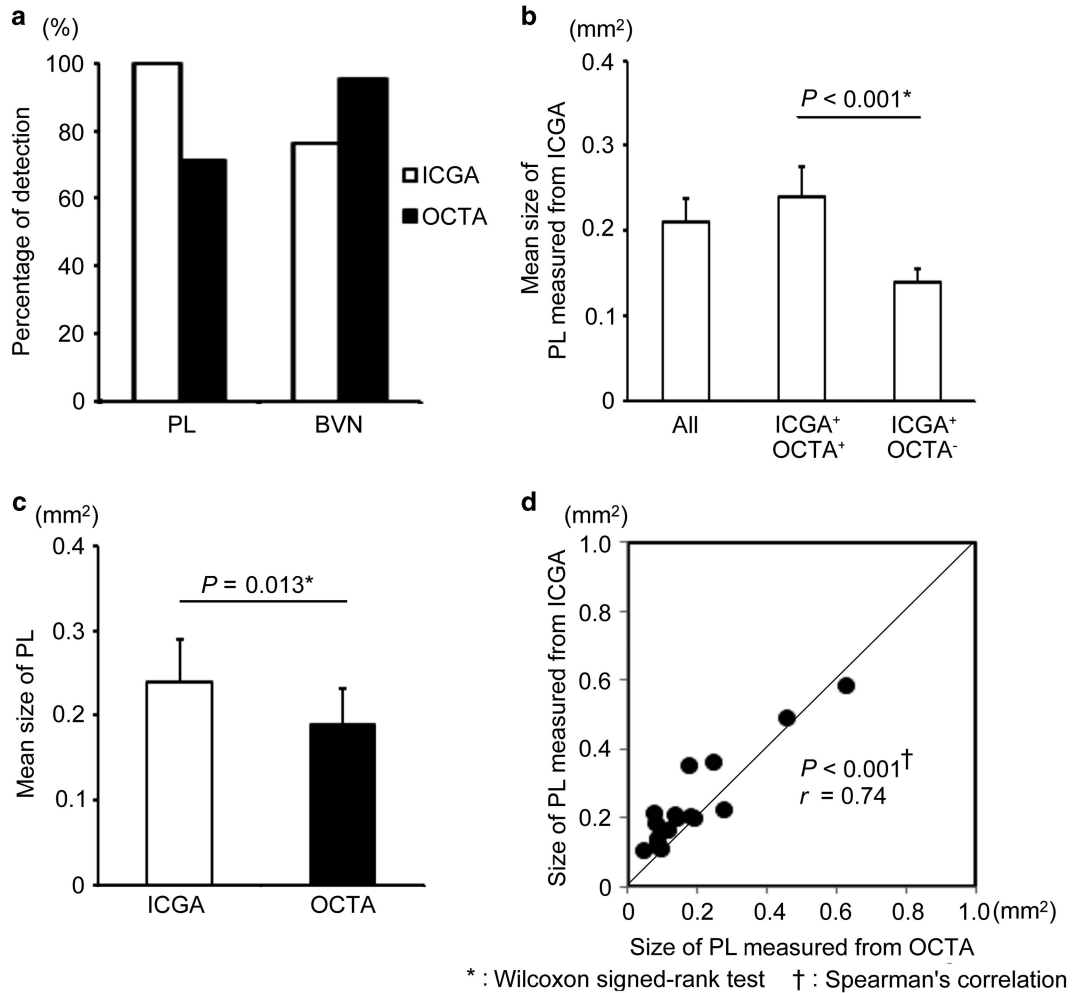
Figure 4 Detection percentages of PL and BVN, and the differences between the PA detected by OCTA and not detected by OCTA, and the PA measured by ICGA and by OCTA. ICGA detected PL more often than ICGA, although ICGA detected BVN less often than OCTA. (a) The mean PAs measured from the ICGA images in all eyes, eyes detected by OCTA (ICGA⁺OCTA⁺), and eyes that were not detected by OCTA (ICGA⁺OCTA⁻). (b) The mean PA measured from the ICGA and OCTA images in 15 eyes. (c) The blots of PA of each eye in ICGA and OCTA (d).

detected areas were smaller than those detected by ICGA. OCTA acquires images by detecting the motion of scattering particles, such as erythrocytes, within sequential OCT cross-sectional scans performed repeatedly at the same location.[20] The temporal changes in the OCT signal caused by erythrocytes generate contrast and allow visualisation of the microvasculature. In PL, CNV are filled in the polyp, and the vessel was curved three-dimensionally.[21] Srour et al[18] reported that OCTA could be used to detect hyperflow structure of only 25% of PL. In this study, smaller values of PL could not be detected by OCTA. The reason for this could be that smaller values of PL correspond to small or sharply curved vessels in which it is more difficult for erythrocytes to move. OCTA could not detect erythrocyte

motion; therefore, smaller values of PL could not be detected. On the other hand, PAs detected by OCTA were smaller than those detected by ICGA in 14 of 16 eyes and the mean PA measured from the OCTA images was significantly smaller than that from the ICGA images. Two assessments might be considered to explain the smaller detection. First, we measured the area from the ICGA image around 60 s after intravenous dye injection. PL consisted of the hyalinisation of choroidal vessels, and massive exudation of fibrin and blood plasma.[22] The dye leaked to the outside of choroidal vessels, and we measured the area as PL. Second, the temporal changes in the OCT signal caused by the erythrocytes generate contrast and allow visualisation of the inside of the microvasculature. The microvasculature shows

hyalinisation of the choroidal vessels like in arteriosclerosis, and the vessel walls are thick.[3] OCTA could detect the inner diameter of CNV from the motion of the erythrocytes, which was smaller than the outer diameter of the vessels.

Tan et al[19] reported that ICGA detected BVN in 77.6% of eyes with PCV. In the present study, all of the eyes exhibited PL, and 15 eyes (71.4%) exhibited BVN as measured by ICGA, which is a similar rate to that from the previous reports.[5,9,20,22,23] However, OCTA detected BVN in 20 eyes (95.2%). This result suggests that eyes with PCV would have a higher BVN than BVN found in the previous ICGA reports; OCTA has a better ability to detect these networks than ICGA.

OCTA is reportedly useful for detecting many diseases,[17,23,24] including age-related macular degeneration.[14,15] When compared with the ICGA images, the OCTA images are comparable to, if not better than, the ICGA images in terms of the ability to visualise PL, although they present several limitations. Kim et al compared the detection percentages of PL and BVN in OCTA and ICGA, and found that OCTA could detect BVN in all eyes, although it only detected half of the PLs. In particular, it requires that the patient fixate on a precise point for several seconds, and the images are restricted to a small area (3 × 3 or 6 × 6 mm). Despite these limitations, OCTA has several distinct advantages over ICGA imaging, such as its noninvasiveness, speed, its ability to detect details of the retinal and choroidal vasculature without intravenous dye injection, and its ability to measure blood flow. Moreover, it is an evolving technique, and the interpretation of the images needs to be refined further.

In conclusion, this study showed OCTA images of eyes with PCV. With this imaging technique, we were able to demonstrate the presence of PL and BVN that was detectable by ICGA. Despite the relatively small number of eyes included in this study, the OCTA findings were consistent and repeatable. Further investigations in larger groups of subjects with PCV are needed to assess the definitive role of this new imaging modality. OCTA might be a useful tool to noninvasively diagnose and maintain eyes with PCV.

Summary

What was known before
- OCT angiography can detect polypoidal lesion as ICGA detect.

What this study adds
- OCTA might detect more BVNs and fewer PLs compared with ICGA, and PLs detected by OCTA might be smaller than those detected by ICGA.

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