

SENSITIVITY AND SPECIFICITY OF DETECTING POLYPOIDAL CHOROIDAL VASCULOPATHY WITH EN FACE OPTICAL COHERENCE TOMOGRAPHY AND OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

TALISA E. DE CARLO, MD,*†‡§¶ GREGG T. KOKAME, MD,†‡§¶** KYLE N. KANEKO, BS,‡§¶ REBECCA LIAN, BA,† JAMES C. LAI, MD,†‡§¶** RAYMOND WEE, MD†‡§¶**

Purpose: Determine sensitivity and specificity of polypoidal choroidal vasculopathy (PCV) diagnosis with structural en face optical coherence tomography (OCT) and OCT angiography (OCTA).

Methods: Retrospective review of the medical records of eyes diagnosed with PCV by indocyanine green angiography with review of diagnostic testing with structural en face OCT and OCTA by a trained reader. Structural en face OCT, cross-sectional OCT angiograms alone, and OCTA in its entirety were reviewed blinded to the findings of indocyanine green angiography and each other to determine if they could demonstrate the PCV complex. Sensitivity and specificity of PCV diagnosis was determined for each imaging technique using indocyanine green angiography as the ground truth.

Results: Sensitivity and specificity of structural en face OCT were 30.0% and 85.7%, of OCT angiograms alone were 26.8% and 96.8%, and of the entire OCTA were 43.9% and 87.1%, respectively. Sensitivity and specificity were improved for OCT angiograms and OCTA when looking at images taken within 1 month of PCV diagnosis.

Conclusion: Sensitivity of detecting PCV was low using structural en face OCT and OCTA but specificity was high. Indocyanine green angiography remains the gold standard for PCV detection.

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Polypoidal choroidal vasculopathy (PCV) is thought to be a subtype of neovascular age-related macular degeneration (AMD).¹ It is characterized by polyps with or without a branching vascular network (BVN).² Polypoidal choroidal vasculopathy is localized as a neovascular complex occurring above Bruch membrane and below the retinal pigment epithelium (RPE). Polypoidal choroidal vasculopathy is thus not in the choroid and actually represents a subtype of Type I subretinal neovascularization.³ Therefore, PCV has also been referred to as “aneurismal Type 1 neovascularization.” Fluorescein angiography is commonly used for diagnosing neovascular AMD, but it does not allow the imaging and diagnosis of PCV except in the rare cases of very large polyps with over-

lying RPE atrophy.¹ Indocyanine green (ICG) angiography is the current gold standard for the detection of PCV because it can image the polyps and the BVN of PCV well. Polyps are seen on ICG angiography as hyperfluorescent polypoidal lesions often adjacent to a BVN.⁴ The prevalence of PCV has been estimated to be highest in Asians with neovascular AMD (approximately 54.7% of Japanese and 24.5% of Chinese).^{5–7} However, it can also be seen in up to one-quarter of neovascular AMD patients in predominantly white populations in the United States and in Brazil.^{8,9}

The diagnosis of this neovascular AMD subtype is important because there is a higher resistance to intravitreal anti-vascular endothelial growth factor

(VEGF) injection monotherapy, the standard treatment for AMD. Alternative therapies may need to be considered, such as combination therapy with photodynamic therapy plus intravitreal anti-VEGF injections with or without steroids.^{10–12} The 12-month data of EVEREST II trial demonstrated that combination therapy was superior to ranibizumab monotherapy for improving best-corrected visual acuity, polyp regression, and central subfield thickness at 12 months and required about one-third fewer injections.¹³

However, ICG angiography is currently the gold standard for the diagnosis of PCV, but its use is limited by availability, cost, time, the need for venipuncture and dye injection, and the risk of adverse side effects ranging from nausea to anaphylaxis. Therefore, two relatively new imaging modalities, structural en face optical coherence tomography (OCT) and OCT angiography (OCTA) have been studied as potential noninvasive and faster options for the diagnosis of PCV.

On structural en face OCT, polyps appear as small highly reflective circles containing some hyperreflective material adjacent to large highly reflective circles representing a large serosanguinous pigment epithelial detachment (PED) in a “snowman” sign or adjacent to geographical shaped BVNs.^{14,15} Nonblinded side-by-side comparisons between structural en face OCT and ICG angiography have shown that sometimes, structural en face OCT delineates the PCV complex better than ICG angiography, but in a similar number of cases, ICG angiography is able to visualize the PCV complex more readily than structural en face OCT.¹⁶ To our knowledge, no previous study has compared ICG angiography and structural en face OCT in a blinded fashion, so it is currently unknown how effective structural en face OCT is in independently diagnosing PCV without the aide of ICG angiography.

On OCTA, PCV appears as circular flow lesions representing polyps and branching flow networks beneath a PED (between Bruch membrane and the RPE). Previous studies have shown that OCTA readily

detects these Type 1 BVNs and may even be more sensitive than ICG angiography for BVN detection.^{17,18} However, OCTA is not able to demonstrate polyps as consistently, visualizing them approximately 75% to 92% of the time.^{17–20} Previous studies comparing ICG angiography and OCTA have had small sample sizes (21 eyes or fewer) or directly compared ICG angiography and OCTA side-by-side in a non-blinded fashion. Additionally, these studies appeared to evaluate the cross-sectional OCT angiograms alone without including the corresponding OCT B-scans in the evaluation of the PCV diagnosis. The corresponding OCT B-scans are automatically coregistered with the OCT angiograms and therefore require no additional time to image. Polypoidal choroidal vasculopathy findings on OCT B-scans have been previously well described with high sensitivity and specificity, showing polyps as elongated, inverted U-shaped elevations of the RPE with hyporeflective lumens and hyperreflective lesions. When there is a vascularized PED, the polyp will be visualized adherent to the underside of the RPE within the PED. The BVN is visualized as a low-lying elevation of the RPE above Bruch membrane or a “double layer” sign.^{21,22} Therefore, using the entire OCTA image (OCT angiogram plus corresponding OCT B-scans) may increase sensitivity and specificity of visualizing the PCV complex without additional cost or imaging time.

The purpose of this study was to determine the sensitivity and specificity of visualizing PCV with structural en face OCT, OCT angiograms alone, and OCTA in its entirety (OCT angiograms plus corresponding OCT B-scans) in a blinded fashion.

Methods

This study was a retrospective review of medical records of all consecutive AMD patients seen on Oahu and Kauai by the Retina Consultants of Hawaii and the Hawaii Macula and Retina Institute for treatment of neovascular AMD from January 2010 through December 2016. The Western Institutional Review Board exempted this study from institutional review board approval because of its retrospective design (#1-987382-1). This study adheres to the policies set forth by the Health Insurance Portability and Accountability Act and the Declaration of Helsinki.

Eyes with AMD (both PCV and non-PCV subtypes) with structural en face OCT or OCTA imaging were included in the study. Exclusion criteria for the study were 1) eyes with concomitant retinal diseases, including diabetic retinopathy, artery and vein occlusion, myopic degeneration, inflammatory disease, and

From the *Department of Medicine, University of Hawaii Transitional Residency Program, University of Hawaii School of Medicine, Honolulu, Hawaii; †John A. Burns School of Medicine, University of Hawaii School of Medicine, Honolulu, Hawaii; ‡The Retina Center at Pali Momi, Aiea, Hawaii; §Retina Consultants of Hawaii, Aiea, Hawaii; ¶Hawaii Macula and Retina Institute, Aiea, Hawaii; and **Division of Ophthalmology, Department of Surgery, University of Hawaii School of Medicine, Honolulu, Hawaii.

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Reprint requests: Gregg T. Kokame, MD, Retina Consultants of Hawaii, 98-1079 Moanalua Road, Suite 470, Aiea, Hawaii 96701; e-mail: retinahi@aol.com

macular telangiectasia, 2) eyes with previous focal laser, major trauma, or intraocular surgery except for uncomplicated cataract surgery, and 3) eyes with AMD lesions outside of the imaging area (macula).

The patients were seen by one or more of the three retinal specialists (G.T.K., J.C.L., R.W.) of the Retina Consultants of Hawaii and the Hawaii Macula and Retina Institute. The patients all received a baseline ophthalmic examination. The data were collected retrospectively from the medical records and included basic demographics, initial diagnosis, fundus findings, affected eye, previous ocular surgery or laser treatment, duration of disease, onset date, best-corrected visual acuity, number of intravitreal anti-VEGF injections, presence of subretinal fluid, presence of macula edema, and presence of subretinal hemorrhage. The medical records were also reviewed for the clinical diagnosis of PCV as determined by the three retinal specialists using the gold standard of ICG angiography (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) and standard spectral-domain OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA). Baseline characteristics of eyes with PCV were noted.

Structural en face OCT (Cirrus HD-OCT; Carl Zeiss Meditec) and OCTA images (Zeiss Angioplex software, Cirrus HD-OCT; Carl Zeiss Meditec) closest to the onset date were retrospectively reviewed for the presence of the PCV complex (BVN with polyps). The structural en face OCT images and OCTA images were reviewed separately by a trained reader (T.E.D.) so as to keep the results of the other imaging modality blinded. The reader was also blinded to the clinical diagnosis noted in the charts and the ICG angiography findings until after all structural en face OCT and OCTA images were read.

Structural En Face OCT Imaging

The structural en face OCT images were segmented to directly below the RPE as previously described.¹⁵ Each image was then reviewed to determine the presence or absence of a PCV complex (small highly reflective circles representing polyps adjacent to large highly reflective circles in a “snowman” sign or adjacent to geographical shaped BVNs). The sensitivity and specificity of structural en face OCT in detecting the PCV complex were determined using ICG angiography as the ground truth.

Optical Coherence Tomography Angiography Imaging

Optical coherence tomography was reviewed in two fashions. We first looked at the OCT angio-

grams alone segmented above Bruch membrane and below the outer plexiform layer in the outer retina, manually adjusting the segmentation to improve visualization. Vascular networks seen below the RPE and above Bruch membrane were determined to be BVN, and circular areas of flow below the RPE and above Bruch membrane were determined to be polyps. The OCT angiograms were determined to have 1) no BVN, 2) BVN without polyps, or 3) PCV complex (BVN with polyps). The sensitivity and specificity of the OCT angiogram alone in detecting the PCV complex were determined using the ICG angiogram as the gold standard for the diagnosis of PCV.

The entire OCTAs (OCT angiogram plus corresponding OCT B-scans that were automatically coregistered by the software) were then evaluated. The presence of an inverted U shape (the polyp) next to a large serous PED or shallow elevation of the RPE above Bruch membrane (“double layer” sign) was used to increase the suspicion for PCV, as did the presence of large amounts of subretinal fluid. The entire OCTAs were determined to have 1) no BVN, 2) BVN without polyps, or 3) PCV complex (BVN with polyps). The sensitivity and specificity of the entire OCTA in detecting the PCV complex were determined using the clinical diagnosis of PCV as the ground truth.

Results

PCV Baseline Demographics

Overall, 256 AMD eyes of 223 patients were included in the study. No eyes were excluded on the basis of poor image quality because all images were deemed to be of sufficient quality for accurate analysis. Polypoidal choroidal vasculopathy was noted to have a prevalence of 44.5% (114 of 256 eyes) overall, 51.3% (81 of 158 eyes) in Asians, 31.1% (23 of 74 eyes) in Caucasians, and 28.6% (4 of 14 eyes) in Pacific Islanders (native Hawaiians, Samoans, and other native people of the Pacific islands). There were nine eyes that did not have a reported ethnicity with six PCV cases in these eyes. One hundred fourteen eyes (107 patients) were determined to have PCV. Of the 107 patients with PCV, 63 patients (58.9%) were male; 76 were Asians, 21 were Caucasians, 0 were African, 4 were Pacific Islanders, 1 was Hispanic, and 5 were other or nonreported races. Of the Asians, 37 were Japanese, 9 were Chinese, 16 were Filipino, 7 were Korean, and 7 were unreported. The average age at diagnosis was 75 years.

Structural En Face OCT Imaging

One hundred eighty-eight AMD eyes (both PCV and non-PCV subtype) had been imaged with structural en face OCT. The average time between clinical PCV diagnosis with ICG angiography and structural en face OCT imaging was 3.8 months. Ninety-seven eyes had PCV as determined by the retinal specialists. Of the 97 eyes with PCV, 30 eyes (30.9%) showed the PCV complex on the structural en face OCTs. Of the 91 eyes without a diagnosis of PCV, 13 eyes demonstrated a PCV complex on the structural en face OCTs that was not seen on ICG angiography. Sensitivity and specificity of structural en face OCT were 30.0% and 85.7%, respectively.

Looking at only the 146 AMD eyes (both PCV and non-PCV subtypes) that had structural en face OCT imaging within 1 month of PCV diagnosis, 25 of 86 eyes (29.1%) with PCV demonstrated PCV on structural en face OCT and 50 of 60 eyes (83.3%) without PCV showed no PCV on structural en face OCT. Sensitivity and specificity was therefore similar to the overall data.

Optical Coherence Tomography Angiography Imaging

Seventy-two AMD eyes (both PCV and non-PCV subtype) had been imaged with OCTA. The average time between clinical PCV diagnosis with ICG angiography and OCTA imaging was 27.3 months. Polypoidal choroidal vasculopathy was only noted to be present if a polyp(s) was noted in addition to the BVN. Forty-one eyes had PCV as determined by the retinal specialists in the chart. Of the 41 eyes with PCV, 34 eyes (82.9%) showed a BVN, but the entire PCV complex was only demonstrated in 11 eyes (26.8%) using the OCT angiograms alone and in 18 eyes (43.9%) using the entire OCTAs (OCT angiograms and corresponding OCT B-scans). Of the 31 eyes without a diagnosis of PCV, a PCV complex that was not seen on ICG angiography was seen in 11 eyes using the OCT angiograms alone and 14 eyes using the entire OCTAs. Sensitivity and specificity of OCT angiograms alone were 26.8% and 96.8%, respectively, and of the entire OCTA were 43.9% and 87.1%, respectively.

Looking at only the 17 AMD eyes (both PCV and non-PCV subtypes) that had OCTA imaging within 1 month of PCV diagnosis, 5 of 13 eyes (38.5%) with PCV demonstrated PCV on the OCT angiograms alone compared with 8 of 13 eyes (61.5%) on the OCTAs in their entirety. Four of four eyes (100.0%) without PCV showed no PCV on the OCT angiograms

alone and on the entire OCTAs. Sensitivity and specificity were therefore improved compared with the overall data.

Figure 1 shows 2 examples of ICG angiography, structural en face OCT, and OCTA showing the PCV complex. Figure 2 depicts an example where ICG angiography and structural en face OCT show the PCV complex, but the OCTA is unable to show the polyps. Figure 3 demonstrates an example of a PCV complex on ICG angiography and OCTA but false-negative imaging with structural en face OCT. Figure 4 shows, however, an example of a false-positive structural en face OCT, and Figure 5 demonstrates an example of a false-positive OCTA.

Discussion

Polypoidal choroidal vasculopathy is an important subtype of neovascular AMD characterized by a PCV complex consisting of a polyp(s) with or without a BVN. Previous studies have suggested that PCV is more likely to be resistant to the standard treatment with intravitreal anti-VEGF injections than other subtypes of neovascular AMD.^{10,11} Therefore, diagnosis of PCV is crucial. A meta-analysis by Tang et al¹² reviewed nine studies that compared ranibizumab monotherapy with combination therapy and with photodynamic therapy monotherapy. Overall, combination therapy demonstrated an improved synergistic effect on regressing polyps and improving visual acuity over either therapy alone. Indocyanine green angiography is the gold standard for the diagnosis of PCV but is minimally invasive and may not be available because of the lack of availability, lack of expertise in ICG angiography diagnosis, higher cost, and more time needed to complete and evaluate the ICG angiogram.

This study evaluated the sensitivity and specificity of diagnosing PCV of two relatively new and non-invasive techniques, structural en face OCT and OCTA. Both of these imaging techniques have been of great interest recently in retina research in hopes that they will provide useful noninvasive options for diagnosing and following patients. Previous studies comparing these imaging modalities with ICG angiography have had small sample sizes and were completed in a nonblinded fashion, comparing the images side by side. Blinding is important to show if these imaging modalities could be realistically used in practice to diagnose PCV.

Structural en face OCT is fast, noninvasive, readily available, and inexpensive because most clinicians already have a standard OCT device with en face capabilities. Specificity in this study was fairly high,

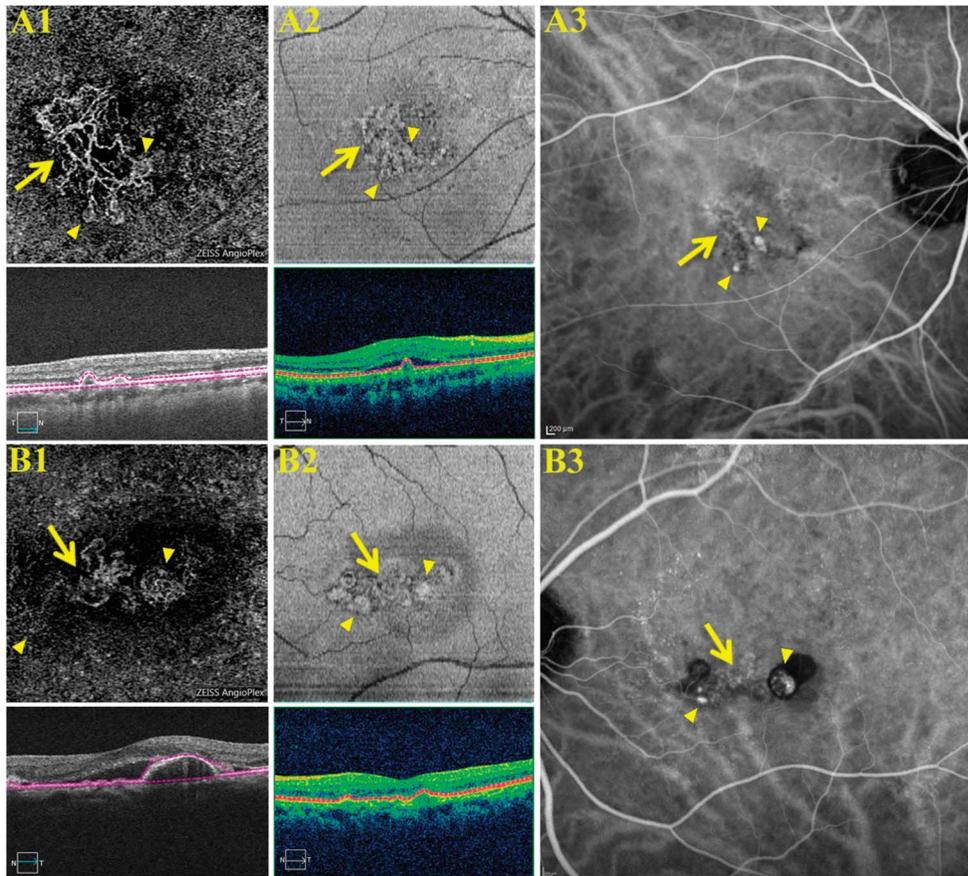


Fig. 1. The right eye of a 72-year-old Korean man (A) and the left eye of a 74-year-old Japanese man (B). The PCV complex can be seen in both eyes on the OCTA and corresponding OCT B-scan (A1 and B1), structural en face OCT and corresponding OCT B-scans (A2 and B2), and ICG angiography (A3 and B3) as a BVN (yellow arrow) and polyps (yellow arrowheads). The corresponding OCT B-scans in A1 and A2 demonstrate subretinal fluid and inverted U-shaped elevations of the RPE suggestive of polyps. The B-scan in B1 indicates subretinal fluid and a large serous PED.

approximately 86%, showing that when PCV is detected using this method, it is likely true PCV. However, according to the results of this study, structural en face OCT was not very sensitive, being able to detect approximately 30% of PCV cases diagnosed by ICG angiography. A major limitation of structural en face OCT seems to be accurate segmentation because this method is highly reliant on precise placement of the segmentation lines.

Segmentation becomes poor when the normal anatomy of the retina becomes distorted because of abnormality. In our study, we manually moved the segmentation lines up or down to place the segmentation approximately beneath the RPE, but in cases where the automated segmentation lines were inaccurate, we did not have the capabilities to manually adjust the fit or shape of the segmentation lines to perfectly hug the RPE. Future advances in manual segmentation

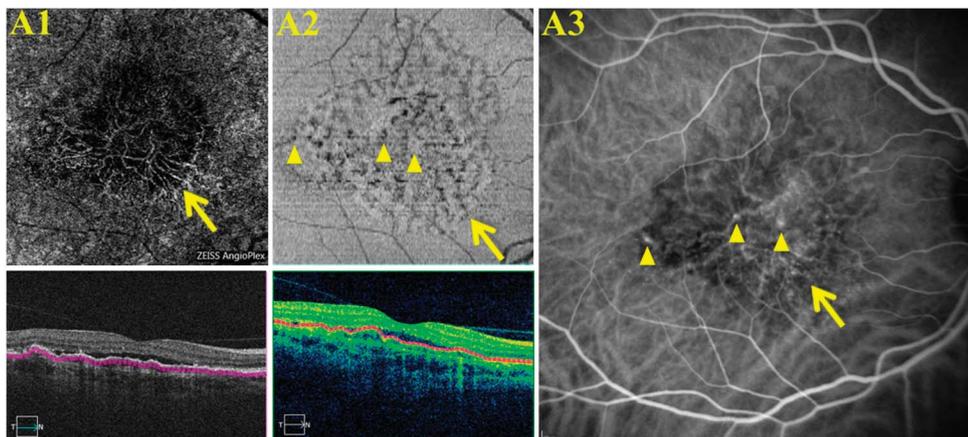
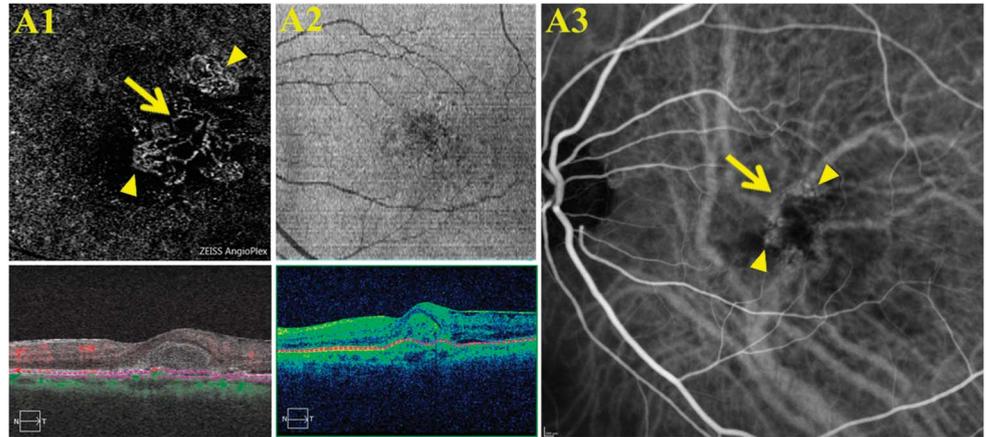


Fig. 2. The right eye of a 52-year-old Caucasian woman. The PCV complex can be seen on the structural en face OCT and corresponding OCT B-scan (A2) and ICG angiography (A3) as a BVN (yellow arrow) and polyps (yellow arrowheads). However, only the BVN is noted on OCTA (A1). The corresponding OCT B-scans demonstrate a shallow PED and subretinal fluid, increasing the suspicion for PCV.

Fig. 3. The left eye of a 78-year-old Asian woman. The PCV complex can be seen on OCT angiogram and corresponding OCT B-scan (A1) and ICG angiography (A3) as a BVN (yellow arrow) and polyps (yellow arrowheads). However, no complex is noted on structural en face OCT (A2). The corresponding OCT B-scans demonstrate a shallow PED and a small amount of subretinal fluid, increasing the suspicion for PCV.



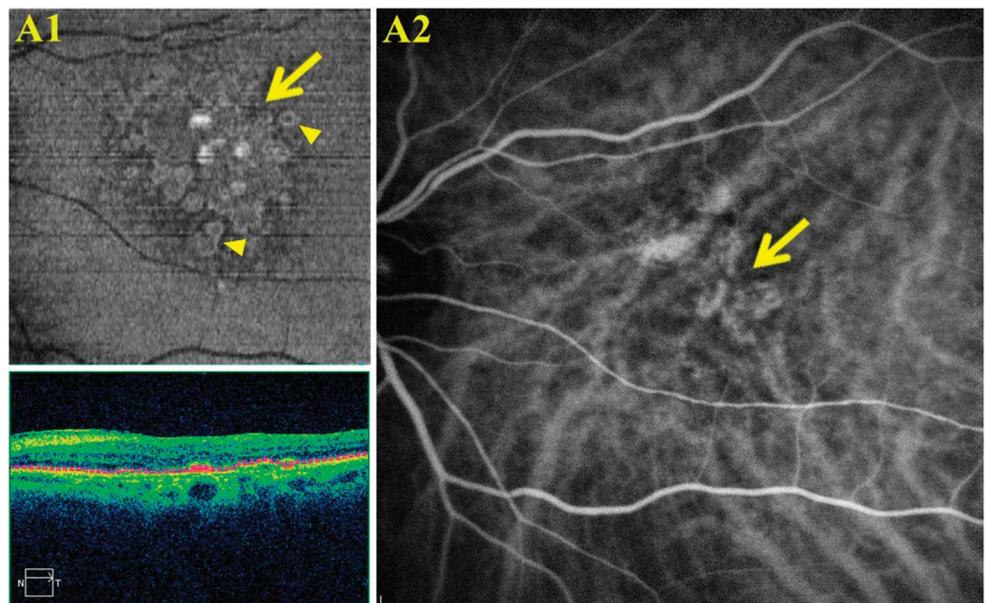
functions may improve upon this limitation but may still be too time consuming in a busy clinic setting. Therefore, improvements in the automated segmentation fit are crucial. Previous studies comparing structural en face OCT side by side with ICG angiography showed that structural en face OCT may be useful in conjunction with ICG angiography, but based on this study, structural en face OCT can identify some cases but is unlikely to be sufficient to diagnose PCV as a stand-alone diagnostic imaging test. Improvement in automatic segmentation and individual optimization of segmentation lines can improve the utility of structural en face OCT.

Also, OCTA is another fast and noninvasive imaging technique, but it is not currently widely available and most clinicians are not yet proficient in reviewing and assessing OCTA images. This study suggested that using the OCT angiograms alone

demonstrated a similarly low sensitivity (approximately 27%) of detecting the PCV complex as structural en face OCT. The OCT angiograms were able to detect the BVN in approximately 83% of eyes but showing the polyps was the major limiting factor. The missed polyps were likely too small to be easily noticed in a blinded fashion or had too slow blood flow to be readily detected using the OCT angiograms. However, OCTA is limited by the principal of “slowest detectable flow” determined by the time between repeated OCT B-scans.²³ Therefore, OCTA has been shown to have difficulty detecting flow in other slow flow lesions, such as microaneurysms.

The sensitivity of PCV complex detection was markedly increased when the OCTA image was reviewed as a whole, including the OCT angiogram and the automatically coregistered corresponding OCT B-scans. Sensitivity was found to be approximately

Fig. 4. The left eye of an 85-year-old Japanese woman. The PCV complex was thought to be apparent as a BVN (yellow arrow) and polyps (yellow arrowheads) on structural en face OCT (A1), but no polyps were seen on ICG angiography (A2).



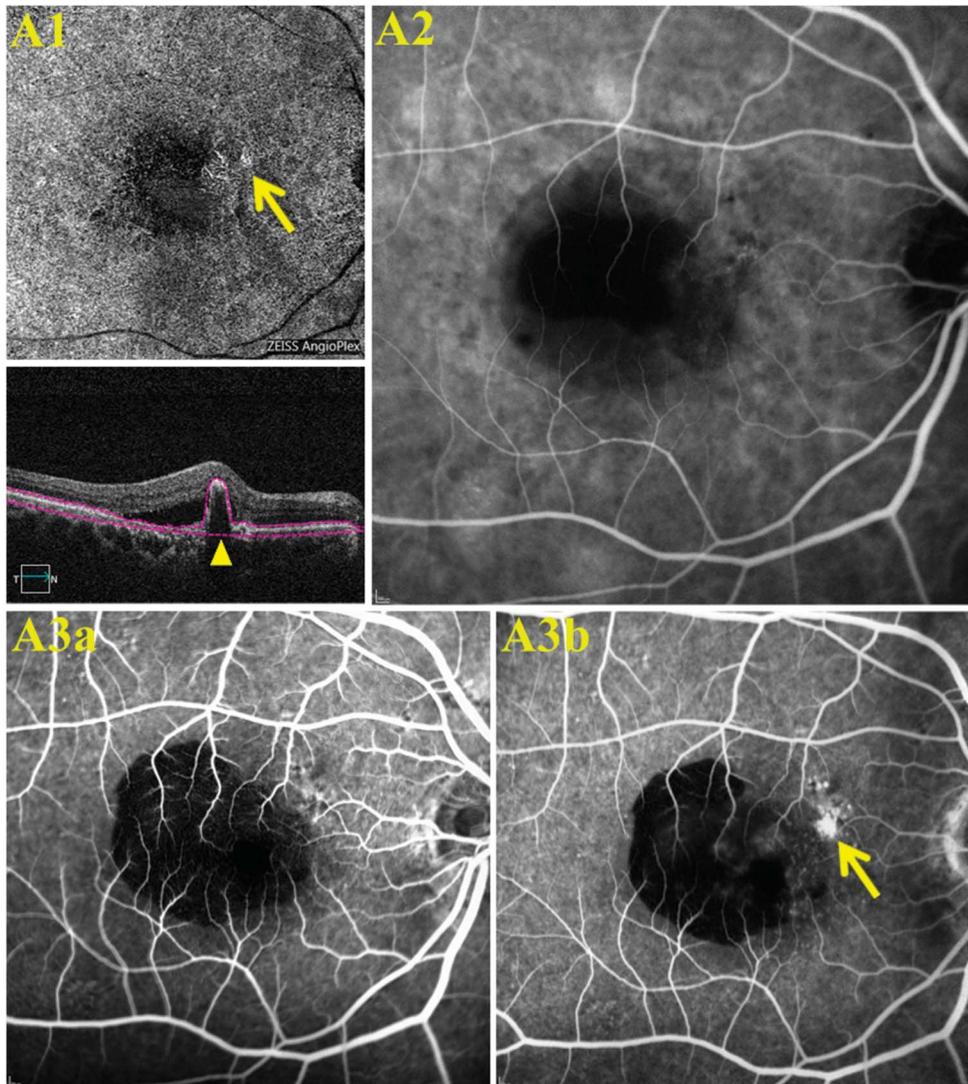


Fig. 5. The right eye of an 83-year-old Japanese man. The PCV complex was thought to be apparent as a BVN (yellow arrow) and subretinal fluid adjacent to an inverted U-shaped elevation of the RPE suggestive of a polyp (yellow arrowhead) on OCTA (A1), but no polyps were seen on ICG angiography (A2). Fluorescein angiography (A3) shows leakage from the BVN (yellow arrow).

44%. Previous studies evaluating OCTA have for the most part used the OCT angiograms alone to evaluate for PCV, but the corresponding OCT B-scans can be an asset in increasing the sensitivity of polyp and PCV detection especially because PCV findings on OCT B-scans are now well characterized in the literature.²⁴

Specificity of OCTA was shown to be high with 97% specificity using OCT angiograms alone and 87% using the entire OCTA. However, OCTA used as a whole was less specific than with using the OCT angiograms alone. This decrease in specificity is likely because specificity of OCT B-scans is not 100%, as other lesions such as large drusen and small PEDs can simulate polyps. Therefore, there is a trade-off of increasing overall sensitivity of detection of the PCV complex with decreasing the overall specificity.

The notion of calculating specificity using ICG angiography, our current gold standard, as the ground

truth is an interesting one because the assumption is that ICG angiography never misses the diagnosis of PCV. This is of course not always true. Therefore, upon reviewing “false-positive” cases where either structural en face OCT or OCTA demonstrated PCV but ICG angiography did not, it appears that maybe these newer imaging modalities add imaging support to a diagnosis of PCV that may have otherwise been missed. This may be particularly true in cases where polyps have regressed after previous treatment but the quiescent polyps can still be seen structurally, as may be the case in Figure 4. In the current age of multimodal imaging for diagnosis of retinal disease, structural en face OCT and OCTA may be beneficial as supportive imaging modalities alongside ICG angiography and fluorescein angiography, which can only rarely show polyps when the polyps are very large.

Table 1. Comparison Between Eyes Correctly Diagnosed With PCV and Eyes Where the Diagnosis of PCV was Missed by Structural En Face OCT

	False-Negative (n = 67)	True-Positive (n = 30)	P
Male	42 (62.7%)	16 (53.5%)	0.19
Age, year	76	73	0.19
Asian	49 (73.1%)	23 (76.7%)	0.64
Caucasian	14 (20.9%)	7 (23.3%)	0.61
Pacific Islander	3 (4.5%)	0 (0.0%)	0.12
Other race	1 (1.5%)	0 (0.0%)	0.25
Pseudophakia	34 (50.7%)	17 (56.7%)	0.71
Prior PDT*	13 (19.5%)	6 (20.0%)	0.53
No. of prior injections	16.6	19.4	0.35

No statistically significant differences were noted in age, race, lens status, gender, previous PDT treatment, or previous number of injections.

*PDT, photodynamic therapy.

Another interesting question proposed while reviewing the results of this study was if there were certain characteristics of the eyes in which structural en face OCT or OCTA failed to detect the PCV that differed from eyes in which PCV was detected. Therefore, eyes with PCV that failed detection with structural en face OCT (false-negatives) were compared with eyes with PCV that were correctly identified by structural en face OCT (true-positives). The same was done for the OCTA as a whole (OCT angiogram plus corresponding OCT B-scan). No statistically significant differences were noted in average age, gender, race, lens status, percentage of eyes with previous photodynamic therapy, or average number of previous injections between the false-negative eyes and true-positive eyes using structural en face OCT (Table 1) or OCTA as a whole (Table 2). Therefore, we were unable to determine any characteristics that made some eyes harder to detect using these two imaging modalities.

A major limitation of the study was that structural en face OCT and OCTA imaging was often from different dates than the original diagnosis. Structural

en face OCT was on average performed 3.8 months later and OCTA was on average performed much later (27.3 months later) because the technology only became available in the past couple of years. Although the BVN in PCV often remains, the polyps may regress with treatment, making later diagnosis of the entire PCV complex more difficult. Therefore, we performed subgroup analysis of sensitivity and specificity of PCV detection in only the eyes with imaging within 1 month from the original diagnosis date. Sensitivity and specificity was very similar for structural en face OCT. For OCTA, the sensitivity and specificity were markedly higher, approximately 39% and 100%, respectively, using the OCT angiograms alone and approximately 62% and 100%, respectively, using the entire OCTA. The greatly increased sensitivity in this subgroup is likely because the OCTAs included in the study as a whole had been obtained sometimes years after treatment had commenced, potentially allowing for decreased flow in the BVN and regression of polyps over time. Therefore, although the sample size was much smaller (17 eyes) in this OCTA subgroup analysis, the sensitivity is

Table 2. Comparison Between Eyes Correctly Diagnosed With PCV and Eyes Where the Diagnosis of PCV was Missed by OCTA

	False-Negative (n = 23)	True-Positive (n = 18)	P
Male	15 (65.2%)	13 (72.2%)	0.68
Age, year	73	71	0.4500
Asian	17 (73.9%)	14 (77.8%)	0.61
Caucasian	6 (26.1%)	4 (28.6%)	0.39
Pacific Islander	1 (4.3%)	0 (0.0%)	0.19
Other race	0 (0.0%)	0 (0.0%)	N/A
Pseudophakia	8 (34.8%)	9 (50.0%)	0.84
Prior PDT*	7 (30.4%)	4 (22.2%)	0.25
No. of prior injections	18.3	17.8	0.91

No statistically significant differences were noted in age, race, lens status, gender, previous PDT treatment, or prior number of injections.

*PDT, photodynamic therapy; NA, not available.

likely more representative. A larger sample size of eyes imaged on the same day as ICG angiography would be useful for confirming the sensitivity and specificity of PCV detection using OCTA. As of current, it is unlikely that OCTA would be sufficient for diagnosing PCV without concurrent ICG angiography.

Two further and important limitations of OCTA are the prevalence of artifacts and that the automated segmentation is currently still inaccurate particularly when there is major distortion of the retina because of significant abnormality. The inaccurate segmentation makes manually adjusting the segmentation lines and reviewing the OCTA images much more arduous and time consuming. It also decreases the ability to detect the BVN and/or polyps in some cases particularly if there is movement artifact and/or poor signal strength. Many OCTA artifacts have been described in the literature. Most significantly, focal areas of movement artifact or inaccurate segmentation may falsely appear as a BVN, and areas of poor signal penetration can mask a PCV complex. Furthermore, in cases of poor signal quality, the vasculature may not appear sharp and reflectance off the edges of a PED is more likely to be mistaken for flow. Additionally, although projection artifact from the overlying inner retina is automatically removed using a toggle function in the software, it depends on accurate segmentation of the inner layers of the retina and therefore does not function properly if segmentation is grossly incorrect. Overall, there is a learning curve to reading OCTA, and even for an experienced reader, accurately interpreting an OCTA image can be time consuming in cases with significant artifact and/or segmentation errors. Improvements in this still-evolving technology can improve image quality and usability and make it more feasible to use as a diagnostic tool for PCV.

Although not a primary end point of this study, the PCV subtype was noted to have a high prevalence in AMD eyes: 44.5% overall, 51.3% in Asians, 31.1% in Caucasians, and 28.6% in Pacific Islanders. This information confirms that PCV is more common in Asians but also demonstrates that PCV is present in many Caucasian eyes. The large sample size and high ethnic diversity in Hawaii enabled the opportunity to determine the first estimation, to our knowledge, of the prevalence of PCV in Pacific Islander patients. However, because of the retrospective nature of this study and small sample size and relative infrequency of neovascular AMD in Pacific islanders, this is only a rough estimate of the prevalence of PCV. In this retrospective study, most eyes with neovascular AMD were evaluated with ICG angiography and OCT, but

a prospective study would be better to determine prevalence more accurately.

Overall, it is important to diagnose the PCV subtype of neovascular AMD because it is more likely to be resistant to standard intravitreal anti-VEGF injections. Indocyanine green angiography remains the gold standard for PCV detection. Although structural en face OCT and OCTA may have roles in evaluating PCV alongside ICG angiography or as noninvasive follow-up imaging techniques, the current technology appear to have insufficient sensitivity for the diagnosis of PCV on their own. Eyes with AMD that are resistant to initial treatment are more likely to have PCV; therefore, ICG angiography should be obtained to diagnose PCV in these eyes to further guide treatment decisions.

Key words: aflibercept, age-related macular degeneration, anti-VEGF resistance, bevacizumab, indocyanine green angiography, optical coherence tomography, polypoidal choroidal vasculopathy, ranibizumab.

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