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Authors

McClintic, Scott M

Kim, Dae Yu

Fingler, Jeff

et al.

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Detection of pigment epithelial detachment vascularization in age-related macular degeneration using phase-variance OCT angiography

Scott M McClintic¹
Dae Yu Kim²
Jeff Fingler³
Susan Garcia⁴
Robert J Zawadzki⁴
Lawrence S Morse⁴
Susanna S Park⁴
Scott E Fraser³
John S Werner⁴
Jason P Ruggiero⁵
Daniel M Schwartz⁶

¹Department of Ophthalmology, Casey Eye Institute, Oregon Health and Science University, Portland, OR, USA; ²Beckman Laser Institute Korea and Department of Biomedical Engineering, Dankook University, Cheonan, South Korea; ³Translational Imaging Center, University of Southern California, Los Angeles, CA, ⁴Department of Ophthalmology and Vision Science, University of California Davis, Sacramento, CA, ⁵Retina Associates, PC, Winchester, VA, ⁶Department of Ophthalmology and Vision Science, University of California San Francisco, San Francisco, CA, USA

Correspondence: Daniel M. Schwartz, Department of Ophthalmology and Vision Science, University of California San Francisco, 10 Koret Way, Room K219, San Francisco, CA 94143-0730 USA
Tel +1 415 476 1152
Email dan.schwartz@ucsf.edu

Purpose: To demonstrate the use of phase-variance optical coherence tomography (PV-OCT) angiography for detection of pigment epithelial detachment (PED) vascularization in age-related macular degeneration (AMD).

Patients and methods: Patients with PEDs and exudative AMD were evaluated by the Retina Services at the University of California, Davis, and the University of California, San Francisco. Each subject underwent fluorescein angiography and structural optical coherence tomography (OCT). Phase-variance OCT analysis was used to create angiographic images of the retinal and choroidal vasculature. PV-OCT-generated B-scans were superimposed on structural OCT B-scans to allow easy identification of perfused vascular structures.

Results: Three patients with vascularized PEDs were imaged with PV-OCT, and each was found to have a vascular signal extending from the choroid into the hyperreflective substance of the PED. Two patients who had no evidence of PED vascularization on fluorescein angiography did not have vascular signals within their PEDs on PV-OCT.

Conclusion: Structural OCT and PV-OCT images can be combined to create composite B-scans that offer high-resolution views of the retinal tissue along with dynamic vascular visualization. This technique offers a fast, noninvasive method for detecting vascularization of PEDs in AMD and may aid in the early detection of neovascular disease.

Keywords: OCT, imaging, retina

Introduction

Pathologic detachment of the retinal pigment epithelium (RPE) is a frequent occurrence in age-related macular degeneration (AMD).¹ Pigment epithelial detachments (PEDs) are classified as serous, drusenoid, or vascularized.² Determining whether a solid PED is drusenoid or vascularized is of clinical importance since vascularization may herald the onset of exudative disease.^{3,4} However, in the absence of clinical signs of neovascularization, including subretinal hemorrhage, subretinal fluid, and macular edema, identification of vascularized PEDs remains difficult. Dye-based angiography methods, including fluorescein angiography (FA) and indocyanine green angiography, can help to detect the presence of neovascular tissue associated with a PED. However, these methods are invasive, require skilled personnel, and can be associated with adverse events.

Phase-variance optical coherence tomography (PV-OCT) angiography is a technique that enables noninvasive, high-resolution vascular imaging.⁵⁻¹¹ Its ability to image flow occurring in choroidal neovascular (CNV) membranes may aid in the early detection of neovascularization. Three cases of exudative AMD are presented to demonstrate the feasibility of using PV-OCT for the detection of vascularized PED.

Two cases of nonexudative AMD with avascular PEDs are also presented for comparison.

Materials and methods

Patients with a history of PED secondary to AMD were evaluated by the Retina Services at the University of California, Davis (UCD; subjects 1, 2, 4, and 5), and the University of California, San Francisco (UCSF; subject 3). Each subject underwent FA and spectral domain OCT (SD-OCT) with phase-variance analysis at their respective institution. When the cavity underlying an RPE elevation showed moderate-to-high reflectance on SD-OCT, the PED was termed solid, whereas when the cavity showed low reflectance, the PED was termed serous.^{2,12} The tenets of the Declaration of Helsinki were observed, and all the subjects provided written informed consent, and was approved by the individual institutional review boards of the University of California, San Francisco and the University of California, Davis, Sacramento, CA, USA.

For FA imaging, each subject's pupils were dilated with a combination of 1% tropicamide and 2.5% phenylephrine. Sodium fluorescein 10% in water (500 mg/5 mL) was injected intravenously, followed by a flush of normal saline. Fundus FA images were acquired with Topcon (TRC-50IX) cameras having resolution of 1,280 (H)×1,024 (V) pixels.

OCT instrumentation

Two different OCT instruments were used in the acquisition of PV-OCT data. Subjects 1, 2, and 4 were imaged using a high-speed (125-kHz A-scan rate) SD-OCT system constructed at UCD that acquired in vivo human retinal images with scanning areas of 1.5×1.5 mm² or 3×3 mm². A bite bar and a forehead rest were used to stabilize the head position. Subject 3 was imaged at UCSF using a commercial SD-OCT instrument (Envisu C-Class Spectral Domain Ophthalmic Imaging Systems; Bioptigen, Inc., Morrisville, NC, USA) with a 32 kHz A-scan rate. A standard chin and forehead rest were used to stabilize the head position. The image acquisition time of each PV-OCT volumetric scan for each device was less than 5 seconds.

A schematic of the UCD SD-OCT instrument used in this study has been reported previously.^{8,10} This system operated at an A-scan rate of 125 kHz, a center wavelength of 855 nm, an axial resolution of ~4.5 μm in tissue, and an approximate lateral resolution of 15 μm. The Bioptigen SD-OCT device at UCSF operated at an A-scan rate of 32 kHz, a center wavelength of 840 nm, an axial resolution of ~3 μm in tissue, and an approximate lateral resolution of 10 μm. Each SD-OCT device was used to obtain volumetric scans comprising sequential B-scans acquired over the same spatial region in

the retina (BM-scans). Phase differences between sequential B-scans within a single BM-scan were extracted for phase-variance contrast calculation. The standard Bioptigen OCT scanning protocol was modified; however, no hardware modifications were made to the device and laser exposures conformed to established American National Standards Institute standards. Graphical programming-based software (LabVIEW, National Instruments, Austin, TX, USA) was used to acquire and process PV-OCT data sets.

Phase-variance method

The phase-variance method has been described previously in detail.^{6,7} Briefly, phase changes were calculated for the entire cross-sectional image from consecutively acquired B-scans. Bulk axial motion was calculated and corrected for each transverse location, reducing the phase noise introduced from the eye and head motion. Phase variance was calculated through the variance of the motion-corrected phase changes acquired within a BM-scan. Intensity thresholding of the average OCT intensity image was used to create a mask for the PV-OCT image that removed contributions of phase noise caused by low signal-to-noise regions. Repeating these calculations over the entire volumetric scan produced a three-dimensional PV-OCT representation of the vasculature.

Image processing

The volumetric data set was processed by the phase-variance contrast method. Color-coded PV-OCT B-scans were layered over standard SD-OCT B-scans to produce composite B-scans. On these scans, red color indicates motion, which is a characteristic of vascular blood flow.

Results

Case 1

A 77-year-old male with a history of nonexudative AMD presented to the Retina Clinic at UCD with reduced vision in his right eye. Visual acuity was counting fingers in the right eye, and subretinal hemorrhage, paracentral geographic atrophy, and soft drusen were noted (Figure 1A). FA demonstrated late hyperfluorescence consistent with occult CNV adjacent to the area of blocked fluorescence from subretinal hemorrhage (Figure 1B). Composite OCT showed a red vascular signal extending from the choroid into a solid PED, consistent with vascularization (Figure 1C).

Case 2

A 67-year-old male presented to the Retina Clinic at UCD with decreased vision in the left eye. The patient had a history of exudative AMD in the left eye since 2008.

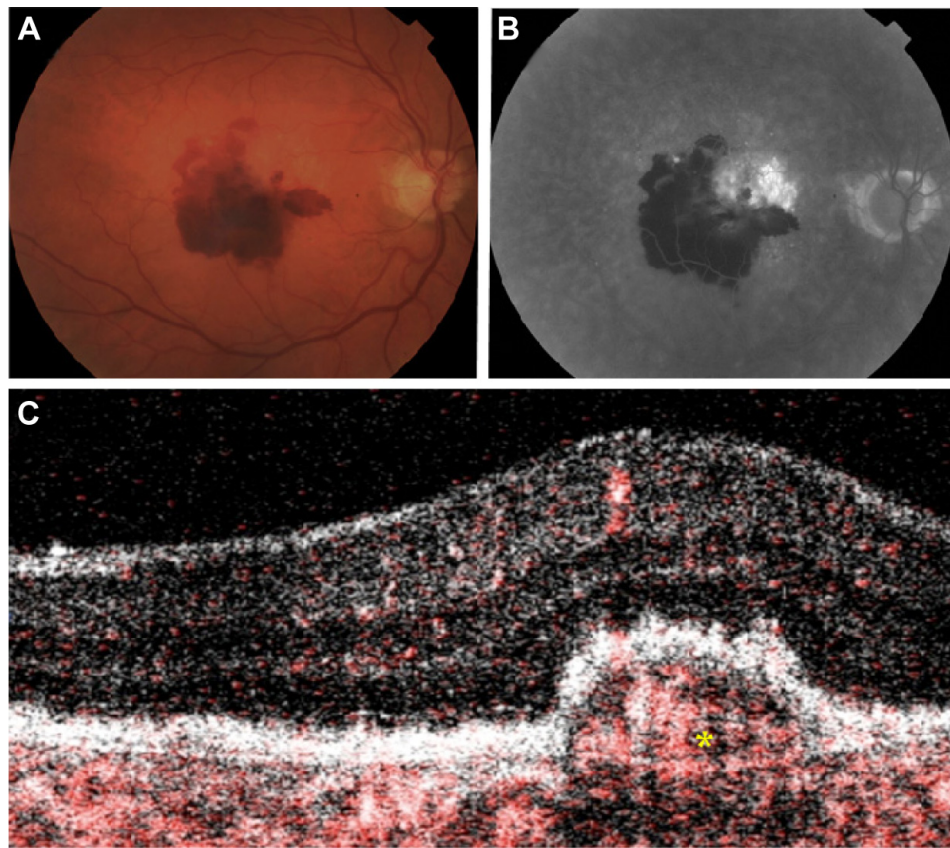


Figure 1 Clinical imaging for Case 1.

Notes: (A) Color fundus photograph showing soft drusen, parafoveal geographic atrophy, and subretinal hemorrhage. (B) Late FA showing blockage from subretinal hemorrhage and perifoveal hyperfluorescence consistent with occult CNV. (C) Composite OCT showing a solid PED with red PV-OCT signal extending from the choroid into the PED (asterisk), consistent with vascularization.

Abbreviations: FA, fluorescein angiography; CNV, choroidal neovascular; OCT, optical coherence tomography; PED, pigment epithelial detachment; PV-OCT, phase-variance optical coherence tomography.

This eye had been treated with multiple intravitreal injections of ranibizumab, bevacizumab, and aflibercept. At the current presentation, visual acuity had decreased to 20/100. FA demonstrated straining of drusen and late, irregular leakage (Figure 2B). Composite OCT showed a multilobed PED with subretinal fluid, along with a dense, confluent, red vascular signal extending from the choroid into a solid lobe of the PED (Figure 2C). No vascular signal was seen in the adjacent serous lobe of the PED. Diffuse stippled red dots in the outer retina and along the RPE likely represent motion artifact. The findings on FA and composite OCT indicated persistent vascularization of the PED, despite ongoing anti-vascular endothelial growth factor therapy. This is consistent with the presence of persistent subretinal fluid on structural OCT.

Case 3

A 79-year-old female presented to the Retina Clinic at UCSF. The patient had a history of exudative AMD in the left eye for which she had received eleven injections of ranibizumab. Visual acuity was 20/100 in this eye. Examination showed

soft drusen, fibrosis, and RPE atrophy (Figure 3A). Structural OCT demonstrated a solid PED with trace intraretinal fluid, and FA showed staining of fibrotic tissue with late punctate hyperfluorescence (Figure 3B). Composite OCT showed a red vascular signal extending from the choroid into the solid PED, consistent with active vascularization (Figure 3C). Diffuse stippled red dots in the inner and outer retina likely represent motion artifact.

Case 4

A 66-year-old man with a history of nonexudative AMD was followed by the Retina Service at UCD. Visual acuity at the time of evaluation was 20/100 in the right eye. Examination showed large soft drusen and a central PED with overlying pigment hyperplasia (Figure 4A). There was no hemorrhage or subretinal fluid, and no leakage was seen on FA (Figure 4B). Structural OCT demonstrated a large PED with solid and serous components and without intra- or subretinal fluid. Composite OCT showed motion-related signals corresponding to the retinal vasculature but none in

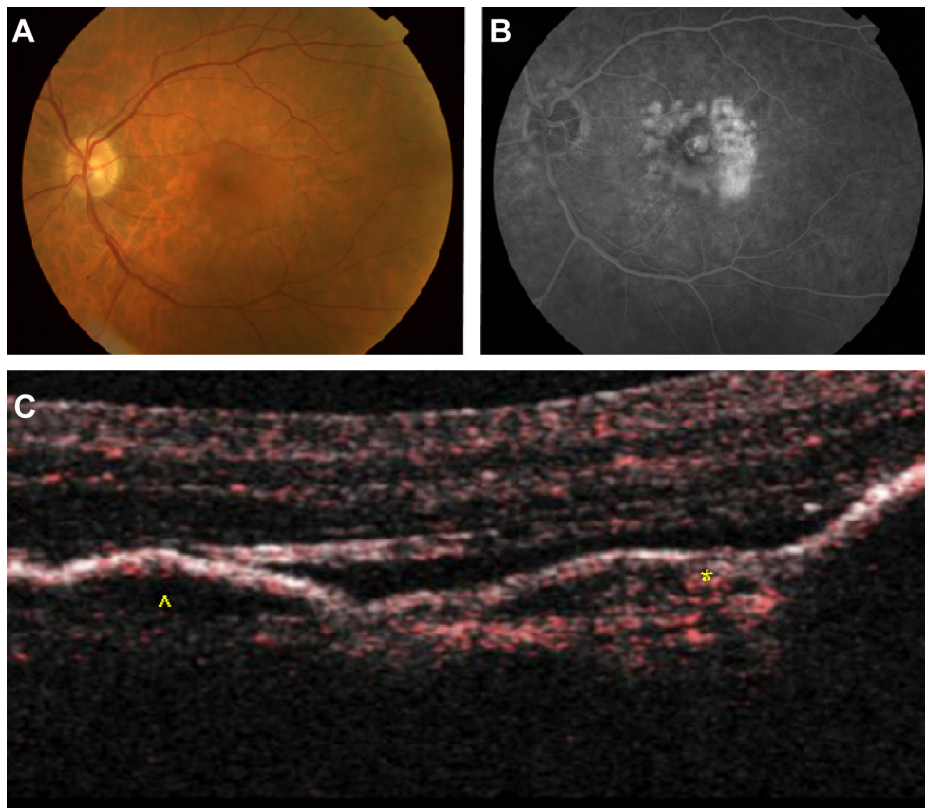


Figure 2 Clinical imaging for Case 2.

Notes: (A) Color fundus photograph showing soft drusen and a subfoveal PED. (B) Late FA showing staining of soft drusen with a late, irregular leakage. (C) Composite OCT showing a multi-lobed PED with subretinal fluid. A red PV-OCT signal extends from the choroid into a solid lobe of the PED (asterisk), consistent with vascularization. The adjacent serous lobe of the PED has no vascular signal (arrowhead).

Abbreviations: PED, pigment epithelial detachment; FA, fluorescein angiography; OCT, optical coherence tomography; PV-OCT, phase-variance optical coherence tomography.

the PED or subretinal space (Figure 4C). Motion signal in the choroid was largely absent, likely due to signal attenuation from the large overlying PED. This finding is consistent with the lack of signs of vascularization on examination, FA, and structural OCT.

Case 5

An 84-year-old man with a history of nonexudative AMD was followed by the Retina Service at UCD. Visual acuity at the time of evaluation was 20/20 in the right eye. Examination showed large soft drusen, calcific drusen, pigment hyperplasia, and PED, and there was no hemorrhage, lipid exudate, or subretinal fluid (Figure 5A). Structural OCT demonstrated a PED with high internal reflectance and without intra- or subretinal fluid. Composite OCT showed motion-related signals corresponding to the retinal and choroidal vasculature, but none in the PED or subretinal space (Figure 5B). Several focal areas with apparent flow signal in the outer retina and RPE are likely artifacts from overlying retinal vessels (Figure 5B; arrows). These findings are consistent

with the lack of signs of vascularization on examination and structural OCT.

Discussion

This report demonstrates the feasibility of composite structural and angiographic OCT images to detect PED vascularization using cases with known neovascular disease. In cases 1–3, PEDs with solid components were shown to have internal motion signals on PV-OCT, consistent with PED vascularization. Cases 4 and 5 featured PEDs without clinical evidence of exudative disease, and appropriately, the composite images in these cases did not show vascular signals within the PEDs.

The use of composite OCT images for PED evaluation has previously been described for PV-OCT as well as other OCT angiography techniques.^{10,11,13–15} However, this is the first series evaluating the use of PV-OCT-based composite scans on subjects with exudative versus nonexudative AMD. Compared to other OCT angiography techniques, PV-OCT may be advantageous. Doppler OCT is more sensitive to flow

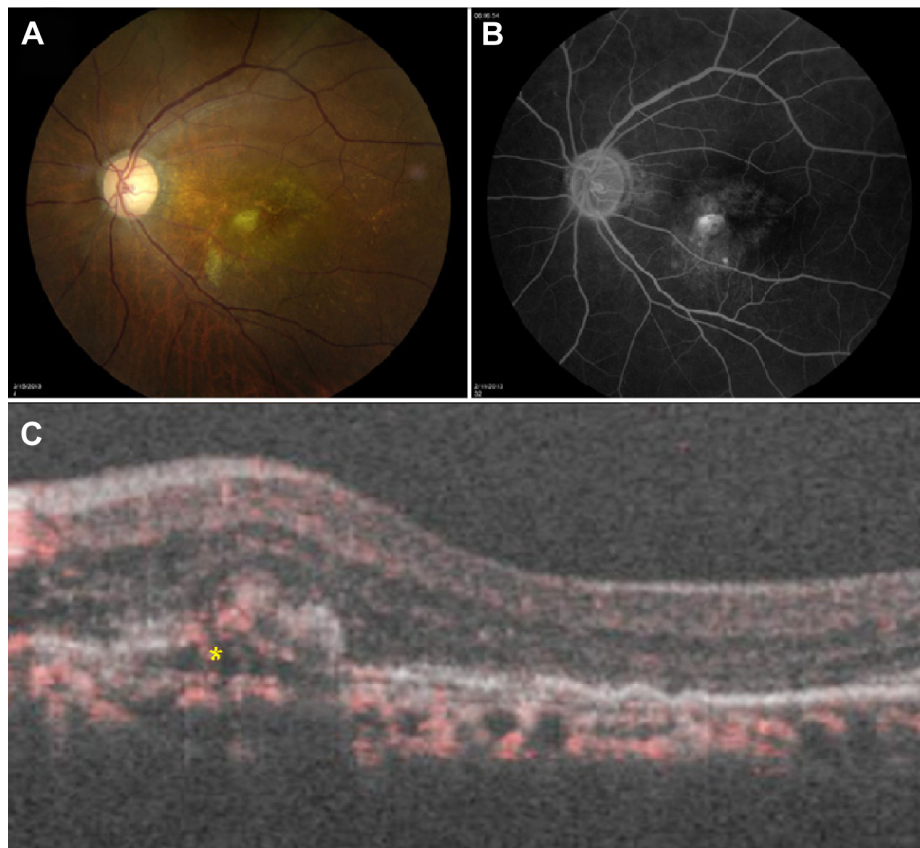


Figure 3 Clinical imaging for Case 3.

Notes: (A) Color fundus photograph showing a PED with associated fibrosis and RPE atrophy. (B) Late FA showing filling and leakage of a perifoveal PED surrounded by an area of stippled hyperfluorescence. (C) Composite OCT showing a solid PED with a trace amount of intraretinal fluid. A red PV-OCT signal extends from the choroid into the solid PED (asterisk), consistent with vascularization.

Abbreviations: PED, pigment epithelial detachment; RPE, retinal pigment epithelium; FA, fluorescein angiography; OCT, optical coherence tomography; PV-OCT, phase-variance optical coherence tomography.

occurring in the axial direction compared to the transverse direction, while PV-OCT has relatively equal sensitivity to flow occurring in both directions. Furthermore, Doppler OCT requires slow scanning speeds in order to detect slow flow from capillaries and fast flow from retinal arteries and veins, and the decorrelation-based method requires high scanning speeds (at least 70,000 A-scans/second) because it does not compensate bulk (or background) eye motion.^{14,16}

This article demonstrates the ability of PV-OCT to produce images at a broad spectrum of imaging speeds. Cases 1, 2, 4, and 5 were imaged using a prototype machine with a high scanning rate, while a commercially available Bioptigen OCT machine with a lower scanning rate was used to produce the images in case 3. This is the first report of the use of a commercial SD-OCT device to perform PV-OCT angiography, suggesting the feasibility of using software upgrades to enable existing OCT machines to perform OCT angiography. The lower scanning rate and lack of rigid subject stabilization contributed to reduced scan quality in the commercially

available machine compared to images obtained in the laboratory; however, flow signals within PEDs were still easily detected. Newer commercial systems with increased scanning rates, as well as the incorporation of eye tracking technology, may improve future commercial PV-OCT scan quality. Furthermore, in clinical practice, separate structural OCT images may be obtained for additional structural detail.

This technology is potentially useful to the clinician, particularly in AMD where management of PEDs can pose a challenge. Vascularization may occur in as many as 34% of PEDs over 25 months and has been associated with worse visual outcomes and an increased risk of RPE tears and subretinal hemorrhage – potentially, catastrophic complications.^{4,17,18} It has been shown that improved visual outcomes are achieved when treatment for exudative AMD is initiated prior to the development of significant visual loss and when CNV membranes remain small.^{19–21} In the absence of leakage on OCT or hemorrhage on examination, FA is not ordinarily performed; however, the safety and convenience

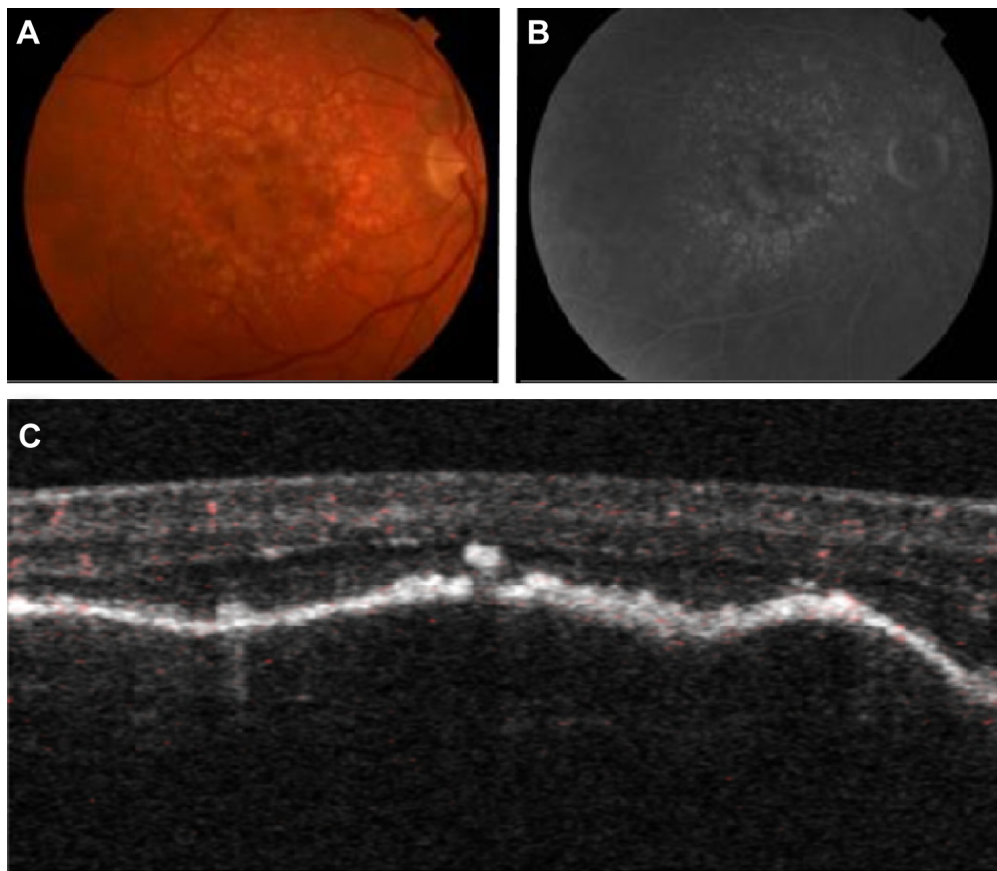


Figure 4 Clinical imaging for Case 4.

Notes: (A) Color fundus photograph showing large soft drusen, a central PED with overlying pigment hyperplasia, and no hemorrhages. (B) Late FA showing staining of the PED and drusen without leakage. (C) Composite OCT showing a large mixed solid and serous PED with overlying pigment migration, but no subretinal or intraretinal fluid. Intraretinal vascular signals correspond to normal retinal blood vessels, but no flow signals are seen in the PED, consistent with avascularity.

Abbreviations: PED, pigment epithelial detachment; FA, fluorescein angiography; OCT, optical coherence tomography.

of PV-OCT enables earlier and more frequent assessments. It is possible that these advantages could guide neovascular PED treatment and lead to improved outcomes. However, further investigation is needed to confirm the ability of PV-OCT to detect PED vascularization prior to the onset of symptomatic exudation.

Conclusion

PV-OCT is a fast, noninvasive, software-based technique that can be performed with existing SD-OCT instruments. The current report illustrates the feasibility of using composite structural and PV-OCT angiographic images to detect vascularization of PEDs in AMD. Future studies

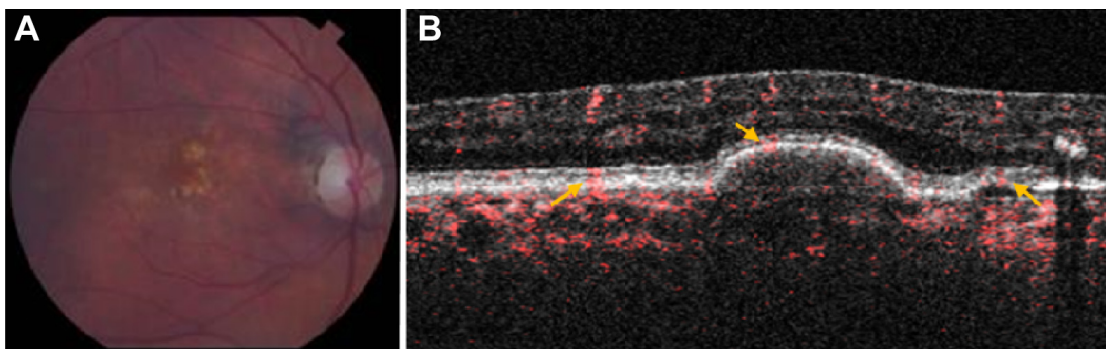


Figure 5 Clinical imaging for Case 5.

Notes: (A) Color fundus photograph showing soft and calcific drusen, pigment hyperplasia, PED, and no exudate or hemorrhage. (B) Composite OCT showing a solid central PED and a smaller adjacent area of RPE elevation with associated pigment migration. There is no sub- or intraretinal fluid. Intraretinal vascular signals correspond to normal retinal and choroidal blood vessels, but no flow signals are seen in the PEDs. Arrows indicate areas of likely artifact from overlying retinal vessels.

Abbreviations: PED, pigment epithelial detachment; OCT, optical coherence tomography; RPE, retinal pigment epithelium.

are needed to demonstrate the detection of vascularization before it becomes apparent on clinical examination, structural OCT, and dye-based angiography and to evaluate whether this information can be applied to improve treatment outcomes.

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Disclosure

Daniel Schwartz, Jeff Fingler, and Scott Fraser are inventors on PV-OCT patents. The other authors report no conflict of interest in this work.

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