Purpose: To use a novel optical coherence tomography angiography (OCTA) algorithm termed variable interscan time analysis (VISTA) to evaluate relative blood flow speeds in polypoidal choroidal vasculopathy (PCV).

Methods: Prospective cross-sectional study enrolling patients with confirmed diagnosis of PCV. OCTA of the retina and choroid was obtained with a prototype swept-source OCT system. The acquired OCT volumes were centered on the branching vascular network (BVN) and polyps as determined by indocyanine-green angiography (ICGA). The relative blood flow speeds were characterized on VISTA-OCTA.

Results: Seven eyes from seven patients were evaluated. Swept-source OCTA enabled detailed enface visualization of the BVN and polyps in six eyes. VISTA-OCTA revealed variable blood flow speeds in different PCV lesion components of the same eye, with faster flow in the periphery of polyps and slower flow in the center of each polyp, as well as relatively slow flow in BVN when compared with retinal vessels. BVNs demonstrated relatively faster blood flow speeds in the larger trunk vessels and relatively slower speeds in the smaller vessels.

Conclusions: Swept-source OCTA identifies polyps in most, but not all, PCV lesions. This limitation that may be related to relatively slow blood flow within the polyp, which may be below the OCTA’s sensitivity. VISTA-OCTA showed heterogeneous blood flow speeds within the polyps, which may indicate turbulent flow in the polyps.

Translational Relevance: These results bring relevant insights into disease mechanisms that can account for the variable course of PCV, and can be relevant for diagnosis and management of patients with PCV.

Introduction

Polypoidal choroidal vasculopathy (PCV), an entity first named by Yannuzzi et al.1 in 1990, is characterized by a branching vascular network (BVN) terminating in polypoidal lesions and is often accompanied by serous or hemorrhagic retinal pigment epithelium detachment (PED). While fluorescein angiography remains the preferred imaging modality for visualizing typical choroidal neovascularization (CNV), it offers a limited documentation of PCV lesions because these are located below the retinal pigment epithelium (RPE). Indocyanine green angiography (ICGA) is the current gold standard...
Investigation for the diagnosis of PCV as it allows better visualization of the choroidal vasculature. Both of these standard angiographic techniques are invasive and involve the use of intravenous contrast that can result in systemic adverse events and, rarely, anaphylaxis.

Optical coherence tomography (OCT) is a fast and noninvasive imaging modality that plays an important role in the diagnosis and clinical monitoring of PCV lesions. Cross-sectional and enface structural OCT suggest the presence of PCV lesions through typical findings such as multiple or multilobulated PEDs, sharp PED peaks, and PED notching, as well as rounded hyporeflective structures correspondent to the polyp lumen. These areas are often seen within the hyperreflective lesions and are adherent to the underside of the RPE. A BVN can also be visualized as a double-layered structure with high reflectivity immediately below the RPE. Despite these characteristic features, it is not always possible to accurately delineate the complete extent of the PCV lesion with structural cross-sectional OCT scans alone, and structural enface OCT is superior in this regard.

OCT angiography (OCTA) is a new OCT-based technology that allows for volumetric and depth-resolved imaging of the retinal and choroidal vasculatures without the need for invasive dyes, by using blood cells as motion contrast. OCTA has enjoyed widespread usage in patients with CNV because it allows for visualization of the neovascular complex both above and beneath the RPE without the use of intravenous dye. There are previous studies showing that the BVN in PCV lesions can be reliably detected using OCTA. However, there have been varying reports on the limited sensitivity of OCTA in detecting polyps compared with ICGA. It has been hypothesized that slow blood flow in this neovascular complex may be below the sensitivity threshold of OCTA systems to detect blood flow, but this has not yet been confirmed nor demonstrated.

In addition to limited flow sensitivities, current commercial OCTA systems primarily report information pertaining to the presence or absence of blood flow—having velocities within a range defined by the interscan time, which is typically close to 5 ms—but provide little-to-no direct information about flow speeds. This is an unfortunate shortcoming, as knowledge of blood flow speeds may provide further insight into PCV pathophysiology. Recently, an OCTA-based algorithm, termed variable interscan time analysis (VISTA), has been developed by our group for detecting and displaying relative blood flow speeds in the retinal and choroidal vasculatures. The aim of the present study is to use high-speed swept-source OCT technology in conjunction with VISTA-OCTA to analyze relative blood flow speeds in PCV lesions.

Methods

This was a cross-sectional, observational study conducted at the New England Eye Center of Tufts Medical Center (Boston, MA) and approved by the Tufts Medical Center and Massachusetts Institute of Technology (Cambridge, MA) institutional review boards. The research adhered to the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act of 1996. Written informed consent was obtained before swept-source OCT imaging.

Patient Selection

Patients with PCV were seen at the New England Eye Center between August 2015 and January 2016 and prospectively recruited to be imaged on swept-source OCT. Patients were submitted to comprehensive ophthalmologic examination, and the diagnosis of PCV was confirmed by ICGA.

Image Acquisition and Analysis

A high-speed swept-source OCT prototype system, developed at the Massachusetts Institute of Technology, was used in this study. The system uses a vertical cavity surface emitting laser operating at approximately 1050-nm wavelength and 400,000-kHz A-scan rate. For each OCT volume, a total of five repeated B-scans from 500 sequentially, uniformly spaced, slow-scan locations were acquired, with each B-scan consisting of 500 A-scans. The interscan time, accounting for the mirror scanning duty cycle, is approximately 1.5 ms, with the total acquisition time being approximately 3.8 seconds. The axial and transverse resolutions are approximately 8 to 9 µm and approximately 20 µm (full-width-at-half-maximum) in tissue, respectively. For both 3 × 3 mm and 6 × 6 mm, the acquired OCT volumes were centered on the area containing the BVN and polyps, as seen on ICGA. Patients were asked to fixate on an internal target during OCT acquisition. Motion correction was performed using registration of two orthogonally acquired volumes, which are merged into a single volume.

A custom C++ application was used for image processing, and ImageJ software (http://imagej.nih.
gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD) was used for visualization. A flat segmentation line was manually adjusted using the orthogonal view, and structural en-face and OCTA images were formed by projecting the OCT data through the depths spanned by the lesion.

VISTA-OCTA was performed as previously described. In brief, VISTA-OCTA images were formed as follows. First, OCTA images corresponding to 1.5-ms interscan times were formed by comparing temporally adjacent repeated OCT cross-sectional scans; OCTA images correspond to 3-ms interscan times were formed by comparing every other repeated OCT cross-sectional scan. Second, 1.5- and 3-ms interscan time OCTA volumes were projected through the depths spanned by the PCV lesion, thereby yielding 1.5- and 3-ms enface OCTA images. A filtered ratio of these enface images was computed and mapped to a color-coded display. In our VISTA color-coded convention, red indicates relatively fast blood flow speeds and blue indicates relatively slow blood flow speeds.

Two independent readers (EAN and DF) of the Boston Image Reading Center analyzed the 3 × 3-mm and 6 × 6-mm enface structural (OCT) and flow (OCTA) images to determine PCV features (e.g., identification of polyps and branching vascular network). VISTA-OCTA images were qualitatively analyzed for blood flow speed information. Disagreement between the two observers was resolved by open adjudication.

Results

Seven eyes from seven patients (5 Asian; 2 African American) were enrolled in this study. The mean age ± standard deviation of the studied population was 71 ± 10.2 years. Five patients (71%) were women and two (29%) were men. One patient had a history of enucleation of the contralateral eye because of massive hemorrhage. All subjects had a history of one intravitreal injection of anti–vascular endothelial growth factor in the study eye to manage exudative manifestations of PCV, prior to enrollment in the study.

ICGA identified the presence of BVN, polyps and dilated choroidal vessels in all study eyes. The mean time of identification through vascular filling of BVN and polyp on video ICGA were 25.2 ± 5.9 and 23 ± 4.5 seconds.

Swept-source OCTA enabled detailed enface visualization of the BVN in six of seven study eyes (85.7%); visualization of polyps was also possible in six of seven study eyes (85.7%). Corresponding cross-sectional structural OCT scans helped identify the depth and location of the polyps relative to the RPE in all seven study eyes (100%).

VISTA-OCTA provided information about relative blood flow speeds in all OCTA images in which the BVN and/or polyps were visible. Blood flow speed within polyps varied from polyp-to-polyp within the same eye, as well as from patient-to-patient. Some polyps demonstrated relatively faster flow speeds (red-yellow color-coded velocity range; Fig. 1) while others demonstrated slower flow speeds (blue-green color-coded velocity range; Figs. 2, 3). A common finding was that VISTA-OCTA–derived relative blood flow speeds within a single polyp were not uniform; there was a range of blood flow speeds within a single polyp (Fig. 4). Based on VISTA-OCTA, blood flow in some polyps appeared slower at the center of the polyp, and faster close to the lesion walls (Fig. 1). In all documented eyes, BVNs have

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Figure 1. PCV on VISTA-OCTA. Variable blood flow speeds in polyps from the same neovascular complex. Left eye of an 84-year-old woman with PCV. (A) ICGA aligned to the same area as the OCTA and VISTA-OCTA images, demonstrates bright spots corresponding to two polyps (yellow and white arrows) and a BVN (white dashed line). (B) OCTA shows both polyps and the BVN in the same projection. (C) VISTA-OCTA demonstrates variable relative blood flow speeds in two polyps in the same eye. The yellow arrow shows a polyp with relatively fast blood flow speed (represented by red color-coded OCTA), while the white arrow shows a polyp with relatively slow blood flow speed (represented by green- and blue color-coded OCTA). (D, E) The structural cross-sectional scan and OCTA cross-sectional scan, respectively, taken through the white line as seen in (A). The yellow arrow points to a polyp. Note that localized decorrelation signal within the polyp in the OCTA cross-sectional scan. (F) Structural enface OCT image shows a polyp and the BVN.
relatively slow flow in comparison to blood flow speed of retinal vessels. Variable blood flow speed was also observed in BVNs, with relatively faster blood flow speeds in the larger trunk vessels and relatively slower speeds in the smaller vessels (Figs. 5, 6).

Discussion

PCV lesions are characterized by polypoidal terminations connected to a BNV. It is still a matter of debate if PCV is a variant of CNV secondary to age-related macular degeneration, or if this is a distinct entity. It has been hypothesized that polypoidal lesions in the vascular terminations occur because of a localized delay in choroidal capillary lobular filling, which causes capillary and venous congestion in the affected lobules. This would impact the RPE–Bruch’s membrane complex and produce a PED. The natural history of PCV is widely variable, as well as its response to treatment including anti–vascular endothelial growth factor agents or photodynamic therapy. Large serosanguinous PEDs typically occur in eyes with PCV, and the polyps commonly bleed between the RPE and Bruch’s membrane. Intriguingly, self-resolution may also be observed in the natural course of polypoidal lesions.

The current gold standard for diagnosing PCV is ICGA, an invasive test with potential risks for the patient. OCTA is a noninvasive imaging technology that can separately visualize the retinal and choroidal vasculatures. This technology is increasingly being used to image CNV because it can visualize the neovascular complex both above and beneath the RPE. However, in recent studies the detection rate of polyps on OCTA compared with ICGA has varied widely, ranging from 45% to 92% detection. Interestingly, Tanaka et al. found that OCTA best detected polyps that were observed to be pulsating on video ICGA. In the current study, the polyp detection rate was in the upper range of previously published studies. The longer wavelengths used in the prototype swept-source OCT device might favor the detection of polyps and other choroidal vascular structures, located deeper in the fundus tissue. Such advantage has been previously demonstrated in documenting typical choroidal neovascu-
While the swept-source OCT technology might contribute to improved rate of polyp detection, the VISTA algorithm on the other hand, does not add to this greater sensitivity. This is because the interscan times used in this study (1.5 and 3 ms) are shorter than those commonly used in standard commercial OCT systems (~5 ms). Thus, all else being equal, the slowest detectable flow using a commercial system should actually be relatively lower than that of our prototype system.

It is important to note that, among the recent literature, the definition of positive identification of polyps on OCTA is a matter of controversy. Some authors consider positive detection of polyps on OCTA as seeing an OCTA decorrelation signal. Other authors have described polyps on OCTA as hyperflow round structure surrounded by hypoflow halo or simply a hypoflow round structure at the level of the choriocapillaris. It has been hypothesized that turbulent blood flow within polyps might underlie this variability.

In this study, a prototype high-speed swept-source OCT device was used in conjunction with the VISTA algorithm to visualize variations in relative blood flow speeds within polypoidal lesions. Our data suggests a range of relative blood flow speeds within the polyps and the BVN. This was demonstrated between different components of the lesion in the same eye, and between different eyes. While the mechanism of this variable flow speed is not yet clear, we believe that the relative blood flow speed information provided by VISTA-OCTA may inform on the diagnosis of PCV based on OCTA, and may help to elucidate the pathophysiology of PCV. In particular, some polyps appeared to have faster blood flow in the periphery and slower blood flow in the center, which might indicate turbulence within the polyps and might be related to the self-obliteration process occasionally observed in the natural course of the disease. With respect to blood flow speeds within BVNs, our results showed relative faster flow in the larger trunk vessels and slower flow speeds in the smaller vessels. Similar findings have been recently shown in CNV and retinal neovascularization in proliferative diabetic retinopathy using VISTA-OCTA. Once treatment para-
digms are properly established on these new technolo-
gies, quantitative assessments of lesion flow may
to potentially contribute to patient management, in-
formation on lesion activity and potentially indicating
response to therapeutic interventions.

Limitations of this study include a relatively small
sample size, but the consistency of our observations
indicates high reproducibility of the results. The fact
that all patients were previously treated with one
intravitreal injection of anti–vascular endothelial
growth factor raises the question whether naïve-
treatment PCV lesions will show similar blood flow
patterns, and naïve-treatment lesions should be
investigated through the same method in a future
study. In addition, we did not establish a direct
comparison between ICGA filling speed and VISTA-
OCTA–relative flow, as this was not within the scope
of this work. There are also limitations with regard to
the data processing that preclude a broader use of the
strategy employed in this study: the custom software
used to process the swept-source OCT data in the
present study does not have automated segmentation,
and therefore manual adjustment of enface projection
boundaries was required to achieve the best quality
image, which is time consuming and requires trained
assessors. Additionally, in its current form, the
VISTA-OCTA algorithm only provides information
about relative blood flow speeds (e.g., “the flow in
vessel A is faster than that in vessel B”), but not about
absolute blood flow speeds (i.e., “the flow in vessel A
is 3 mm/s, and that is vessel B is 2 mm/s”). Future
development of the VISTA algorithm to allow for
quantitative measurements of absolute blood flow
speed is an important step to enabling further
investigation into blood flow speeds in PCV and
other clinical presentations of CNV. Finally, there are
some factors that might confound the interpretation
of VISTA-OCTA. In particular, VISTA-OCTA sig-
nals are derived from OCTA signals, which are in turn
derived from repeated OCT scans. Thus, artifacts in
either the OCT or OCTA imaging can degrade the
VISTA-OCTA signal. For example, low OCT signals
generates noisy OCTA images, which in turn generate
noisy VISTA-OCTA images; similarly, errors in
projection ranges, patient motion artifacts, poor
optical focusing, and other factors known to corrupt
OCTA signal may also corrupt the VISTA-OCTA
images.40 While we have taken measures to reduce the
likelihood of such errors, for example, by inspecting
coregistered OCT and OCTA data in an orthoplane
manner, manually selecting projection ranges, and
using a longer wavelength swept-source OCT system
that has reduced attenuation artifacts, we have not yet
performed formal repeatability analyses of the VIS-
TA-OCTA, particularly in the context of PCV. It is
therefore possible that additional imaging artifacts
are also present in our dataset.

In conclusion, even though ICGA remains the gold
standard for diagnosing PCV, it is invasive and lacks
depth resolution.2,32,41 OCTA is a noninvasive and
fast technique for three-dimensional and depth-
resolved fundus imaging, allowing different vascular
layers of the retina and choroid to be independently
documented. Previous studies have had mixed success
in identifying polypoidal lesions on OCTA, and, as in
our study, found that OCTA was not able to visualize
lesions in all cases. VISTA-OCTA, a recently
proposed OCTA enhancement that enables visualize-
tion of relative blood flow speeds, shows slow and
variable blood flow speed in polypoidal lesions, and
may increase our understanding of PCV pathophys-
iology.
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