Noninvasive Investigation of Deep Vascular Pathologies of Exudative Macular Diseases by High-Penetration Optical Coherence Angiography

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PURPOSE. A newly developed high-penetration Doppler optical coherence angiography (HP-OCA) with a 1-μm probe beam for noninvasive investigation of vascular pathology of exudative macular diseases is introduced. A descriptive case series is presented to discuss the clinical utility of HP-OCA.

METHODS. Eleven eyes of 10 subjects with exudative macular disease, including two eyes with myopic choroidal neovascularization (mCNV); four eyes with AMD; and five eyes with polypoidal choroidal vasculopathy (PCV) were investigated. Two Doppler scanning modes (bidirectional and high-sensitive) of HP-OCA were used for the investigation. HP-OCA provides depth-resolved and en face angiograms and a structural OCT noninvasively. The HP-OCA images were compared with fluorescein angiography (FA); indocyanine green angiography (ICGA); and color fundus images.

RESULTS. The abnormal vasculature patterns observed with high-sensitive HP-OCA presented high similarity to the midphase of ICGA. Several abnormal Doppler signals were observed in the en face high-sensitive HP-OCA and were colocated with FA leakage. This colocation was found in one eye with mCNV, four eyes with AMD, and one eye with PCV. Doppler tomogram of the bidirectional mode showed abnormal Doppler signals in three of five PCV cases beneath the pigment epithelium detachment. With the high-sensitive mode, Doppler signals were found beneath the elevated retinal pigment epithelium in all untreated cases.

CONCLUSIONS. HP-OCA revealed depth-resolved abnormal vasculatures in exudative macular diseases. The en face HP-OCA images showed high similarity with FA and ICGA images. These results suggest HP-OCA can be used for noninvasive and three-dimensional angiography in a clinical routine.

Keywords: noninvasive angiography, choroid, vasculature, Doppler, optical coherence tomography

EXUDATIVE MACULAR DISEASES Threaten Vision Ability of Humans. Among them, pathological myopia and AMD are representative causes of blindness worldwide.1-5 These diseases frequently appear with choroidal neovascularization (CNV). Polypoidal choroidal vasculopathy (PCV) is one form of CNV and it is characterized by a branching vascular network (BVN) terminating in polypoidal lesions.6,7 In Asian countries, PCV represents between 56% and 72% of all neovascular AMD patients.1

One of the most effective treatments of CNV is intravitreal injection of bevacizumab or ranibizumab. This treatment requires repeated injection with several rounds, with 1- to 3-month periods, and fluorescence angiography (FA) and indocyanine green angiography (ICGA) images are required for the initial diagnosis. However, FA and ICGA imaging is sometimes restricted because they are invasive methods requiring dye injection into a vein, which makes patients uncomfortable and sometimes induces adverse reactions.8,9 Hence, it is clinically important to establish a new modality that noninvasively reveals the vasculature including abnormal vasculature.

Optical coherence tomography (OCT) has been an innovative ophthalmic diagnostic modality that provides noninvasive optical biopsy imaging.10 However, conventional OCT with an 840-nm probe beam can visualize only limited structures beneath the RPE. It is known that light with a wavelength of around 1050 nm is less scattered in the choroid and less absorbed in the RPE, and OCT with a 1050-nm probe beam, also referred to as high-penetration OCT (HP-OCT), has been demonstrated for high-penetration imaging of the posterior eye.11 Visualization of sub-RPE morphologies in exudative macular disease by HP-OCT has also been demonstrated.12,13

In addition to structural imaging, Doppler OCT, a functional extension of OCT, has been demonstrated to image flow in living tissues.14-20 Doppler OCT provides depth-resolved flow contrast by detecting the Doppler shift of a probe beam
induced by the motion of scatterers in the sample. This technique and its variations are utilized both for quantitative flow investigation\textsuperscript{21–24} and detailed structural investigation of the vasculature.\textsuperscript{25–29} The former is now possible with a commercially available OCT device, such as the RTVue (Optovue Inc., Fremont, CA). The latter, so-called “OCT angiography” or optical coherence angiography (OCA), is still in the research phase, but has been successfully applied in the investigation of exudative macular diseases.\textsuperscript{29}

Recently, the OCA method has been combined with an HP-OCT engine.\textsuperscript{30–32} This high-penetration optical coherence angiography (HP-OCA) enables vascular imaging of the deep posterior eye.

The purpose of this paper is to evaluate the clinical utility of HP-OCA as a noninvasive angiographic modality. We introduce a custom-built HP-OCA\textsuperscript{32} to investigate the vascular pathology of exudative macular diseases. A descriptive case series of myopic CNV (mCNV), AMD, and PCV are presented. Through detailed discussion of the cases, the clinical utility of HP-OCA is also discussed.

**Subjects and Methods**

Eleven eyes of 10 subjects were involved in this study as summarized in Table 1. The study included two eyes of two subjects with mCNV, four eyes of four subjects with AMD, and five eyes of four subjects with PCV. All subjects were Japanese. The mean age of the patients was 61.3 ± 14.2 years (mean ± standard deviation), and the age ranged from 32.8 to 82.5 years. Specifically, the mean age of the subjects with each type of disease was 38.8 ± 8.5 years for mCNV, 61.9 ± 5.8 years for AMD, and 72.0 ± 7.5 years for PCV. The mean of the spherical equivalent refraction error of the eyes was −2.3 ± 3.8 diopters (D), ranging from −11 D to 1.5 D. Specifically, the mean refraction error of the eye for each type of disease was −8.5 ± 3.9 D for mCNV, 0.1 ± 0.6 D for AMD, and −1.9 ± 2.9 D for PCV.

The patients were diagnosed at Ibaraki Medical Center Hospital, Tokyo Medical University. All subjects received a comprehensive ophthalmic examination including color fundus photography, spectral domain OCT with an 830-nm probe (3D OCT-2000; Topcon Corp., Tokyo, Japan), FA, and ICGA. Subjects who showed an allergic reaction to fluorescein—one (3D OCT-2000; Topcon Corp., Tokyo, Japan), FA, and ICGA.

Patients who were diagnosed as exudative macular disease were transferred to an optics laboratory at the University of Tsukuba, where their eyes were scanned with a custom built HP-OCA.

The research protocol adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of Tokyo Medical University and the University of Tsukuba. Informed consent was obtained from the subjects after providing an explanation of the nature and possible consequences of the research.

**High-Penetration Doppler Optical Coherence Angiography**

The HP-OCA device is a prototype built by the Computational Optics Group at the University of Tsukuba. This OCA is based on swept-source OCT technology and offers a measurement speed of 100,000 A-lines/s. With a single scan of the eye, HP-OCA provides both high-penetration OCT and Doppler tomograms. The Doppler tomography signal is obtained by the phase difference between two OCT A-lines, and reflects the Doppler shift of the probe beam. Doppler shift is induced by the flowing red blood cells in the vessels. Based on this mechanism, the Doppler tomography selectively visualizes the ocular vasculature.

This device has two measurement modes for two types of Doppler tomography. The first mode is a bidirectional mode, which calculates the Doppler signal from two successive A-lines. This mode is sensitive to relatively fast flow; in our particular configuration, it was from 1.75 mm/s to 19.2 mm/s (axial velocity) and it provides bidirectional axial flow velocity. A potential drawback of this mode is the relatively high minimum measurable velocity (1.75 mm/s). A flow signal slower than this limit is not detectable. In this paper, the bidirectional cross-sectional tomogram in which the bidirectional Doppler signal overlaid on structural OCT is denoted as bidirectional Doppler tomogram, while en face projection of the squared bidirectional Doppler tomogram is denoted as bidirectional OCA.

The second mode is the high-sensitive mode, in which the Doppler signal is calculated from two A-lines in two successive B-scans. This mode is sensitive to relatively slow flow, such as >5.2 μm/s (axial velocity) in our particular configuration. A potential drawback of this mode is relatively low maximum measurable velocity (60 μm/s) for quantitative measurement. A flow signal faster than this limit is wrapped into the measureable Doppler range and appears as a strong but random pattern. Hence this high-sensitive mode is not suitable for qualitative bidirectional measurement, but suitable for high-contrast selective imaging of small vessels. In this mode, the image is displayed in the form of the squared energy of the Doppler signal, and is utilized for small vascular observation with flow-selective contrast. In this paper, a high-sensitive Doppler signal overlaid on structural cross-sectional OCT is denoted as high-sensitive Doppler tomogram, and the en face projection of the high-sensitive Doppler signal is denoted as high-sensitive OCA.

The details of this HP-OCA are described elsewhere,\textsuperscript{32} except for a new signal processing method for eye motion correction. The details of this modification are presented in Supplementary Material S1. It should be noted that the bidirectional mode and high-sensitive mode are denoted as the fast Doppler mode and slow Doppler mode, respectively, in Hong et al.\textsuperscript{32}

The HP-OCA scans the 6-mm × 6-mm area around the pathologic region with 2048 A-lines (horizontal) × 256 B-scans (vertical) for bidirectional mode and 256 A-lines (horizontal) × 2048 B-scans (vertical) in the high-sensitive mode. Each measurement took 6.6 seconds. It should be noted that a finally obtained en face OCA image in high-sensitive mode is

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Eye</th>
<th>Sex</th>
<th>Age, y</th>
<th>D</th>
<th>Diagnosis</th>
<th>No. of IVR*</th>
</tr>
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<tbody>
<tr>
<td>Subject 1</td>
<td>R</td>
<td>M</td>
<td>44.9</td>
<td>−11.0</td>
<td>mCNV</td>
<td>3</td>
</tr>
<tr>
<td>Subject 2</td>
<td>L</td>
<td>M</td>
<td>32.8</td>
<td>−5.5</td>
<td>mCNV</td>
<td>0 and 2</td>
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<tr>
<td>Subject 3</td>
<td>L</td>
<td>F</td>
<td>68.5</td>
<td>1.0</td>
<td>AMD (classic)</td>
<td>0 and 3</td>
</tr>
<tr>
<td>Subject 4</td>
<td>L</td>
<td>M</td>
<td>61.5</td>
<td>0.0</td>
<td>AMD (classic)</td>
<td>0 and 5</td>
</tr>
<tr>
<td>Subject 5</td>
<td>L</td>
<td>M</td>
<td>63.1</td>
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<td>Subject 6</td>
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<td>Subject 8</td>
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<td>0</td>
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<tr>
<td>Subject 9</td>
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<td>1.5</td>
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<td>0</td>
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<tr>
<td>Subject 10</td>
<td>L</td>
<td>M</td>
<td>64.9</td>
<td>−0.5</td>
<td>PCV</td>
<td>0</td>
</tr>
</tbody>
</table>

R: right; l: left; No. of IVR, number of intravitreal injection of ranibizumab prior to the investigation with HP-OCA.

\* The multiple numbers in the column labeled “No. of IVR” represent multiple measurements by HP-OCA after the each number of treatments.
not always perfectly rectangular. This is because of invalid A-lines caused by high-frequency scanning of a scanning mirror in the OCT scanner and its resulting synchronization imperfection between the scanning mirror and data acquisition.

Figure 1 shows typical images of en face OCA (Figs. 1e, 1f); OCA tomogram (Figs. 1g, 1h); and corresponding color fundus (Fig. 1a) and ICGA (Figs. 1b, 1c) images, which were obtained from a normal macula of a 37-year-old Japanese male with –6.0 D myopia. The en face OCT projection image (Fig. 1d) was obtained by the depth average of the logarithmic OCT. Thick choroidal vessels were observed with moderate hyposcattering in the OCT en face projection (Fig. 1d); however, the visualization of choroidal vessels was limited compared with the midphase of ICGA (Fig. 1c). Bidirectional OCA (Fig. 1e) and high-sensitive OCA (Fig. 1f) showed different vasculatures. The retinal vasculature of the macular region was rarely imaged with bidirectional OCA, while high-sensitive OCA visualized similar vasculature to that of color fundus photograph and the midphase of ICGA. For imaging of the choroidal vasculature, the bidirectional OCA showed mainly thick choroidal vasculatures that had fast axial blood flow and appeared in the early-phase of ICGA (Fig. 1b), while high-sensitive OCA showed a similar choroidal vasculature to that of the midphase of ICGA. In addition, several choroidal vessels that did not appear in the midphase ICGA were also visualized in the high-sensitive OCA.

The depth locations of the blood flow are identifiable in Doppler tomogram. In bidirectional Doppler tomogram (Fig. 1g), the colors red and blue represent axial flow directions to the anterior or to the posterior, respectively, and the locations of the flow are indicated with arrows. Figure 1h is a vertical high-sensitive Doppler tomogram. The weaving appearance in this Doppler tomogram was caused by imperfect axial motion correction among the horizontal frames.

RESULTS

Case 1: Myopic CNV

Figure 2 shows a case of mCNV. The subject was a 45-year-old man who had received intravitreal ranibizumab injection three times prior to the HP-OCA examination. Figures 2a, 2b, and 2c represent the color fundus: FA (late-phase); and ICGA (midphase) images, respectively, corresponding to the area of the HP-OCA examination.

RPE elevation was observed in structural OCT (Fig. 2f), which was simultaneously obtained with bidirectional tomogram as well as in the high-sensitive Doppler tomogram as indicated by the yellow arrows (Fig. 2g). In high-sensitive Doppler tomogram, abnormal Doppler signals were observed in the sub-RPE space beneath the elevated RPE and above Bruch's membrane, as indicated by a red arrow.

The region of RPE elevation appeared with hyperscattering in en face structural OCT (Fig. 2d) and with hyper-Doppler signals in high-sensitive OCA as indicated by the arrows (Fig. 2e). These signals were colocated with the hyperreflective spot in the color fundus (Fig. 2a, arrow) and the hyperfluorescence signal in FA (Fig. 2b, arrow), which is the indicator of inactive CNV. The hyperscattering in the structural OCT projection was surrounded by a hyposcattering rim, as a similar appearance was shown in the color fundus. Similarly, the hyper-Doppler spot in the en face OCA was surrounded by
a hypo-Doppler rim, which was similar to a pattern that appeared in the ICGA image (Fig. 2c, arrow). The pattern of CNV appearance in the en face structural OCT and OCA was found in two of two cases with mCNV, four of four cases with AMD, and one of four cases with PCV. It is also noteworthy that high-sensitive OCA showed a high overall similarity to the midphase of ICGA.

Case 2: Myopic CNV With Ranibizumab Injection

Figure 3 summarizes another case with mCNV. The subject was a 33-year-old man who was treated with intravitreal ranibizumab injection (0.05 mL of 10 mg/mL solution for each injection) two times with a 28-day separation. HP-OCA examination was performed 6 days before the first injection and 59 days after the second injection.

Figures 3a, 3b, and 3c are midphase ICGA, high-sensitive OCA, and en face structural OCT projection taken before the treatment, respectively. Figures 3d, 3e, and 3f are corresponding images taken after the injection. The CNV was observed as a hyperfluorescent region surrounded by a dark rim in the ICGA image (Fig. 3a, red arrow) before the treatment. This CNV area became smaller after the ranibizumab injection (Fig. 3d, red arrow). This CNV appeared as a hyper-Doppler region surrounded by a dark rim in the OCA image (Fig. 3b, red arrow), and it also became smaller after the ranibizumab injection (Fig. 3e, red arrow). This appearance was well correlated with ICGA. This CNV region appeared as a large hyper-scattering region in en face OCT (Fig. 3c, circle), and this region became smaller after the injection (Fig. 3f, circle).

Figures 3g and 3h are vertical high-sensitive Doppler tomographies. These tomographies were created from the same datasets of Figures 3b and 3c, and Figures 3e and 3f, respectively, and the locations of the tomograms are indicated by dashed lines in the en face images. Note that the vertical gap in Figure 3g was created by an eye blink. Before the ranibizumab injection, subretinal fluid (blue arrow) and exudates (yellow arrow) were evident in the structural OCT (Fig. 3g). The RPE in the exudative region was hardly visible. In addition to structural tomogram, Doppler tomogram provided more detailed insight. Hyper-Doppler signals were observed in the exudates and the choroid beneath the exudates (Fig. 3g, red arrow), which indicated abnormal flow in this region. After ranibizumab injection, as shown in Figure 3h, subretinal fluid disappeared and the CNV related elevation became smaller. The RPE became clearly visible with structural OCT. With Doppler tomogram, it was found that the abnormal blood flow disappeared (Fig. 3h).

Case 3: AMD

Figure 4 summarizes a case of AMD with classic CNV. The subject was a 62-year-old man. An active CNV was observed at the fovea by dye leakage in the late-phase of FA (Fig. 4b, arrow). The midphase of ICGA (Fig. 4c) shows CNV that appeared as hyperfluorescence surrounded by a dark rim...
Several hard drusen were observed in the color fundus as white spots (Fig. 4a).

OCT en face projection (Fig. 4d) shows a similar appearance to the color fundus photograph including hyperscattering spots and choroidal vasculatures. It is noteworthy that the choroidal vasculature around the CNV appeared with hyper-scattering signal (red arrow inside a circle), while other choroidal vessels in nonpathologic regions generally appeared with hyposcattering, as indicated by a yellow arrow. This appearance would be caused by the deeper penetration beneath the choroidal vessels around the CNV, as indicated by red arcs in the horizontal structural OCT cross-section taken with the bidirectional scanning protocol (Fig. 4f).

High-sensitive OCA (Fig. 4e) showed almost all of the retinal and choroidal vessels shown in the midphase of ICGA (Fig. 4c) even with higher contrast. Remarkably, the detailed abnormal choroidal vasculature was observed at the CNV region, as indicated by arrows in Figures 4e and 4g, where a hyper-Doppler signal was surrounded by a hypodoppler rim. The size of this appearance was also reduced by the ranibizumab injections.

In en face OCT projection (Fig. 5d), active CNV appeared with hyperscattering (red arrow). This hyperscattering decreased after the ranibizumab injection (Fig. 5h, red arrow). In the postinjection OCT image, some other hyperscattering spots were observed (Fig. 5h, yellow arrows). These hyperscattering spots were well correlated with the hyperfluorescence of FA (Fig. 5e, arrows).

A clear difference was observed between the OCT cross-sections taken before and after the injections. Before the treatment (Fig. 5i), exudates were observed as indicated by a yellow arrow. In this region, the RPE was not clearly observed. In the corresponding high-sensitive Doppler tomogram, hyper-Doppler signals were observed in the exudates, as indicated by an arrow.

**Case 4: AMD With Ranibizumab Injection**

Figure 5 summarizes another case of AMD with classic CNV. The subject was a 69-year-old woman treated with intravitreal ranibizumab injection three times within time periods of 28 days and 35 days. The first HP-OCA examination was performed 4 days before the first injection and the second examination was done 49 days after the third injection.

Figures 5a to 5d represent late-phase FA, midphase ICGA, high-sensitive OCA, and structural OCT projection, respectively, taken before the first injection. Figures 5e to 5h are corresponding images taken after the third injection. The active CNV, indicated by a red arrow in the FA image (Fig. 5a) became inactive after three injections, as shown in Figure 5e. In the ICGA images, the CNV appeared as hyperfluorescence surrounded by a dark rim, as indicated by arrows in Figures 5b and 5f. The size of the CNV region was reduced by the injections. A similar appearance with ICGA was found in high-sensitive OCA images, as indicated by arrows in Figures 5c and 5g, where a hyper-Doppler signal was surrounded by a hypodoppler rim. The size of this appearance was also reduced by the ranibizumab injections.

In en face OCT projection (Fig. 5d), active CNV appeared with hyperscattering (red arrow). This hyperscattering decreased after the ranibizumab injection (Fig. 5h, red arrow). In the postinjection OCT image, some other hyperscattering spots were observed (Fig. 5h, yellow arrows). These hyperscattering spots were well correlated with the hyperfluorescence of FA (Fig. 5e, arrows).
a red arrow in Figure 5j. After the injections, exudates disappeared and only a small RPE elevation was observed (Fig. 5k, yellow arrow). In high-sensitive Doppler tomogram (Fig. 5l), nearly no abnormal Doppler signal was observed (arrow).

Case 5: PCV

Figure 6 summarizes a case of PCV that appeared with a large abnormal vascular network. The subject was a 65-year-old man and his left eye was examined. The eye was not treated at the time of the examination. Widely spread exudates were observed with white color in the fundus photograph (Fig. 6a). The hyperfluorescent region in the late-phase FA (Fig. 6g) indicated a large pigment epithelial detachment (PED). Abnormal vasculature and polypoids were observed in the midphase of ICGA (Fig. 6c). In en face OCT projection (Fig. 6d), a strong hyperscattering (left circle) and a moderate hyperscattering (right circle) were observed. This corresponded to the hyperfluorescence regions in FA (Fig. 6g).

In the bidirectional Doppler tomogram (Fig. 6h), clear Doppler signals were observed beneath the moderate PED (red arrow). Figure 6e shows the bidirectional OCA, where the red arrow indicates the Doppler signal in Figure 6h. When comparing this OCA and early phase ICGA (Fig. 6b), it is evident that this Doppler signal corresponds to a feeder vessel.

In high-sensitive Doppler tomogram (Fig. 6i), many abnormal Doppler signals were observed beneath the PED as indicated by the red arrows. Remarkably, some Doppler signals, such as that indicated by the leftmost arrow, represented abnormal vessels that penetrated Bruch’s membrane into the sub-RPE space. The high-sensitive OCA (Fig. 6f) shows a highly correlated pattern with the midphase of ICGA (Fig. 6c).

Case 6: PCV

Figure 7 summarizes another case of PCV. The subject was a 69-year-old man. The early-phase of ICGA (Fig. 7a) shows a clear BVN at the PED area. The late-phase of ICGA (Fig. 7d) shows terminal aneurismal dilatation of the BVN. High-sensitive OCA (Fig. 7b) shows a highly correlated vascular pattern including the BVN with the early-phase of ICGA. High-sensitive Doppler tomogram (Fig. 7g) presents several Doppler signals beneath the PED (arrows). The location of this Doppler tomogram is indicated on ICGAs (Figs. 7a, 7d) and en face OCA (Fig. 7b) with yellow lines. This indicates that the Doppler signals beneath the PED in Figure 7g are associated with the BVN.

A volume rendering of the high-sensitive OCA provides more intuitive understanding, as shown in Figure 7e, where the Doppler signal and the structural OCT signal are respectively displayed in orange and green colors. In this image, the comprehensive three-dimensional structure of the BVN is clearly visualized. In addition, a blood vessel connecting the BVN to the choroid is clearly observed, as indicated with an arrow.

An active CNV is observed in FA, as indicated by a circle in Figure 7c. A similar pattern is observed in high-sensitive OCA.
(Fig. 7b) and OCT en face projection (Fig. 7f), with hyper-Doppler and hyperscattering, respectively. Corresponding Doppler signals are observed in the choroid under the PED (Figure 7h, arrow).

**Visibility of Doppler Signals at Abnormal Choroidal Vessels**

Two graders (Y-JH and MM) graded the visibility of abnormal Doppler signals. A fly-through sequence of structural OCT, Doppler tomogram, and the Doppler tomogram overlaid on the structural OCT were presented to the graders. In this grading, the eyes with Doppler signals at abnormal regions found in structural OCT were labeled as positive and the other eyes were labeled as negative. This grading was independently done for the following three regions: an abnormal region anterior to the RPE; a region between the RPE and Bruch’s membrane; and within Bruch’s membrane (i.e., Doppler signal penetrated through Bruch’s membrane).

Table 2 summarizes the occurrence of Doppler signals at abnormal choroidal vessels graded by two graders and their agreements. In this table, the three regions described above were denoted as “above RPE,” “RPE-Bruch,” and “in Bruch.” The three numbers in each cell represent, from the left: the number of positive eyes found by grader Y-JH, that found by grader MM, and the number of eyes in which the grading of the two graders are agreed.

With bidirectional Doppler tomogram, abnormal flows were observed in PCV eyes with 80% by grader Y-JH and 60% by MM. Conversely, no abnormal flow was observed in mCNV and AMD cases. High-sensitive OCA showed a high occurrence of abnormal Doppler signals within the untreated eyes with both graders. The grading of the two graders were perfectly agreed, except the following three cells: the bidirectional Doppler of untreated PCV at the “RPE-Bruch” and “in Bruch” region, high-sensitive Doppler of untreated PCV at the “In Bruch” region, and high-sensitive Doppler of mCNV at the “RPE-Bruch” region. Hence, the overall agreement of all cells in Table 2 was 89% (82/90).

**DISCUSSION**

In the en face OCT projections of one eye with AMD (Fig. 4d) and two eyes of a single case of PCV, the choroidal vessels appeared with hyperscattering at the pathologic regions, while it appeared with hyposcattering in nonpathologic regions. It is also known that the choroidal vessels appeared with hyposcattering in the en face OCT projection of normal eyes. In these pathologic regions, abnormal hyperpenetration to the deep choroid and sclera was observed as exemplified in Figure 4f. This hyposcattering could be explained by abnormality in the choroidal or RPE tissue, such as reduction of melanin content, abnormal thinning of the choroid, or both. The
The hyposcattering appearance of choroidal vessels can be utilized as an indicator of the choroidal abnormality.

Since the bidirectional mode is only sensitive to fast blood flow, it is selectively sensitive to the arteries among the choroidal vessels. This property of the bidirectional mode provides a similarity between bidirectional OCA and the early-phase (arterial phase) of ICGA as exemplified in Figures 1b and 1e. For ICGA imaging of the PCV, feeder vessels were imaged at

![Figure 6](image)

**TABLE 2.** Visibility of Doppler Signal at Abnormal Choroidal Vessels Graded by Two Graders and Their Agreement

<table>
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<th>Doppler Mode</th>
<th>Region</th>
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<th>Treated</th>
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<td>mCNV, N = 1</td>
<td>AMD, N = 4</td>
<td>PCV, N = 5</td>
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<td>Above RPE</td>
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<td></td>
<td>RPE-Bruch</td>
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<td></td>
<td>In Bruch</td>
<td>0, 0, 1</td>
<td>0, 0, 4</td>
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<td>1, 1, 1</td>
<td>3, 5, 4</td>
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<tr>
<td></td>
<td>In Bruch</td>
<td>1, 1, 1</td>
<td>4, 4, 4</td>
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</table>

A summary occurrence of Doppler signals in bidirectional and high-sensitive Doppler tomograms. The values in each cell, from the left, represent the number of eyes in which the Doppler signal was found by grader YJH, that found by MM, and agreement between two graders. N is the number of eyes. Three regions are defined as: (1) an abnormal region anterior to the RPE (above the RPE); (2) a region between the RPE and Bruch’s membrane (RPE-Bruch); and (3) within Bruch’s membrane (in Bruch), in which case, a Doppler signal penetrated through Bruch’s membrane.
the early phase. It would be expected that the feeder vessels can be visualized by bidirectional OCA. In the current study, bidirectional OCA visualized choroidal vessels beneath or close to the PED in three of five PCV eyes to both graders. These choroidal vessels were correlated with the feeder vessels that appeared in early-phase ICGA. This indicates the utility of bidirectional OCA for noninvasive imaging of feeder vessels of PCV.

The high-sensitive OCA of PCV cases visualized the three-dimensional (3D) structure of the BVN and polypoids. It is known that a cluster of abnormal vessels are colocalized in some region beneath the PED and a feeder vessel connects the abnormal vessel cluster and a choroidal vessel.7

The abnormal vessel cluster of PCV has been investigated by structural OCT with an 830-nm probe beam,7 structural high-penetration OCT with a 1-μm probe beam,13 and Doppler OCT with an 840-nm probe beam.29 However, none of them has been used to visualize the comprehensive 3D structure of PCV, including the vessel cluster and the feeder vessel. As exemplified by Figure 7e, high-sensitive OCA has enabled comprehensive visualization of the 3D structure of the PCV, including the vessel cluster and the feeder vessel. This comprehensive investigative ability of high-sensitive OCA can provide a detailed understanding of the pathology.

The appearance of a high-sensitive Doppler en face projection image is generally well correlated with midphase ICGA, as exemplified in Figures 1c and 1f, 2c and 2e, 3a and 3b, 3d and 3e, 4c and 4e, 5b and 5c, 5f and 5g, and 6c and 6f. The CNV appearance with high-sensitive OCA was also similar to that of ICGA. Furthermore, in some cases, such as shown in Figures 4, 6, and 7, high-sensitive OCA provided higher contrast than ICGA.

In the current study, FA images showed leakages in some untreated cases, including one eye with mCNV, four eyes with AMD, and one eye with PCV. The number of leakages was six in total. In all leakage spots, a similar pattern was observed in en face high-sensitive OCA as exemplified in Figures 2b and 2e, 4b and 4e, 5a and 5c, and 7b and 7c. The leakage in FA is an indicator of abnormal penetration of a choroidal vessel into the retina, while the Doppler OCT, and hence OCA, is sensitive to localized motion and selectively contrasts the structure of the blood vessels. Although the leakage is not directly detectable by OCA, its related structural abnormality can be detected. Hence, high-sensitive OCA has indirectly indicated the region of the leakage. Because of the difference in the contrast mechanism, OCA cannot be the full alternative for FA. However, the high correlation between OCA and FA and the noninvasive nature of OCA would make OCA a comparable utility to FA.

While FA and ICGA use fluorescent dye as a vessel contrast agent, HP-OCA uses blood flow as a contrast source. The different vessel contrast mechanism between conventional angiography and HP-OCA would result in different characteristics. FA and ICGA have advantages of time elapse imaging after dye injection and investigation of tissue damage through dye leakage. Conversely, OCA has the two major advantages of 3D investigation and noninvasiveness. The 3D visualization of the ocular vasculature would provide more detailed insight of the pathology. The noninvasiveness enables safe and repetitive application of OCA to the patient. This repetitive examination is particularly useful for the frequent monitoring of the
outcome of treatments. This could provide insights in natural history and response to the treatment of retinal illness. In addition, OCA can be utilized for mass-screening not only for the specific clinical diagnosis and the time-sequence monitoring. Since HP-OCA provides vast amount of information, including a structural OCT volume and two types of Doppler OCT volumes, a conventional static page-oriented patient report is not always convenient for clinicians. Alternatively, a sophisticated data browser is necessary. Figure 8 shows a screenshot of our custom-made HP-OCA browser. It consists of an en face projection image of structural OCT and en face Doppler OCA in its left column, while cross-sectional images of structural OCT, Doppler tomogram, and the Doppler tomogram overlaid on the structural OCT are displayed on the right column. An operator is allowed to quickly find the point of pathology in the en face images. By pointing the position of pathology in the en face images with a line cursor, corresponding cross-sections are displayed in the right column. Hence, the operator can utilize both the structural OCT projection and en face OCA to quickly find the pathologic region. This simultaneous usage of the structural projection and en face OCA reduces the risk of overlooking of pathologies in comparison to a conventional OCT. The operator is also allowed to mark up one of the cross-sectional images. As marking up an image, the same mark simultaneously appears at the same location in the other cross-sectional images. This function enables quick coregistration of structural and Doppler findings. By using a well-designed data browser, such as this HP-OCA browser, the operator can quickly and effectively review the huge amount of information provided by HP-OCA.

In this paper, we demonstrated vasculature imaging of exudative macular diseases by HP-OCA. HP-OCA provided two measurement modes (i.e., bidirectional OCA and highsensitive OCA). With bidirectional OCA, feeder vessels of the PCV were successfully visualized. Conversely, the high-sensitive OCA provided similar angiograms to the midphase of ICGA but with higher contrast. This new modality can be partially utilized as an alternative to FA and ICGA. In addition, the noninvasive and 3D imaging ability of OCA enables wider applications than FA and ICGA.

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References