AMERICAN ACADEMY
OF OPHTHALMOLOGY®

Plexus-Specific Detection of Retinal Vascular Pathologic Conditions with Projection-Resolved OCT Angiography

Rachel C. Patel, MD,[1,2] Jie Wang, MS,[1] Thomas S. Hwang, MD,[1] Miao Zhang, PhD,[1] Simon S. Gao, PhD,[1] Mark E. Pennesi, MD, PhD,[1] Steven T. Bailey, MD,[1] Brandon J. Lujan, MD,[1] Xiaogang Wang, PhD,[1,3] David J. Wilson, MD,[1] David Huang, MD, PhD,[1] Yali Jia, PhD[1]

Purpose: To evaluate the projection-resolved (PR) OCT angiography (OCTA) algorithm in detecting plexus-specific vascular abnormalities in retinal pathologic conditions.

Design: Cross-sectional observational clinical study

Participants: Patients diagnosed with retinal vascular diseases and healthy volunteers.

Methods: Eyes were imaged using an OCT system operating at 840 nm and using the split-spectrum amplitude decorrelation algorithm. A novel algorithm suppressed projection artifacts inherent to OCTA. The volumetric scans were segmented and visualized on different plexuses.

Main Outcome Measures: Qualitative observation of vascular abnormalities on both cross-sectional and en face PR-OCTA images.

Results: Eight illustrative cases are described. In cases of diabetic retinopathy, retinal vessel occlusion, and retinitis pigmentosa, PR-OCTA detected retinal nonperfusion regions within deeper retinal plexuses not visualized by conventional OCTA. In age-related macular degeneration, cross-sectional PR-OCTA allowed the classification of choroidal neovascularization, and, in a case of retinal angiomatous proliferation, identified a vertical vessel contiguous with the deep capillary plexus. In macular telangiectasia, PR-OCTA detected a diving perifoveal vein and delineated subretinal neovascularization.

Conclusions: Application of PR-OCTA promises to improve sensitive, accurate evaluation of individual vascular plexuses in multiple retinal diseases. *Ophthalmology Retina 2017;■:1–11 © 2017 by the American Academy of Ophthalmology*

Although evaluation of retinal vasculature has historically depended on fluorescein angiography (FA), optical coherence tomography angiography (OCTA) has recently been developed as a noninvasive alternative imaging modality. OCTA systems, which harness the variability in reflectance of flowing red blood cells to differentiate vasculature from static tissue, afford 3-dimensional (3D) visualization of the vascular networks and are suitable for quantitative analysis.[1] One of the major limitations of OCTA, however, lies in the presence of flow projection artifact. As the infrared beam interacts with the inner retina, the flowing blood cells in the more superficial vessels cast time-varying shadows on the deeper layers. An algorithm to detect decorrelation misinterprets these shadows as blood flow, thus confounding the 3D interpretation of OCTA.

Our group has proposed a projection-resolved OCTA (PR-OCTA) algorithm that resolves the ambiguity between in situ flow and projection artifact at the level of single volumetric pixels,[2] rather than conventional projection removal by slab subtraction or masking, which was adopted by AngioVue (Optovue, Fremont, CA) and AngioPlex (Zeiss Medical Technology, Dublin, CA) commercial systems. Our method is based on the observation that intensity-normalized projection artifact signal does not exceed the value of the original, more superficial signal. Hence, at each axial position, flow signal peaks are successively analyzed, selectively removing those with lesser values than more superficial peaks. The resulting 3D macular angiogram appears to demonstrates 3 distinct retinal vascular plexuses in the analogous anatomic location described by perifoveal histopathology.[3] Compared with conventional projection removal techniques, en face PR-OCTA better preserves the continuity of the deeper vessels, enabling detailed analysis of individual vascular plexuses.[2]

We present 8 cases of normal and pathologic conditions to illustrate the potential utility of PR-OCTA in research and clinical settings. Visualization of the distinct vascular plexuses can better discern regions of nonperfused retina, classify the depth of invasion of neovascular vessels, and delineate vertical vessels that define certain disease states. With these capabilities, PR-OCTA stands to further our understanding of various disorders and provide valuable information for diagnosis and monitoring of disease progression.

Methods

Participants were enrolled after informed consent was obtained in accordance with a protocol approved by the institutional review

https://doi.org/10.1016/j.oret.2017.11.010
ISSN 2468-6530/17

board at Oregon Health & Science University. This study adhered to the tenets of the Declaration of Helsinki and was conducted in compliance with the Health Insurance Portability and Accountability Act. Patient records were reviewed to identify cases of potential interest with clear media and ability to maintain fixation. In total, 100 healthy subjects and patients with the following conditions were enrolled: diabetic retinopathy (DR; 118 patients), retinal vein occlusion (14), retinal artery occlusion (5), neovascular age-related macular degeneration (62), retinal angiomatous proliferation (10), macular telangiectasia (12), and retinitis pigmentosa (35). To better demonstrate the potential clinical application of this novel OCT methodology, 8 cases with characteristic pathologic and clinical features were selected for this article.

Clinical imaging was acquired, including color fundus photography, en face OCT, and FA. FA was performed by intravenous injection of 10% sodium fluorescein in water with excitation by a 488 nm wavelength laser.

OCTA was obtained using AngioVue, RTVue XR Avanti (Optovue, Inc.), a commercial spectral-domain instrument with a center wavelength of 840 nm and an axial scan rate of 70 kHz. The 3×3 or 6×6 mm scanning region was centered at the fovea. Each volumetric macular data set consisted of 2 orthogonal scans. In both the fast transverse and slow transverse directions, 304 A-scans were sampled; 2 repeated B-scans were obtained at each position before proceeding to the next sampling location.

The AngioVue software uses the split-spectrum amplitude-decorrelation angiography algorithm, which compares consecutive B-scans at the same location to detect flow using motion contrast.[4] Each scan set consists of of 2 volumetric scans: 1 vertical-priority raster and 1 horizontal-priority raster. The AngioVue software uses an orthogonal registration algorithm to register the 2 raster volumes to produce a merged 3D OCT angiogram.[5,6]

The merged volumetric angiograms were then exported for custom processing. Before segmentation the PR-OCTA algorithm was applied to each merged volumetric OCTA scan, as described in detail previously.[2] As the flow projection artifact tends to be intensity dependent, decorrelation values were first normalized to the log amplitude of the OCT reflectance signal. After normalization the projected flow signals were found almost uniformly to demonstrate decreased decorrelation values compared with in situ flow. Hence, by searching for successive greater decorrelation values along each A-line, the PR algorithm was capable of distinguishing true vessels from projection artifact. Decorrelation values at successive peaks were maintained while weaker values were set to zero.

The volumetric angiogram was segmented using a previously described directional graph search approach[7] to identify the boundaries of the inner limiting membrane, inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), and retinal pigment epithelium (RPE)/Bruch membrane. Manual adjustment of the segmentation (<10 minutes) was applied when necessary. En face angiograms were constructed from maximum flow projection within set slabs determined by the segmentation. The superficial vascular complex (SVC) was composed of flow signal from the inner 80% of the ganglion cell complex, which includes all structures between the inner limiting membrane and IPL/INL border; the inner capillary plexus (ICP) from the outer 20% of the ganglion cell complex to the inner 50% of the INL; the deep capillary plexus (DCP) from the outer 50% of the INL and the OPL; the inner retina from the inner limiting membrane to the OPL/ONL border; and the outer retina from the OPL/ONL border to the RPE/Bruch membrane. For different en face plexus angiograms, the display range differs slightly; the decorrelation value range of the inner retina and SVC is from 0.025 to 0.2, and that of the ICP, DCP, and outer retina is from 0.025 to 0.15.

Results

Distinction of the Retinal Vascular Plexuses in the Healthy Eye

A normal human retina contains distinct retinal and choroidal circulations. At the macula, 3 permeating retinal vascular plexuses supply the inner retina, whereas the avascular outer retina is supplied by the underlying choroidal blood flow.[8] In conventional OCTA, the signal from the innermost SVC projects onto the ICP and DCP, such that images of the 2 deeper plexuses contain artificially dense flow signal resembling the SVC (Fig 1B, C). Moreover, projection from the retinal vessels appears in the avascular outer retina (Fig 1D, E), particularly at the level of structurally hyperreflective layers such as the RPE.

Application of PR-OCTA selectively removes projection artifact from the en face views of the ICP and DCP, allowing improved evaluation of deeper capillary morphology (Fig 1G, H). On cross-sectional angiograms, the vertical streaks below superficial vessels are removed, distinguishing the deeper capillary plexuses (Fig 1F). In addition, the algorithm minimizes artificial flow signal within the outer retina on both en face and cross-sectional images to more accurately reflect the avascular state (Fig 1F, I).

Detection of Nonperfusion in Diabetic Retinopathy

Screening for DR and assessing its severity are essential for reducing morbidity related to diabetes. Objective, repeatable, and predictive biomarkers can improve screening and treatment. Macular ischemia is known to correlate with the severity of retinopathy and the risk of progression in DR.[9,10] Although trained graders can qualitatively identify nonperfusion regions using FA, the technique is poorly suited for automated quantification of nonperfusion due to variable contrast from dye leakage or pigmentation. OCTA, with consistently high contrast of capillary details generated by intrinsic flow motion, is better suited for quantified analysis.[11,12] Therefore, the nonperfusion area measured from OCTA has the potential to be a useful biomarker in DR.

Furthermore, OCTA improves on the 2D representation afforded by FA with the potential for a 3D construct of the retinal vasculature. However, projection artifact from superficial vessels hinders separation of distinct vascular layers in conventional OCTA. PR-OCTA resolves these artifacts and allows visualization of the 3 plexuses. In cases of DR, these separate slabs reveal a region of nonperfusion in deeper vascular plexuses (Fig 2G, H), not evident in full-thickness retinal OCTA or FA, nor in three slabs without the PR algorithm applied (Fig 2E, F), thus improving the sensitivity of detecting microangiopathy.[13,14] The advantages of 3D information and consistent contrast amenable to automated quantification merit exploration of a PR-OCTA–derived biomarker in DR.

Assessment of Ischemic Vascular Diseases

After DR, retinal vein occlusion is the second most common vascular disorder causing significant visual impairment, with a