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Visualizing Structure and Vascular Interactions: Macular Nonperfusion in Three Capillary Plexuses

Justin J. Park, BS, Christopher S. Chung, MS, and Amani A. Fawzi, MD

Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago.

Abstract

BACKGROUND AND OBJECTIVE: To assess the relationship between retinal vascular and structural changes in the superficial, middle, and deep capillary plexuses (SCP, MCP, DCP) using optical coherence tomography angiography (OCTA) and en face OCT.

PATIENTS AND METHODS: Patients with diabetic retinopathy were imaged using the Cirrus HD-OCT with AngioPlex. Using manual segmentation of the retinal layers, the authors compared OCTA to en face OCT images to examine corresponding patterns in each of the three capillary plexuses.

RESULTS: Areas of decreased perfusion and capillary dropout on OCTA were found to be associated with three corresponding lesions on en face OCT: hyporeflectivity, cystic edema, and hard exudates. Vascular changes in individual capillary plexuses corresponded with structural changes in their respective perfused retinal layers.

CONCLUSIONS: Using manual segmentation on OCTA, the authors provide a framework to visualize the relationship between vascular pathology on OCTA and structural changes on en face OCT within specific capillary plexuses.

INTRODUCTION

Optical coherence tomography angiography (OCTA) is a rapidly evolving and noninvasive imaging modality that has the ability to visualize blood flow within retinal vessels. Although clinical studies of retinal vasculature have long been performed by fluorescein angiography (FA), injected fluorescein carries well-documented side effects,¹ and imaging is limited to two dimensions without visualization of the deeper retinal capillaries.² In contrast, OCTA offers the distinct advantage of resolving vascular layers of the retina in three dimensions,³ allowing study of the retinal microvasculature in finer detail.

Although OCTA analysis has been applied to a vast array of retinal vascular pathologies, a majority of software for OCTA has limited the retinal capillary analysis to two plexuses: a superficial capillary plexus (SCP) and deep capillary plexus (DCP). However, evidence from anatomical and developmental studies points to a third capillary plexus, the middle capillary

Address correspondence to Amani Fawzi, MD, Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, 645 N. Michigan Ave., Suite 440, Chicago, IL 60611; afawzim@gmail.com.

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plexus (MCP). Along with the SCP and DCP, these three capillary plexuses supply the macula in three neural compartments, with the SCP at the level of the retinal nerve fibers and the MCP and DCP along the inner and outer border of the inner nuclear layer (INL), respectively.^{4–6} The MCP has generally been “hidden” in current OCTA software that incorporates segments of the MCP into either the SCP or DCP angiograms. However, our group has recently shown that with the use of manual segmentation, OCTA can be used to visualize the MCP as a distinct and separate capillary network in healthy patients and patients with diabetes.⁷ This approach provides the exciting opportunity to expand the application of OCTA analysis to three capillary plexuses and study microvascular changes in the retina in finer detail in patients with ischemic states such as diabetic retinopathy (DR).

Distinguishing the three capillary plexuses as separate entities may have important clinical implications, as pathologic states such as disorganization of the retinal inner layers⁸ and paracentral acute middle maculopathy,⁹ which can occur in the setting of diabetic retinopathy, are likely manifestations of ischemia in the SCP and MCP, respectively. Furthermore, recent studies by our group have shown that diabetic capillary nonperfusion, specifically in the DCP, can be associated with photoreceptor and outer retinal disruption on OCT.^{10–12} Thus, imaging the three capillary plexuses as distinct networks can further elucidate the complex and multilaminar manifestations of macular ischemia.

Macular ischemia is a well-established clinical feature of DR, and recent efforts have focused on objective and reproducible methods of quantifying capillary loss and retinal nonperfusion using OCTA, highlighting the importance of this clinical feature in DR.^{13–15} OCTA is a well-suited tool to study vascular changes in eyes with diabetic retinopathy, including vascular abnormalities and changes such as microaneurysms and retinal capillary dropout.^{16,17}

However, despite the well-established role of OCTA in imaging and quantifying nonperfusion in the setting of DR, little is known about the structural changes in retinal tissue that occur secondary to macular ischemia. This gap in knowledge provides the opportunity to explore the relationship between capillary nonperfusion in a specific capillary plexus (SCP, MCP, and DCP) and the corresponding perfused tissue. We used manual segmentation to obtain angio-grams of each capillary plexus and compared areas of nonperfusion on angiograms to structural changes on en face OCT images of retinal tissue. Our study successfully shows that vascular changes on OCTA correlate with structural anomalies in the corresponding en face OCT slabs.

PATIENTS AND METHODS

Participants

This prospective study was approved by the institutional review board at Northwestern University and is Health Insurance Portability and Accountability compliant. Informed consent was obtained from all subjects. All patients in this study had been diagnosed previously with varying stages of DR, ranging from nonproliferative to proliferative. Patients were recruited during their routine ophthalmologic visit and were examined and imaged in

the Department of Ophthalmology, Feinberg School of Medicine of Northwestern University, Chicago, IL. OCTA photographs were taken on the same day of recruitment.

Image Acquisition

Images were obtained on the Cirrus HD-OCT with AngioPlex (Carl Zeiss Meditec, Dublin, CA), which uses an OCT-based microangiography (OMAG) algorithm with an A-scan rate of 68 Khz, center wavelength of 840 nm, and bandwidth of 90 nm. In a 3 mm × 3 mm scan pattern, OMAG is achieved by four repeated B-scans at each position in the slow Y-axis (245 total B-scans) with 245 A-scans per B-scan in the fast X-axis. Real-time tracking is accomplished by scanning laser ophthalmoscope to reduce motion artifacts.¹⁸ In this study, a 3 mm × 3 mm scan area centered on the fovea was chosen. The captured images were exported with a 429 pixel × 429 pixel resolution.

The superficial, middle, and deep capillary networks were segmented post-acquisition on the Cirrus. The segmentation boundaries were manually adjusted to demonstrate the three capillary sublayers as previously reported in our prior study characterizing the MCP on the Optovue device (Optovue, Fremont, CA).⁷ In brief, the SCP was adjusted on the preset superficial plexus window such that the boundaries were set at the preset internal limiting membrane (ILM) to 55 μm above the inner plexiform layer (IPL). The SCP boundaries thus encompassed the nerve fiber layer, ganglion cell layer (GCL), and IPL. The MCP was established using the preset deep plexus setting and adjusting the boundaries to 55 μm and 6 μm above the IPL, thus capturing the INL. Projection removal included in the machine software was also applied to all MCP images to remove projection artifacts of more superficial vessels casting shadows onto the MCP. The DCP was established by adjusting the preset deep plexus layer to 6 μm above to 20 μm below the IPL, capturing the outer plexiform layer (OPL) while activating the projection artifact removal option. This segmentation method is shown in Figure 1.

Image Analysis

For each capillary plexus layer, the corresponding en face structural OCT images were obtained and analyzed for cysts, exudates, and regions of hyporefectivity. The images were imported into ImageJ (National Institutes of Health, Bethesda, MD), an open-source image-processing software, to identify structural findings.¹⁹ Each of the three structural features was then assigned a color in ImageJ to aid in the illustration of these structural pathologies. Black areas on en face OCTs, which included the foveal avascular zone (FAZ) and areas of cystic macular edema, were assigned the color pink. Areas of hyporefectivity appeared as a darker shade of gray relative to normal surrounding tissue and were assigned the color blue. Lastly, areas of exudate were defined as discrete white hyperreflective foci on en face OCT and were assigned the color white. For each eye, the en face OCT and angiogram were then combined into a composite image, with blood vessels assigned the color yellow, and each structural feature on en face OCTs appearing as described. Each composite image in this series combines information relevant to blood flow as well as the adjacent structural changes in the surrounding retinal tissue.

RESULTS

This study included 18 eyes of 10 patients diagnosed with various stages of DR. Qualitative analysis of angiograms and structural OCT images in these eyes revealed three patterns, summarized in Table 1. The first finding is hyporefectivity on structural OCT that corresponds to areas of decreased capillary perfusion, observed in 14 eyes. This hyporefectivity appeared as darker regions on en face OCT, distinct from the surrounding normal retinal reflectivity. This is shown in Figure 2B, in which the blue circle highlights an area of capillary closure matching with an area of hyporefectivity, confirmed by the composite that overlays the two images (Figure 2, bottom row).

We also observed that cystic macular edema on structural OCT corresponded to avascular zones on the corresponding sublayer angiograms in five eyes. On cross-sectional B-scans, cystic lesions could be identified as discrete low reflective spaces that displaced the surrounding normal retinal tissue. Similarly, on structural en face OCT, macular edema formed well-defined circular zones of “homogenous black pixels” distinct from the surrounding normally reflective retinal tissue. This is shown in Figure 3, in which cystic edema, highlighted by pink circles, corresponds to avascular zones in the SCP and MCP. In the composite image, there is a tight correlation between the avascular zones on the angiogram and areas of cystic edema on structural OCT, observed in each of the five eyes.

The third pattern we observed is areas of hard exudates on structural OCT corresponding to areas of decreased perfusion on angiograms in three eyes. Hard exudates are a sign of leakage and loss of the endothelial barrier integrity in DR, leading to the deposition of lipids and proteins within the neural retina.²⁰ Due to their composition, hard exudates strongly scatter light and appear as hyperreflective lesions with sharp borders on OCT.^{21–23} Hard exudates in the current study were thus identified as hyperreflective foci on en face OCT and were not detectable as artifact on angiograms. Notably, retinal zones that contained large numbers of hard exudates on structural OCT correlated with zones of decreased capillary perfusion on the corresponding angiogram. This is shown in Figure 4C, in which hard exudates in the OPL, color-coded white and highlighted by the green circle, correspond to an area of decreased perfusion in the DCP.

DISCUSSION

Using manual segmentation to visualize the three capillary plexuses of the macula, we have shown structural abnormalities on en face OCT that correlated with areas of flow abnormality on OCTA. Specifically, we have found that areas of decreased perfusion and capillary loss on OCTA are associated with three potential lesions on en face OCT: hyporefectivity, cystic edema, and hard exudates.

In areas of decreased capillary perfusion on OCTA, we identified corresponding areas of hyporefectivity on en face OCT, which appeared as darker regions distinct from surrounding tissue on en face OCT. In their study of eyes with various retinal vascular disease, Farinha et al. showed that similar hyporefective OCT areas correspond to intraretinal fluid associated with vascular changes such as nonperfusion and microaneurysms

on FA and OCTA.²⁴ Our study links areas of hyporeflectivity with nonperfusion, specifically in DR, in which we postulate that the decreased reflectivity is related to tissue ischemia. Hyporeflectivity on OCT may also be related to increased retinal tissue thickness. In eyes with DR, Francis et al. showed that localized regions of retinal thickening and thinning corresponded to retinal edema and atrophy, respectively, with regions of increased thickness appearing as reduced reflectivity on OCT.²⁵ Similarly, Wanek et al. also showed structural OCT changes in eyes with nonproliferative DR, including increased thickness of the GCL and IPL and increased reflectivity in the INL.²⁶ Although these previous studies show that OCT reflectance can potentially be used to study retinal tissue integrity in eyes with DR, our study complements this information by combining with depth-resolved OCTA. Specifically, we found that retinal thickness and reflectivity abnormalities correlated to areas of decreased perfusion on OCTA and could be mapped to the relevant depth within the three macular capillary plexuses. For example, abnormal GCL and IPL reflectivity could be matched to corresponding perfusion abnormalities in the SCP, whereas INL disruption corresponded to changes in the MCP, reflecting the metabolic dependence of these retinal layers on the corresponding capillary plexuses.⁷ Thus, areas of hyporeflectivity on OCT may reflect retinal metabolic changes in response to vascular compromise in the corresponding capillary plexuses.

Another feature identified in our study related to zones of cystoid macular edema, which were shown by de Carlo et al. as morphologically distinct from capillary nonperfusion on OCTA. Cystoid spaces were shown to be completely devoid of flow signal with characteristic oblong shape and smooth borders, while areas of capillary nonperfusion had internal flow signal and more irregular borders.²⁷ Our study agrees well with these findings, as macular cysts were identified as distinct oblong hyporeflective lesions on en face OCT corresponding to zones of complete absence of flow on OCTA, evidenced by the overlap shown in composite images (Figure 3). On the other hand, areas of nonperfusion had higher reflectivity on both OCT and OCTA, with poorly demarcated borders, as shown in Figure 2.

Similarly, Mané et al. distinguished cystoid edema as discrete well-demarcated zones devoid of flow from areas of nonperfusion and found these cystoid spaces were often located within areas of nonperfusion, suggesting a possible link between capillary loss and intraretinal edema.²⁸ In the study by Mané et al., cysts were more visible and more numerous in the deeper retina. This finding correlates well with other studies of macular edema. For example, a study by Byeon et al. showed that leakage evident on FA from deeper retinal vasculature, presumably the MCP and DCP, caused edema predominantly in the INL and secondarily in the OPL.²⁹ Cunha-Vaz also showed that diabetic macular edema preferentially localizes to the INL.³⁰ Our study provides additional detail complementing these studies, as areas of cystoid edema were best visualized in the MCP, which was segmented to capture the INL. Whereas cysts were visualized in layers perfused by the SCP and DCP, we observed that the INL/middle retina (supplied by the MCP) showed the most distinct areas of cystic edema, as shown in Figure 3. Our study thus provides evidence to connect the preferential location of cysts in the INL to nonperfusion at a specific capillary plexus, the MCP, a distinction not made in previous studies using automated OCTA segmentations that incorporate the MCP with the other capillaries.

Another feature in our study was related to hard exudates on en face OCT, which aggregated within zones of perfusion abnormality in OCTA, suggesting a possible link between these two pathologic changes. Although color fundus photography has been traditionally used as a highly sensitive tool for evaluating hard exudates, OCT could be used as a reliable tool to evaluate the sublocation of hard exudates in the middle and outer retina.³¹ This is supported by the correspondence between areas of hard exudates on color fundus photographs and areas of hyperreflective foci on SD-OCT, which were most commonly found in the OPL.³² In our study, hard exudates were visualized as hyperreflective foci on structural en face OCT images in deeper retina, specifically in the OPL, which corresponded to DCP abnormalities (Figure 4). As previous studies have suggested that hard exudates may be associated with neuronal element and photoreceptor degeneration in the OPL,^{33,34} our study links the associated disruption to ischemia in a specific capillary plexus. However, further studies are needed to quantify hard exudates in retinal sublayers to more fully assess the relationship to the vascular abnormalities in the DCP.

Our study had several limitations. Notably, our analysis was entirely qualitative and thus did not have quantitative data to further define or support our observations. Our study was also a cross-sectional design, and thus a cause-and-effect relationship between the disease state and pathologic features observed cannot be discerned. Lastly, our study size was relatively small, including 18 eyes, limiting the applicability and scope of our study.

In conclusion, our study illustrates the correlation between OCTA and en face OCT structural images, showing that nonperfused capillaries can be correlated to structural abnormalities at the corresponding retinal sublayer, including hyporefectivity, cystic edema, and hard exudates. This approach provides a framework that links retinal structure to corresponding vascular changes, while resolving these changes to the corresponding macular capillary plexus. Our composite images combine information from OCTA and en face OCT, matching perfusion abnormalities to corresponding structural abnormalities in the multilayered neurovascular retinal tissue. Future studies are needed to assess these patterns across larger patient populations. In addition, we need to develop approaches to quantify the retinal reflectivity changes as well as studies to evaluate the relative functional and visual consequences of these findings.

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Figure 1.

Optical coherence tomography angiography segmentation used to visualize the three capillary plexuses. (A) The superficial capillary plexus (SCP) was set by adjusting the preset superficial plexus window such that the boundaries were set at the preset internal limiting membrane to 55 μm above the inner plexiform layer (IPL). The SCP boundaries thus encompassed the nerve fiber layer, ganglion cell layer, and IPL. (B) The middle capillary plexus (MCP) was established by adjusting the preset deep plexus by setting the boundaries to 55 μm and 6 μm above the IPL, thus capturing the inner nuclear layer. Projection removal included in the machine software was applied to remove projection artifacts from vessels that lie superficially. (C) The deep capillary plexus (DCP) was established by adjusting the preset deep plexus by setting the boundaries to 6 μm above to 20 μm below the IPL, capturing the outer plexiform layer.

Figure 2.

Area of hyporeflectivity corresponding to decreased capillary perfusion in diabetic retinopathy. A to C represent the three capillary plexuses of an eye in a patient with diabetic retinopathy. For each plexus, the optical coherence tomography angiogram (OCTA) is shown along with the corresponding retinal tissue on structural en face OCT. The B-scan shows the segmented layers on cross-section used to image each capillary plexus. Each column shows a composite image in the last row with OCTA flow in yellow, areas of hyporeflectivity in blue, and areas devoid of flow in pink. (A) The superficial capillary plexus (SCP) shows healthy retinal vasculature with an appropriate area devoid of flow in the foveal avascular zone (FAZ). (B) The middle capillary plexus (MCP) shows areas of decreased perfusion highlighted by the blue circle around an area of capillary thinning with corresponding area of hyporeflectivity on structural en face OCT. On the composite image, the area of blue matches the area of capillary thinning to hyporeflectivity. (C) The deep capillary plexus (DCP) does not show the same area of hyporeflectivity as the MCP, with an expected area of avascularity in the FAZ.

Figure 3.

Areas of cystoid macular edema corresponding to capillary dropout in diabetic retinopathy. A to C represent the three capillary plexuses of an eye in a patient with diabetic retinopathy. For each plexus, the optical coherence tomography angiography (OCTA) is shown along with the corresponding retinal tissue shown on structural en face OCT. The B-scan shows the segmented layers on cross-section used to image each capillary plexus. Each column shows a composite image in the last row with OCTA flow in yellow, areas of hyporeflectivity in blue, and areas devoid of flow in pink. (A) The superficial capillary plexus (SCP) shows a black area devoid of flow highlighted by the pink circle. On the structural en face OCT, there is a corresponding area of black reflecting an area of edema. In the composite image, the area of capillary dropout corresponds to the black area on OCT. (B) The middle capillary plexus (MCP) similarly shows a different area of capillary dropout, with pockets of edema shown on structural OCT again highlighted by a pink circle. The areas of edema again correspond to areas devoid of flow in the composite image. (C) The deep capillary plexus (DCP) does not show distinct areas of edema but rather shows projection artifacts of the edema in the more superficial MCP and SCP.

Figure 4.

Area of hard exudates corresponding to decreased capillary perfusion in diabetic retinopathy. A to C represent the three capillary plexuses of an eye in a patient with diabetic retinopathy. For each plexus, the optical coherence tomography (OCT) angiogram is shown along with the corresponding retinal tissue shown on structural en face OCT. The B-scan shows the segmented layers on cross-section used to image each capillary plexus. Each column shows a composite image in the last row with OCTA flow in yellow, areas of hyporeflexivity in blue, and areas devoid of flow in pink. A and B show the superficial and middle capillary plexuses (SCP and MCP), respectively. C shows the deep capillary plexus (DCP) with areas of hyperreflectivity in the structural OCT representing hard exudates. This area of hard exudates, highlighted by a green circle, corresponds to an area of decreased capillary perfusion in the angiogram. In the composite image, the hard exudates, shown in white, are shown to reside in an area with decreased capillary perfusion.

TABLE 1

Summary of Demographic Subject Data and En Face OCT Findings

Case #, Age, Sex	DR Stage	Eye	Hyporeflectivity	Cystic Macular Edema	Hard Exudate
1, 41, M	NPDR	OD OS			X X
2, 62, M	PDR	OS	X		
3, 33, F	NPDR	OD	X		
4, 30, F	NPDR	OD OS	X X		
5, 51, F	PDR	OD OS	X	X	X
6, 52, F	PDR	OD OS	X X		
7, 53, M	NPDR	OD OS	X	X	
8, 71, M	PDR	OD OS	X X	X X	
9, 68, F	PDR	OD OS	X X		
10, 39, M	NPDR	OD OS	X X	X	
Total		18	14	5	3

M = male; F = female; DR = diabetic retinopathy; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; OD = right eye; OS = left eye