Review Article

The applications of optical coherence tomography angiography in diabetic retinopathy

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Abstract: Optical coherence tomography angiography (OCTA), an extent function of traditional optical coherence tomography (OCT), is a non-invasive, high-resolution imaging system designed to display vascular networks. The fundamental principle of OCTA is to achieve the signal of blood flow based on the analysis of complex OCT signal, amplitude of OCT signal or phase of OCT signal. OCTA can display and monitor the vascular abnormalities in patients with diabetic retinopathy (DR), including microaneurysms, vessel density (VD), nonperfusion, neovascularization, and other lesions. OCTA offers a new and potential horizon in the monitor of the DR progress and evaluation of DR treatment.

Keywords: Diabetic retinopathy; optical coherence tomography (OCT); angiography; optical coherence tomography angiography (OCTA)

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Diabetes is one of the most common diseases in the world and affects about 6% of the world's population. The estimated cases of diabetes will keep on rising and almost double in year 2030 compared to year 2000. There will be 30 million diabetic patients in USA and more than 40 million in China in 2030 (1). Diabetic retinopathy (DR) is one of the most common complications of type 1 or type 2 diabetes. According to WHO 2002 census, 1.8 million blindness cases have been reported due to DR (2).

DR is the most common cause of blindness in the working-age population (3). Therefore, the early diagnosis, prompt prevention and treatment are very important for patients with DR. According to the severity and clinical progress, DR can be graded into two periods, nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) characterized by the presence of neovascularization (4). Monitoring the severity scales of DR guides treatment and indicates prognosis.

Rise of OCT angiography

The grading of DR severity can be based on certain fundus images and the pathological changes of DR are now better visualized than before. As we all know, fundus photography (FP) is most commonly used to grade DR severity (ETDRS study). It is easy, cheap, non-invasive, but fails to show vessel leakage and nonperfusion area. Fluorescein angiography (FA) can visualize leakage, nonperfusion and vessel abnormalities to guide treatments. However, FA is invasive and requires intravenous dye injection, which can cause anaphylaxis side effects.

Optical coherence tomography (OCT) provides instant, depth-resolved and direct imaging of live eye tissue based on low-coherence interferometry. Without ionizing radiation, OCT has been widely used to obtain detailed morphology of the retina (5). However, it cannot display and identify retinal vascular abnormalities.

In order to visualize vascular structures, many techniques

have been devised to measure blood flow, such as ultrasound technique, blue field entoptoscopy, and laser Doppler velocimetry (6,7). However, these techniques are restricted for widely clinical use because of the poor reproducibility, difficulty of application and large variation in parameters of blood flow among human beings. Considering the commonly use of OCT system in ophthalmology, researchers have improved contrast to identify the signal of blood flow from periphery tissues and explored the traditional OCT to the OCT angiography (OCTA) successfully. OCTA not only inherits the non-invasive depth-resolved features in living tissues with high resolution of traditional OCT, but also can identify retinal vascular abnormalities which traditional OCT is unable to do (8).

The intrinsic principles of OCT angiography are based on complex OCT signal, amplitude of OCT signal, or phase of OCT signal (9,10). Angiography of complex OCT signal is captured by the related changes between signal frequency and phase, mainly by the Doppler Effect and backscattering. An algorithm called optical angiography (OAG) technique, and later an algorithm known as ultrahigh sensitive optical microangiography (OMAG) have been developed to distinguish blood flow from background (11,12); By analyzing the spatial and temporal statistics of speckle patterns, Enfield *et al.* (13) have proposed an intensity-based algorithm called correlation mapping to differentiate vessels from static tissues. Another algorithm named split-spectrum amplitude-decorrelation angiography (SSADA) is proposed by Jia *et al.* to improve signal-to-noise in the axial direction (14). Flow information can also be obtained by calculating differences in phase between consecutive scans, so the use of phase variance between adjacent B-scans has been made in an OCTA system with an A-scan rate of 25 kHz to the analysis of vessel structures (15). To reduce eye motion artifacts and increase the scanning area, a faster A-scans rate system has been proposed to OCTA (16).

OCTA is used as an en face imaging modality in clinical practice (17), similar to the presence of FA and indocyanine green angiography (ICGA), but it can visualize 3-dimensional image sets of vascular plexuses at different depths from internal limiting membrane (ILM) to choroid. In most studies, OCTA is used to segment retinal capillary network into two parts, the superficial capillary plexus (SCP) in the level of retinal nerve fiber (NFL) and deep capillary plexus (DCP) in the level between inner nuclear layer (INL) and outer plexiform layer (OPL) (18). When needed, different layers of choroidal vasculature are also able to be clearly visualized by OCTA (19,20), while these different layers of choroidal vasculature could not be displayed by ICGA.

Compared to OCTA, the intravenous fundus angiography such as FA and ICGA has the risk of causing allergic adverse effects during intravenous injection (21,22), and cannot display the details of the deep vessel structures (23). Therefore, OCTA offers a relatively safe, easy and less time-consuming method to generate stratified vascular structural images (9,24). OCTA has been used to detect many fundus vascular abnormalities now, including retinal vein occlusion (RVO) (25), exudative age-related macular degeneration (AMD) (26), polypoidal choroidal vasculopathy (PCV) (27), and diabetic retinopathy (DR) (28). In this review, we summarize the use of OCTA in detecting most vascular abnormalities in DR, such as microaneurysms, nonperfusion, and neovascularization (29).

Applications of OCTA in diabetic retinopathy

Due to heterogeneity among human beings, the exact segmentation criterion of SCP and DCP varies from different studies. The vessel layer between 3 μm beneath the ILM and 15 μm beneath the INL is usually considered as SCP, and the vessel layer between 15 μm beneath the INL and 70 μm beneath the INL is considered as DCP (24,30). Park *et al.* (31) have found the middle capillary plexus (MCP) between SCP and DCP is qualitatively and functionally distinct from SCP and DCP in patients with DR. However, this MCP is not widely adopted yet.

Display of microaneurysms

Microaneurysms are identified as focally dilated and abnormally shaped capillaries in SCP and/or DCP in OCTA images (30,32). Because information in depth is unable to be precisely displayed in FA, researchers have utilized OCTA to identify the distribution of microaneurysms and found that microaneurysms in DCP in patients with DR are more than those in SCP (32,33), similar to the study result of donor eyes from patients with DR (34).

The compatibility between OCTA and FA in demarcating microaneurysms is uncertain among studies. Schwartz *et al.* (35) fail to find the complete correspondence in the depicted microaneurysms between FA and OCTA images. Some microaneurysms-like patterns observed in FA are not shown in OCTA, and vice versa (30,32). Hence, two approaches should complement each other to overcome their own deficiencies in demarcating

microaneurysms. Hyperfluorescent dots surmised to represent microaneurysms on FA may be small tufts of neovascularization extending above ILM (36), or just focal leakage (32). On the other hand, the process of recanalisation and sclerosis in microaneurysms makes OCTA hard to detect their flood signal by turbulence and slow flow (37).

Display of neovascularization

OCTA not only provides high-resolution imaging of vascular structures of neovascularization, but also reveals detailed information about depth. With the settings to project vasculature above the ILM in OCTA, de Carlo *et al.* (38) have visualized preretinal neovascularization in eyes of patients with PDR. The further distribution analysis proves that almost all the neovascularization is adjacent to retinal capillary nonperfusion and half occurs close to intraretinal microvascular abnormalities.

OCTA is equivalent in demarcating neovascularization images with FA. Studies have shown that OCTA has the ability to detect almost all the neovascularization determined by FA in the posterior area of retina (39,40). Apart from the allowance of a better visualization than FA in neovascularization (39), OCTA can be easily and safely applied on patients consecutively to monitor the disease progression when frequent fluorescein dye injection is apparently not cost-efficient and convenient. OCTA has been used to quantify the changes of the neovascularization at the disc (NVD) in a case of 32-year-old patient with PDR at the time of 2, 4 and 8 weeks after intravitreal anti-vascular endothelial growth factor (VEGF) injection (32), while OCTA cannot show the leakage of neovascularization like FA. Since OCTA is a transformative approach based on blood flow, the decreased activity of blood flow in neovascularization detected by OCTA does not always indicate the disappearance of its vessel structures (32).

Monitor of retinal vessel density (VD) in perifoveal region

FA is incapable of measuring accurate deep VD. More details of superficial and deep retinal vessels can be clearly seen in OCTA images scanned in 3 by 3 mm, while, artifacts may confound images quality and accuracy. Projection artifacts, caused by encountering tissues below the detected vessels which refract, absorb and scatter the detection beam to various degrees (41), make the SCP images superimposed on the DCP images (42-45). It may also have image artifacts caused by eye emotions or poor eye vision (46,47).

Using generated en face retinal vascular images by OCTA, researchers find that the VD of both SCP and DCP in perifoveal region of patients with DR is lower than those of normal individuals, and declines further along with the progress of retinopathy severity, leading a repeatable method at monitoring the progress of DR (43-45,48). Measurement of the VD also shows high reproducibility and repeatability. Although both SCP and DCP are affected in patients with DR compared with normal controls, the mean VD of SCP in patients with DR is significantly lower than that of DCP (45,48), consistent with the recent studies which suggest that nonperfusion area in SCP tends to be larger than area in DCP (30,32). OCTA makes it possible to assess the two main layers of the retinal capillaries noninvasively and easily in monitoring the progress of DR in patients.

Monitor of foveal avascular zone (FAZ)

Surrounded by capillaries, FAZ is a specific capillary-nonvisible zone where central fovea provides high-resolution vision. OCTA can display the FAZ zone more clearly than FA. Using OCTA, the enlargement of FAZ area in patients with DR has been reported in almost all the related studies (44,48-51) and is deduced by the degradation of capillaries (48,49). OCTA can be also used to assess longitudinal parameters of FAZ. Measurement of FAZ parameters (area, perimeter, circularity index) conducted by OCTA and FA shows no significant variance in patients with vascular abnormalities (including patients with DR) (52).

However, recent studies have not found the correlation between the enlargement of FAZ and visual loss (46,53). Substantial inter-individual variance in dimensions makes the FAZ area not suitable for predicting visual acuity of patients with DR (49).

Monitor of nonperfusion area in the posterior retina

Retinal nonperfusion areas can be visualized by FA or OCTA as capillary-nonvisible areas between the relatively large retinal vessels. Through measurement by OCTA, two independent research groups find that nonperfusion area in SCP tends to be larger than area in DCP (30,32). Generally, OCTA is able to detect nonperfusion areas in the posterior

area of retina identified by FA. However, some of the nonperfusion areas not detected on FA are better delimited on OCTA (30,32,43). The weighted kappa between conventional FA and OCTA by grading diabetic macular ischemia in SCP indicates a moderate agreement (49).

OCTA allows the measurement of nonperfusion-related parameters in various layers. A retrospective study calculates the capillary perfusion density values of SCP, DCP, and choriocapillaris in both patients with DR and normal controls using the OCTA (19), and demonstrates that the decrease rate of perfusion density values may be related to the severity of DR, suggesting an objective method to evaluate the progress of DR (54). However, image acquisition area, usually scanned in 3 by 3 mm or in 6 by 6 mm, is relatively small for the generation of nonperfusion area extended to the peripheral retina (32,55).

Evaluation of diabetic macular edema (DME)

DME is characterized by fluorescein leakage from certain capillary areas, possibly surrounded by hard exudates (56), which OCTA is unable to detect. Generally, OCTA is not used to observe DME solely, but it has the ability to identify DME (57).

OCTA does not access leakage whereas FA does. Leakage in FA may blur the view on the one hand, but it could characterize DME on the other. However, OCTA is still capable of identifying DME, measuring retinal thickness like traditional OCT. What is more important, OCTA can additionally explore the correlation between DME and vessel abnormalities. The studies demonstrate that the mean VD in patients with DME is significantly lower than patients without DME (45,48). Whether DME is a risk factor or a result of lower VD needs a longitudinal study following up patients with DR by OCTA. Moreover, DME might be evaluated indirectly by OCTA through the evaluation of FAZ dimensions and nonperfusion areas in perifoveal region, since FAZ dimensions are strongly positively correlated with the severity of capillary nonperfusion (58,59), and macular ischemia is a risk factor for DME at the meantime (20,60,61).

Conclusions

OCTA is a novel and non-invasive method which can quickly show retinal vessel networks, nonperfusion area and retinal thickness with high-resolution. OCTA owns some important roles of both FA and OCT, and it will be a very promising tool for monitoring the progress of DR.

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Footnote

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