Optical Coherence Tomography Angiography: A New Tool in Glaucoma Diagnostics and Research

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Abstract

Optical coherence tomography angiography (OCTA) is a new modality in ocular imaging which provides high resolution view of the vascular structures in the retina and optic nerve head. This technology has the advantages of being noninvasive, rapid and reproducible. OCTA is becoming a valuable tool for evaluating many retinal and optic nerve diseases. This article provides a brief introduction to the technology and its application in the field of glaucoma diagnostics.

Keywords: Angiography; Glaucoma; Optic Nerve; Optical Coherence Tomography Angiography

Glaucoma is a major cause of blindness around the globe; however, its physiopathology is not fully understood and many diagnostic and therapeutic challenges remain. A vascular etiology for glaucoma has been suspected for many decades.[1-4] Various findings such as optic disc hemorrhage, presence and enlargement of peripapillary atrophy, higher prevalence of vasospastic phenomena like migraine and Raynaud's syndrome and the possible effect of nocturnal hypotension point to a role for vascular dysregulation in development of glaucoma and its progression.

Various devices have been explored to investigate blood flow in glaucoma patients including laser Doppler flowmetry (LDF),[5] laser speckle flowgraphy (LSFG),[6] ultrasonic Doppler imaging of the retrobulbar blood flow,[7] retinal fluorescein and indocyanine green angiography (FAG/ICGA),[8,9] Heidelberg retinal flowmetry (HRF),[10-12] and most recently optical coherence tomography angiography (OCTA). Most of the studies using available technologies demonstrated reduced blood supply in the optic nerve and peripapillary retina of glaucoma patients and some confirmed a correlation between severity of the disease and the degree of hemodynamic disturbance.[13-17]

Principles of Optical Coherence Tomography Angiography

Optical coherence tomography angiography is an emerging technology, with the potential to lead to a paradigm shift in glaucoma diagnostics. A major advantage of OCTA is that the hardware and software are already available on many current versions of SD-OCT devices. Many newer, high-speed spectral domain OCT devices could be upgraded by installing the required software. Optical coherence tomography

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angiography uses the same light source and recording elements as that of structural OCT; however, since the OCTA measures dynamic changes in OCT data to extract blood flow parameters, higher scanning rates, speed and resolution are needed. There are many algorithms currently available for OCTA.[18] One of the most widely used is the Split-Spectrum Amplitude Decorrelation Angiography (SSADA) algorithm.[19] This algorithm measures variations in the amplitude of the returning OCT signals on consecutive images, recorded at very high speed, from the same location. Typically, static tissues such as neuronal elements in the retina have a constant amplitude on the reflected OCT signal and therefore, variations over time on repeated scans are minimal. However, moving elements, such as blood cells in the vessels, result in variations of the amplitude of the returning OCT signal on repeated measurements at any single point. In technical terms, the correlation between the amplitude of the returning signals is high for static tissue and low for moving structures. Decorrelation is defined as "*1 – Correlation*", so the dynamic tissues have a high decorrelation value.[19] Another aspect of the SSADA algorithm is the splitting of spectrum. As mentioned earlier, OCTA require high speed imaging of any single point to extract the changing amplitude and decorrelation data. Some prototype OCT devices in research labs have scanning speeds up to 400,000-1,000,000 scans/second (400-1,000 KHz).[13,20] These ultra-high speed devices can produce high-quality OCTA images with a very short scanning time. However, the currently available commercial devices have scanning rates in the range of 70-150 KHz. To compensate for these relatively lower scanning speed, the SSADA technique takes advantage of splitting the full spectrum wavelengths into several (4-12) smaller bandwidths. This way, the number of possible comparisons for each scan is multiplied.[19,21] Although this approach reduces the axial resolution of the image, the transverse resolution remains almost unchanged. Indeed, reduction of axial resolution is a desired phenomenon, as it reduces the artifact of axial eye movements caused by the pulsation of large retrobulbar blood vessels. Finally, to improve signal-to-noise ratio and enhance image quality, the device carries out multiple scans (usually more than 200 scans) in orthogonal horizontal and vertical directions and averages the data to yield high quality images. The imaging typically can be performed in 2-3 seconds.

Using ultrahigh scanning speed and eye tracking, OCTA could have very high resolution and detect fine capillary networks. The technique does not require any contrast media and could be easily fitted into the workflow of a busy clinical practice. Moreover, the technique has very good repeatability and reproducibility and provides valid data for intersession comparisons.[13,22,23] Another major advantage of the OCTA over other angiographic methods is that it can provide depth data and can segment the vascular layers in slabs of varying thicknesses [Figure 1].

Optical Coherence Tomography Angiography and Glaucoma

During the past few years, a rapidly growing body of evidence has accumulated on the potential role of OCTA in glaucoma diagnosis. Various vascular parameters have been investigated in glaucoma suspects and established glaucoma patients including vascular density in the optic nerve head,[15,24] flow index of the optic disc,[13] vascular density in the peripapillary retina,[16,25] and vascular density in the macula.[26] Moreover, various segmentation algorithms have been used to estimate the density of blood vessels in different anatomical locations in glaucoma patients. Almost all published articles demonstrated a significant reduction of blood flow, capillary diameter and vascular density in glaucomatous eyes. Interestingly, these differences were detectable even in glaucoma suspects and eyes with preperimetric glaucoma and increased proportional to the severity of glaucoma damage.[16,27–37] A few studies demonstrated temporal (time-related) and spatial correspondence between a decrease in vascular density and capillary dropout and visual field and retinal nerve fiber layer (RNFL) loss.[15,17,27,28] Some studies suggested a higher correlation between vascular indices and functional (visual field) data compared to thickness parameters.[13,17] In one of the largest study to date (261 eyes), Yarmohammadi and colleagues showed that mean peripapillary and whole optic disc cube vascular density were significantly lower in open angle glaucoma (OAG) eyes than glaucoma suspects or healthy eyes after adjusting for patients' age.[17] In this study, whole image vascular density had the highest area under receiver operating curves (AUC) for differentiating glaucoma from healthy eyes (AUC = 0.94 compared with 0.92 for average RNFL thickness). Another study reported similar diagnostic accuracy for peripapillary vessel density measured by OCTA and peripapillary
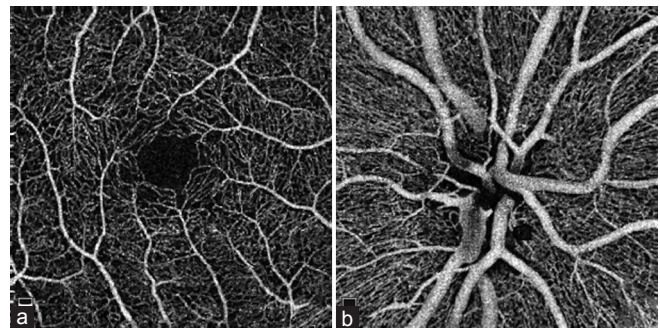

Figure 1. Representative images of macular (a) and optic nerve head (b) vasculature, from an optical coherence tomography angiography (OCTA) device (OCT RT XR Avanti with the AngioVue software, OptovueInc Fremont, CA, USA).

RNFL for detecting glaucoma.[16] Wang et al reported a significantly lower disc flow index and vessel density in 62 eyes with OAG compared to 20 healthy eyes.[14] It is remarkable that in OAG eyes, disc flow index and vessel density had a significant correlation with visual field mean deviation, peripapillary RNFL thickness and macular ganglion cell complex (GCC) thickness.[14]

A few recent studies demonstrated alterations in macular circulation in glaucoma, especially in eyes with central visual field loss. Xu et al reported decreased macular vascular density in eyes with POAG compared to healthy eyes.[26] The authors reported that for each standard deviation (SD) decrease in macular vessel density, total and inner macular retinal thickness diminished by 1.5% and 4.2%, respectively. Moreover, given a reduction of macular vessel density by one SD, visual field mean sensitivity (MS) and pattern standard deviation (PSD) decreased by 13% and 34%, respectively. The authors also reported a spatial correlation between decreased vascular density and location of hemifield defects. Kwon et al also demonstrated that perifoveal microvascular alterations could be detected in glaucomatous eyes with central visual field defects.[23] The investigators measured foveal avascular zone (FAZ) area and circularity in the macular superficial vascular plexus with Cirrus HD-OCT angiography. Foveal avascular zone area was related to severity of visual field loss and FAZ circularity was associated with presence of central visual field loss in multivariate models taking into account the effect of age, gender, intraocular pressure and macular ganglion cell/inner plexiform layer (GCIPL) thickness. In patients with central hemifield defect, the FAZ was expanded in the corresponding hemimacula and there was a spatial relationship between the vascular and functional changes. Table 1 summarizes the current literature on application of OCTA in glaucoma. Figure 2 is a representative image demonstrating drop-off of peripapillary radial capillaries (PRC) with advancing glaucoma damage.

There is significant controversy whether vascular attenuation and dropout is a consequence of ganglion cell loss and reduced blood supply demand or if the vascular changes predate RGC loss and have a causative role. Future longitudinal studies may elucidate whether vascular changes precede structural damage.

Optical Coherence Tomography Angiography and other Diseases

OCTA has many applications in various retinal disorders, such as age-related macular degeneration,[21,38-42] diabetic retinopathy,[20,21,43-46] retinal vasoocclusive disorders (branch and central retinal arterial and venous occlusion),[47-49] ocular tumors (mainly uveal melanoma),[50-52] macular telangiectasia,[53,54] and retinopathy of prematurity.[55,56] One major advantage of this technology is that it can
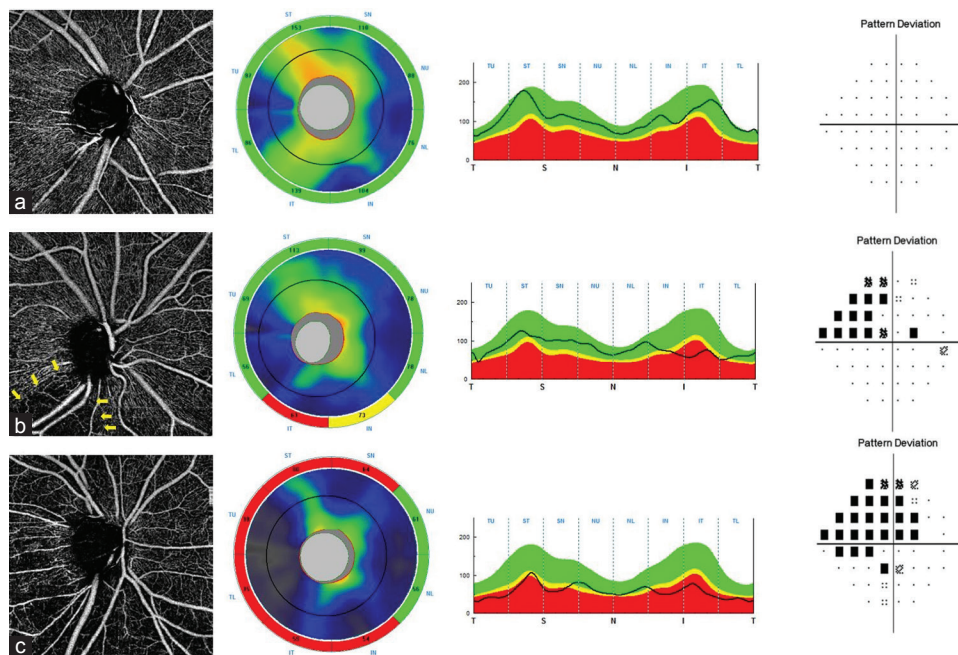

Figure 2. Three representative examples of optical coherence tomography angiography (OCTA) of the optic nerve head (left column) along with corresponding structural OCT images (middle 2 columns) and pattern deviation plots from standard achromatic perimetry (right column). (a) Normal eye: note the compact capillary network around the optic nerve head. (b) Glaucomatous eye with localized damage in the inferotemporal sector. Marked capillary drop-off is obvious on OCTA and is demarcated with yellow arrows. There is a corresponding inferotemporal retinal nerve fiber layer (RNFL) loss and a superior nasal step. (c) Glaucomatous eye with widespread damage. There is a diffuse reduction in vascular density around the optic nerve head. Accordingly, there is widespread RNFL loss and severe visual field loss.

Table 1. Summary of available literature on application of optical coherence tomography in glaucoma evaluation

Investigators	Year of publication	Major findings
Jia Y, et al[19]	2012	First report on OCTA: ONH perfusion was significantly lower in 3 preperimetric glaucomatous eyes compared to 3 normal eyes
Jia Y, et al[13]	2014	A dense microvascular network was visible in the optic disc in the normal group (24 eyes), whereas it was attenuated in 11 glaucomatous eyes. Glaucoma eyes had a significantly lower DFI. DFI was highly correlated with visual field PSD
Liu L, et al[22]	2015	Microvascular network around ONH demonstrated both global and focal attenuation in 12 glaucoma eyes when qualitatively compared with 12 normal eyes. On quantitative assessment, peripapillary vessel density and peripapillary flow index were lower in glaucomatous eyes and were significantly correlated with visual field PSD
Wang X, et al[14]	2015	Vessel density and DFI were significantly lower in 62 OAG eyes than 20 normal eyes. In glaucomatous eyes, vessel density and DFI were significantly correlated with RNFL and GCC thickness and visual field MD.
Akagi T, et al[15]	2016	In 60 POAG eyes with glaucomatous hemifield defect, peripapillary vessel density was significantly reduced in the area corresponding to visual field loss and correlated with total deviation values in the affected hemifield. There was a significant, but lower and less uniform correlation between optic disc vessel density and visual field loss
Bojikian KD, et al[29]	2016	Optic disc perfusion in the prelaminar region was significantly lower in POAG (30 eyes) and NTG (31 eyes) compared to normal group (28 eyes). This parameter was significantly correlated with visual field MD and PSD and ONH rim area. There was no significant difference between POAG and NTG eyes
Chen CL, et al[30]	2016	Prelaminar ONH perfusion (flux, normalized flux and vessel density) was significantly lower in 21 glaucomatous eyes than 20 normal eyes. In glaucoma eyes, prelaminar perfusion correlated with disease severity and structural changes
Ichiyama Y, et al[28]	2016	Capillary dropout correlated spatially with RNFL defects and visual field loss in 3 glaucomatous eyes
Kumar R, et al[31]	2016	Vascular parameters (including vessel density and the space between large vessels) were significantly different between 74 normal, 28 preperimetric and 171 perimetric glaucoma eyes. Vascular parameters had better discrimination ability than structural parameters
Lee EJ, et al[32]	2016	Peripapillary vascular impairment, defined as decreased microvascular density, was detected in 100% of 98 POAG eyes and none of the 45 healthy eyes. This finding was spatially correlated with RNFL defect location
Leveque PM, et al[24]	2016	Total and temporal ONH vessel densities were significantly lower in 50 glaucomatous eyes compared to 30 normal eyes. The vessel densities correlated significantly with rim area, RNFL and GCC thickness, and visual field MD or VFI
Rao HL, et al[25]	2016	Peripapillary vessel density, especially in inferotemporal sector, had good diagnostic ability to differentiate 63 POAG and 49 PACG eyes from 48 normal eyes. Diagnostic performance was comparable to peripapillary RNFL thickness in both types of glaucoma
Rao HL, et al[27]	2016	Vessel density parameters had moderate diagnostic ability to differentiate 64 POAG eyes from 78 normal eyes. Peripapillary vessel density had significantly better diagnostic ability than ONH and macular vessel density. The diagnostic ability improved with increasing disease severity
Scripsema N, et al[33]	2016	Perfused peripapillary capillary density was significantly lower in 40 POAG and 26 NTG eyes compared to 26 normal eyes. This parameter correlated with visual field MD and PSD and average RNFL thickness in glaucoma eyes

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Investigators	**Year of publication**	**Major findings**
Suh MH, et al[34]	2016	Peripapillary microvascular dropout was seen in 52% of 37 POAG eyes. This finding was associated with more advanced glaucoma, defects in lamina cribrosa, reduced superficial vessel density in RNFL, thinner choroid and lower diastolic blood pressure
Suh MH, et al[35]	2016	In 41 glaucomatous eyes with focal lamina cribrosa defects, circumpapillary vessel density was significantly lower than 41 glaucoma eyes without such a defect. This difference was significant after matching for disease severity
Xu H, et al[26]	2016	Macular capillary density was lower in 68 POAG eyes compared to 31 normal eyes. Macular capillary density correlated with inner retinal thickness and severity of visual field damage
Yarmohammadi A, et al[17]	2016	In a cohort of 31 healthy subjects, 48 glaucoma suspects and 74 glaucoma patients, microvascular network in peripapillary RNFL was denser in normal eyes compared to glaucoma suspects and glaucomatous eyes. The vessels density highly correlated with visual field MD and this association was stronger than that of RNFL or rim area and MD
Yarmohammadi A, et al[16]	2016	Peripapillary and whole image vascular density measured by OCTA had similar diagnostic accuracy to peripapillary RNFL thickness measurement for detection of glaucoma eyes in a sample of 261 eyes
Chihara E, et al[36]	2017	Peripapillary vessel density and prelaminar flow index were significantly lower in 66 POAG eyes than in 25 normal eyes. Peripapillary RNFL thickness performed better for discriminating POAG from normal eyes
Lee EJ, et al[37]	2017	Peripapillary capillary density was significantly lower in affected eyes of 11 unilateral NTG patients compared to unaffected eyes of the same patients and 11 eyes of healthy subjects. Retinal capillary network was compromised in the area corresponding to RNFL defect. In these cases, choroidal and ONH vessels did not show apparent changes
Kwon J, et al[23]	2017	FAZ circularity demonstrated a significant association with presence of central visual field loss in 78 OAG patients with central or peripheral visual field damage and FAZ area was correlated with the severity of central field loss. There was a spatial correlation between the hemimacula showing enlarged FAZ and the hemifield with field loss

DFI, disc flow index; FAZ, foveal avascular zone; GCC, ganglion cell complex; NTG, normal-tension glaucoma; ONH, optic nerve head; OAG, open-angle glaucoma; POAG, primary OAG; PSD, pattern standard deviation; MD, mean deviation; RNFL, retinal nerve fiber layer; VFI, Visual Field Index

provide depth information and precisely differentiate various types of choroidal neovascularization.[57]

Beside ophthalmology, OCT and OCTA have also found their way into other fields of medicine. In cardiology, OCT is used for evaluation of thrombotic plaques, atherosclerotic plaques, and intravascular stents.[58-62] In neuroscience, OCTA has been proposed as a means for evaluating stroke, traumatic brain injuries and subarachnoid hemorrhage.[63] In dermatology, OCT has become a popular tool for evaluation of various skin disorders in the clinic[64-68] and OCTA is used for exploring vascular skin lesions.[69,70]

Limitations

Despite its promising features and strengths, OCTA is a rather new technology and is still evolving. In its current state, OCTA has limited resolution and field of view. Increasing the field of view would dramatically decrease image resolution. The best image resolution is attained with a 3 × 3 mm measurement area; however, montage images could be easily produced using the available software to create wide-field OCTA images.[21] At current scanning speed, OCTA is highly vulnerable to various artifacts, such as motion artifacts, shadow artifacts from superficial vessels and vitreous opacities, artifacts from pigment epithelial detachments, and blinking artifacts. Importantly, OCTA cannot detect vascular leakage.

Future Horizons

With the current rapid pace of innovations in OCTA, ultra-high speed OCTA, perhaps with multiple laser sources (including swept-source laser), would be available in near future. Moreover research is actively

being carried out to create some form of noninjectable, "inducible" contrast to enhance OCTA images.[71]

SUMMARY

Optical coherence tomography has emerged as the most widely used imaging modality in the field of Ophthalmology. Optical coherence tomography angiography is a further advancement in the spectrum of OCT imaging modalities and has widespread applications in many ocular conditions, including glaucoma. It is expected to lead to a paradigm shift in glaucoma diagnostics in near future.

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Conflicts of Interest
There are no conflicts of interest.

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