Available online at www.sciencedirect.com

ScienceDirect

Journal of Current Ophthalmology 29 (2017) 1−4

http://www.journals.elsevier.com/journal-of-current-ophthalmology

Editorial

Optical coherence tomography angiography of the retina and choroid; current applications and future directions

Keywords: Age-related macular degeneration; Diabetic retinopathy; Optical coherence tomography angiography; Retinal vascular occlusion; Central serous chorioretinopathy

Dye-based angiography has been the standard of care for the diagnosis of retinal, choroidal and optic nerve vascular disorders for a long period of time. Since its introduction in 1961, angiography techniques and instrumentation have remarkably improved.[1] These advancements include, but are not limited to, the development of confocal scanning laser ophthalmoscopy, digital angiography, and wide-field imaging techniques. However, dye-based angiography remains a time-consuming, invasive procedure that requires skilled photographers. In addition, the images have limited depth resolution.

Recently, a novel imaging strategy, optical coherence tomography angiography (OCTA) has been introduced. OCTA is a noninvasive modality for vascular mapping without dye injection. It provides high speed, 3-dimensional images of the retinal, choroidal and optic disc vasculature. Several studies have illustrated the normal vascular mapping of the healthy human retina in OCTA images[2,3] and have demonstrated an age related reduction in the retinal capillary density (at both the superficial and deep level) and an age related increase in the foveal avascular zone.[4] In addition, the ability of OCTA to identify and quantify vascular changes in different ocular diseases including retinal vascular occlusive disorders, neovascular age related macular degeneration (AMD) and other related conditions, uveitic disorders and optic neuropathies has been described.[2,3] OCTA vessel density measurements have been found highly repeatable and reproducible.[4,5] For the foveal avascular zone (FAZ) measurements, interobserver reproducibility have been reported to be 0.78−0.99 in superficial capillary plexus (SCP) and 0.67−0.92 in Deep capillary plexus (DCP), and intraobserver repeatability 0.64−0.93 in SCP and 0.63−0.87 in DCP.[6]

In neovascular AMD, OCTA is able to detect choroidal neovascularization (CNV) in 34−100% of the patients, depending on the type and activity of the lesions.[7−10] A retrospective cohort study in patients with type 1 CNV reported that the combination of the en face OCTA and structural OCT can detect CNV lesions in 85.7% of cases compared to 66.7% for fluorescein angiography (FA) alone and OCTA alone.[11] OCTA offers additional benefits for the evaluation of CNV. Several morphologic characteristics including margin, core, and shape have been described.[7,12] Also, OCTA quantitative measures of the CNV lesion including area, vessel density, and branching complexity may enhance evaluation.[7,8] However, the clinical relevance of these descriptions remains to be confirmed. Although several features have been suggested to be able to illustrate the maturity of the CNV lesions, differentiating active from inactive lesions based on OCTA may be difficult.[7,12]

OCTA may also help to differentiate CNV from mimicking lesions. Subretinal hyperreflective material (SHRM) with structural OCT may have different etiologies including subretinal hemorrhage, vitelliform deposition, subretinal inflammatory membranes (e.g. fibrin) and scar tissue as well as true neovascular tissue. Dansingani et al.[13] showed that OCTA can distinguish vascular from avascular SHRM components. The ability of OCTA is especially important in detection of neovascularization in pachychoroid spectrum diseases. In eyes with pachychoroid features harboring new vessels, the detection rate of the OCTA is higher than dye-based angiography (95% versus 29%).[14] In contrast, OCTA may not be able to demonstrate all polypoidal lesions in eyes with idiopathic polypoidal vasculopathy due to the low flow characteristics.[15]

OCTA can be effective in illustrating microvascular abnormalities in retinal vascular occlusive disease. In diabetic

Financial interest: Dr Sarraf receives research grants from Allergan, Genentech, Regeneron, and Optovue and is a consultant for Genentech and Optovue and a paid speaker for Optovue. Dr Falavarjani has no financial interest.

Peer review under responsibility of the Iranian Society of Ophthalmology.

http://dx.doi.org/10.1016/j.joco.2017.02.005

retinopathy (DR), OCTA can identify microaneurysms, macular non-perfusion or ischemia and neovascularization in each layer of the retinal capillaries.[16] In addition, automated or semi-automated quantitative measurements of the FAZ, vessel density and area of non-perfusion can be performed.[16,17] Although OCTA can show the precise location of the microaneurysms, the detection rate is lower compared to the FA.[18] However another study demonstrated the OCTA detection of microvascular abnormalities in diabetic patients prior to the onset of clinically evident retinopathy. It has been illustrated that decreasing capillary density and branching complexity, and increasing average vascular caliber with OCTA were associated with worsening DR and that diabetic macular edema was associated with a significant change in FAZ, and capillary density and morphology.[19] Also, a correlation has been found between visual acuity and OCTA measured vessel density and FAZ area.[20] Similarly, microvascular abnormalities in central and branch retinal vein and artery occlusions and sickle cell retinopathy can be sensitively depicted using OCTA.[21−23] Perhaps more importantly OCTA can differentiate the level of macular ischemia. Disorders such as diabetic retinopathy, retinal artery and vein occlusion and sickle cell retinopathy can illustrate ischemia exclusively at the level of the deep retinal capillary plexus.[23,24] OCTA findings have also been helpful to understand the pathogenesis of macular edema associated with DR and retinal vein occlusion.[25]

The benefit of quantitative biomarkers of retinal disease cannot be underestimated. OCTA provides the capability to measure the density and area of retinal capillaries and vascular abnormalities, allowing quantitative comparison before and after treatment and correlation of baseline findings with treatment outcomes. Lee et al.[26] reported that poor anti-vascular endothelial growth factor responders had a larger FAZ area and more significant abnormalities including microaneurysms in the DCP of eyes with diabetic macular edema. Suzuki et al.[27] reported that capillary non-perfusion decreased and blood flow improved in retinal vein occlusion after anti-VEGF therapy. We could not find a significant change in vessel density and FAZ area after anti-VEGF therapy in eyes with diabetic macular edema (DME) and retinal vein occlusion.[28]

The benefits of OCTA analysis have also extended to more uncommon retinal and choroidal disorders. OCTA has illustrated retinal and choroidal vascular abnormalities in diseases like retinopathy of prematurity, uveitis, foveal hypoplasia, choroidal tumors, macular telangiectasia, and Stargardt disease.[29−34] These OCTA findings have provided new insights into the pathogenesis of these interesting diseases.

OCTA has provided useful information regarding the microvascular network in the peripapillary and prelaminar area. A dense microvascular network with no evidence of focal capillary dropout is observed around healthy optic discs.[35] While the radial peripapillary capillary network cannot be visualized by FA, it is readily visible with OCTA.[36] The benefit of OCTA has been demonstrated in different optic nerve diseases including ischemic, inflammatory and glaucomatous optic neuropathy.[35] In glaucomatous eyes, OCTA illustrated microvascular abnormalities including focal or diffuse attenuation of capillaries in the prelaminar and/or peripapillary regions.[35] OCTA can differentiate glaucomatous eyes and glaucoma suspects from healthy eyes with a high level of sensitivity and specificity.[37,38] In addition, OCTA based peripapillary vessel densities have been reported to be significantly correlated with visual field defects and have similar diagnostic accuracy as nerve fiber layer thickness measurements for differentiating healthy and glaucoma eyes.[38,39] In other types of optic neuropathy such as ischemic optic neuropathy, idiopathic intracranial hypertension, dominant optic atrophy and leber's hereditary optic neuropathy, OCTA studies have illustrated various microvascular changes including dilated and tortuous peripapillary capillaries and an increase or decrease in the visibility of the peripapillary capillary network in disc edema, and decreased visibility of the peripapillary capillary network corresponding to the region or sector of nerve fiber layer thinning in eyes with optic atrophy.[40]

Despite promising results of studies on the broad application and efficacy of OCTA in different ocular diseases, several factors may limit the incorporation of OCTA into daily practice. Several types of artifacts have been reported that limit the reliable interpretation and analysis of OCTA images.[41−43] Early versions of OCTA devices were especially limited by severe motion artifacts from the patients' saccades. Post-acquisition software correction of the images improved the quality of the images. Later, implementation of eye-tracking software further eliminated motion artifact. Projection artifact of the superficial vessels on the deep structures interferes with the visualization and interpretation of the vascular lesions. Different methods have been employed for removal of the projection artifacts.[44] Projection-resolved OCTA shows three distinct vascular plexuses in the inner retina with a high level of precision.[44] In recent studies, at least one form of artifact was identified in 73−89.4% of OCTA images with more prevalence in eyes with ocular pathology and poor visual acuity.[33,45] The artifacts were severe enough to preclude accurate grading of the images in 17.6%.[41] In addition, correction of artifacts such as segmentation artifact can be challenging. Also, OCTA is not able to illustrate blood flow velocity or retinal vascular leakage. In addition, the detection rate for certain lesion types such as polyps and retinal angiomatous lesions may be low.[8,15] Probably, the most important limitation of OCTA to be implemented in the routine clinical practice is limited data from well-designed studies.

In conclusion, due to various limitations with the current OCTA devices, OCTA may be best applied in the research setting or as a part of a multimodal approach for the diagnosis and management of the retinochoroidal diseases in daily practice. Eyes with suspected CNV and no clear evidence of neovascularization with FA, especially eyes with pachychoroid spectrum abnormalities may benefit from OCTA more than others. OCTA may provide a fast, practical and noninvasive tool to detect neovascularization in AMD and other related disorders. Also, OCTA is helpful to image the FAZ in eyes with unexplained visual loss and can provide depth resolved information regarding ischemia at the deep retinal capillary level.

References

1. Novotny HR, Alvis DL. A method of photographing fluorescence in circulating blood in the human retina. *Circulation*. 1961;24(1):82−86.
2. de Carlo TE, Romano A, Waheed NK, Duker JS. A review of optical coherence tomography angiography (OCTA). *Int J Retin Vitr*. 2015;1(1):5.
3. Chalam KV, Sambhav K. Optical coherence tomography angiography in retinal diseases. *J Ophthalmic Vis Res*. 2016;11:84−92.
4. Iafe NA, Phasukkijwatana N, Chen X, Sarraf D. Retinal capillary density and foveal avascular zone area are age-dependent: quantitative analysis using optical coherence tomography angiography. *Investig Ophthalmol Vis Sci*. 2016;57(13):5780−5787.
5. Shahlaee A, Samara WA, Hsu J, et al. In vivo assessment of macular vascular density in healthy human eyes using optical coherence tomography angiography. *Am J Ophthalmol*. 2016;165:39−46.
6. Coscas F, Sellam A, Glacet-Bernard A, et al. Normative data for vascular density in superficial and deep capillary plexuses of healthy adults assessed by optical coherence tomography angiography. *Investig Ophthalmol Vis Sci*. 2016;57(9). OCT211−OCT223.
7. Kuehlewein L, Bansal M, Lenis TL, et al. Optical coherence tomography angiography of type 1 neovascularization in age-related macular degeneration. *Am J Ophthalmol*. 2015;160(4), 739−748e2.
8. Kuehlewein L, Dansingani KK, de Carlo TE, et al. Optical coherence tomography angiography of type 3 neovascularization secondary to age-related macular degeneration. *Retina*. 2015;35(11):2229−2235.
9. El Ameen A, Cohen SY, Semoun O, et al. Type 2 neovascularization secondary to age-related macular degeneration imaged by optical coherence tomography angiography. *Retina*. 2015;35(11):2212−2218.
10. Liang MC, de Carlo TE, Baumal CR, et al. Correlation of spectral domain optical coherence tomography angiography and clinical activity in neovascular age-related macular degeneration. *Retina*. 2016;36(12): 2265−2273.
11. Inoue M, Jung JJ, Balaratnasingam C, et al. A comparison between optical coherence tomography angiography and fluorescein angiography for the imaging of type 1 neovascularization. *Investig Ophthalmol Vis Sci*. 2016;57(9). OCT314−23.
12. Carnevali A, Cicinelli MV, Capuano V, et al. Optical coherence tomography angiography: a useful tool for diagnosis of treatment-naive quiescent choroidal neovascularization. *Am J Ophthalmol*. 2016;169:189−198.
13. Dansingani KK, Tan ACS, Gilani F, et al. Subretinal hyperreflective material imaged with optical coherence tomography angiography. *Am J Ophthalmol*. 2016;169:235−248.
14. Dansingani KK, Balaratnasingam C, Klufas MA, Sarraf D, Freund KB. Optical coherence tomography angiography of shallow irregular pigment epithelial detachments in pachychoroid spectrum disease. *Am J Ophthalmol*. 2015;160(6):1243−1254.
15. Wang M, Zhou Y, Gao SS, et al. Evaluating polypoidal choroidal vasculopathy with optical coherence tomography angiography. *Investig Ophthalmol Vis Sci*. 2016;57(9). OCT526−32.
16. Ishibazawa A, Nagaoka T, Takahashi A, et al. Optical coherence tomography angiography in diabetic retinopathy: a prospective pilot study. *Am J Ophthalmol*. 2015;160(1), 35−44.e1.
17. Hwang TS, Gao SS, Liu L, et al. Automated quantification of capillary nonperfusion using optical coherence tomography angiography in diabetic retinopathy. *JAMA Ophthalmol*. 2016;134(4):367−373.
18. Salz DA, de Carlo TE, Adhi M, et al. Select features of diabetic retinopathy on swept-source optical coherence tomographic angiography compared with fluorescein angiography and normal eyes. *JAMA Ophthalmol*. 2016;134(6):1−7.
19. Kim AY, Chu Z, Shahidzadeh A, Wang RK, Puliafito CAKA. Quantifying microvascular density and morphology in diabetic retinopathy using spectral-domain optical coherence tomography angiography. *Investig Ophthalmol Vis Sci*. 2016;57:362−370.
20. Samara WA, Shahlaee A, Adam MK, Khan MA, Chiang A, Maguire JI, et al. Quantification of diabetic macular ischemia using optical coherence tomography angiography and its relationship with visual acuity. *Ophthalmology*. 2017;124(2):235−244.
21. Bonini Filho MA, Adhi M, de Carlo TE, et al. Optical coherence tomography angiography in retinal artery occlusion. *Retina*. 2015;35(11): 2339−2346.
22. Suzuki N, Hirano Y, Yoshida M, et al. Microvascular abnormalities on optical coherence tomography angiography in macular edema associated with branch retinal vein occlusion. *Am J Ophthalmol*. 2016;161, 126−132e1.
23. Ghasemi Falavarjani K, Scott AW, Wang K, et al. Correlation of multimodal imaging in sickle cell retinopathy. *Retina*. 2016;36(Suppl 1):S111−S117.
24. Nemiroff J, Kuehlewein L, Rahimy E, et al. Assessing deep retinal capillary ischemia in paracentral acute middle maculopathy by optical coherence tomography angiography. *Am J Ophthalmol*. 2016;162:121−132.
25. Spaide RF. Volume-rendered optical coherence tomography of retinal vein occlusion pilot study. *Am J Ophthalmol*. 2016;165:133−144.
26. Lee J, Moon BG, Cho AR, Yoon YH. Optical coherence tomography angiography of DME and its association with anti-VEGF treatment response. *Ophthalmology*. 2016;123:2368−2375.
27. Suzuki N, Hirano Y, Tomiyasu T, et al. Retinal hemodynamics seen on optical coherence tomography angiography before and after treatment of retinal vein occlusion. *Investig Ophthalmol Vis Sci*. 2016;57:5681−5687.
28. Ghasemi Falavarjani K, Iafe NA, Hubschman JP, et al. Optical coherence tomography angiography analysis of the foveal avascular zone and macular vessel density after anti-VEGF therapy in eyes with diabetic macular edema and retinal vein occlusion. *Investig Ophthalmol Vis Sci*. 2017;58(1):30−34.
29. Ghasemi Falavarjani K, Iafe NA, Velez FA, et al. Optical coherence tomography angiography of the fovea in children born preterm. *Retina*. 2017 Jan 16. http://dx.doi.org/10.1097/IAE.0000000000001471 [Epub ahead of print].
30. Pichi F, Srvivastava SK, Chexal S, et al. En face optical coherence tomography and optical coherence tomography angiography of multiple evanescent white dot syndrome: new insights into pathogenesis. *Retina*. 2016;(36 suppl):S178−S188.
31. Dolz-Marco R, Phasukkijwatana N, Sarraf D, Freund KB. Optical coherence tomography angiography in fovea plana. *Ophthalmic Surg Lasers Imaging Retin*. 2016;47(7):670−673.
32. Spaide RF, Suzuki M, Yannuzzi LA, Matet AB-CF. Volume-rendered angiographic and structural optical coherence tomography angiography of macular telangiectasia type 2. *Retina*. 2016 Sep 30. http://dx.doi.org/10.1097/IAE.0000000000001344.
33. Shields CL, Say EA, Samara WA, Khoo CT, Mashayekhi A, Shields JA. Optical coherence tomography angiography of the macula after plaque radiotherapy of choroidal melanoma: comparison of irradiated versus nonirradiated eyes in 65 patients. *Retina*. 2016 Aug;36(8):1493−1505.
34. Battaglia Parodi M, Cicinelli MV, Rabiolo A, Pierro L, Bolognesi G, Bandello F. Vascular abnormalities in patients with Stargardt disease assessed with optical coherence tomography angiography. *Br J Ophthalmol*. 2016 Sep 14. http://dx.doi.org/10.1136/bjophthalmol-2016-308869 [Epub ahead of print].
35. Akil H, Falavarjani KG, Sadda SR, Sadun AA. Optical coherence tomography angiography of optic disc; an overview. *J Ophthamic Vis Res*. 2017;12:98−105.
36. Spaide RF, Klancnik JM, Cooney MJ. Retinal vascular layers imaged by fluorescein angiography and optical coherence tomography angiography. *JAMA Ophthalmol*. 2015;133(1):45.
37. Jia Y, Wei E, Wang X, et al. Optical coherence tomography angiography of optic disc perfusion in glaucoma. *Ophthalmology*. 2014;121(7):1322−1332.
38. Yarmohammadi A, Zangwill LM, Diniz-Filho A, et al. Optical coherence tomography angiography vessel density in healthy, glaucoma suspect, and glaucoma eyes. *Investig Ophthalmol Vis Sci*. 2016;57(9). OCT451−OCT459.
39. Liu L, Jia Y, Takusagawa HL, et al. Optical coherence tomography angiography of the peripapillary retina in glaucoma. *JAMA Ophthalmol*. 2015;4197(9):1045−1052.
40. Ghasemi Falavarjani K, Tian JJ, Akil H, Garcia GA, Sadda SR, Sadun AA. Swept-source optical coherence tomography angiography of the optic disk in optic neuropathy. *Retina*. 2016;(36 suppl):S168−S177.

41. Ghasemi Falavarjani K, Al-Sheikh M, Akil H, Sadda SR. Image artefacts in swept-source optical coherence tomography angiography. *Br J Ophthalmol*. 2016. http://dx.doi.org/10.1136/bjophthalmol-2016-309104.
42. Spaide RF, Fujimoto JG, Waheed NK. Image artifacts in optical coherence tomography angiography. *Retina*. 2015;35(11):2163−2180.
43. Ghasemi Falavarjani K, Al-Sheikh M, Darvizeh F, Sadun AA, Sadda SR. Retinal vessel calibre measurements by optical coherence tomography angiography. *Br J Ophthalmol*. 2016. http://dx.doi.org/10.1136/bjophthalmol-2016-309678.
44. Zhang M, Hwang TS, Campbell JP, et al. Projection-resolved optical coherence tomographic angiography. *Biomed Opt Express*. 2016;7(3):816−828.
45. Say EA, Ferenczy S, Magrath GN, Samara WA, Khoo CT, Shields CL. Image quality and artifacts on optical coherence tomography angiography: comparison of pathologic and paired fellow eyes in 65 patients with unilateral choroidal melanoma treated with plaque radiotherapy. *Retina*. 2016. http://dx.doi.org/10.1097/IAE.0000000000001414.

Khalil Ghasemi Falavarjani*
Eye Research Center, Rassoul Akram Hospital, Iran University of Medical Sciences, Sattarkhan-Niaiesh St, Tehran, Iran

David Sarraf
Stein Eye Institute, University of California Los Angeles, Los Angeles, CA, USA

Greater Los Angeles VA Healthcare Center, Los Angeles, CA, USA

**Corresponding author.*
E-mail address: drghasemi@yahoo.com (K.G. Falavarjani).