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Title: Optical Coherence Tomography Angiography: A Review of Current and Future Clinical Applications

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ABSTRACT

Optical coherence tomography angiography is a non-invasive imaging technique that now allows for simultaneous in vivo imaging of the morphology as well as the vasculature in the eye. In this review, we provide an update on the existing clinical applications of optical coherence tomography angiography technology from the anterior to posterior segment of the eye. We also discuss the limitations of optical coherence tomography angiography technology, as well as the caveats to the interpretation of images. As current optical coherence tomography angiography systems are optimised for the retina, most studies have focused on interpreting images from conditions such as age related macular degeneration and retinal vascular diseases. However, the interpretation of these optical coherence tomography angiography images should be taken in consideration with other multi-modal imaging to overcome the limitations of each technique. In addition, there are a growing variety of clinical applications for optical coherence tomography angiography imaging in optic nerve evaluation for glaucoma and optic neuropathies. Further developments in anterior optical coherence tomography angiography have now allowed for evaluation of anterior segment pathology such as glaucoma, ocular surface diseases, corneal vascularisation, and abnormal iris vasculature. Future developments in software could allow for improved segmentation and image resolution with automated measurements and analysis.

Keywords: optical coherence tomography; angiography; vascularisation; retina; glaucoma; cornea

INTRODUCTION

Today, classical optical coherence tomography (OCT) is able to provide structural information on ocular tissues with unprecedented resolution. Typically, structural OCT scans produce poor delineation of blood vessels as light is scattered by moving erythrocytes.[1] This scatter also leads to a shadow effect behind or beneath the blood vessels and thus, images of deeper layers underneath larger vessels are typically lost.[2] However, with increased sensitivity and speed of OCT systems, it is now possible to delineate blood vessels using OCT by using decorrelation between consecutive scans. The basis of OCT angiography (OCTA) is essentially comparing consecutive B-scans, which is now possible with B-scan rates of several hundred hertz (Hz) - optimal for detecting flow in the microvasculature of the eye. This can either be done based on comparing changes in intensity, phase speckle contrast or a variation of the full complex OCT signal.[3]

Thus, OCTA is a rapidly emerging, non-invasive imaging modality that provides three-dimensional delineation of vascular structures within the eye, without the need to intravenously administer fluorescent dyes.[4, 5] The other potential advantages include a fast acquisition time that allows for repeated scans, higher resolution of capillaries without obscuration by leakage, and the ability to perform depth-resolved analysis, in which the flow within a specific axial location of the retinal or choroid can be analysed.[6] However, its current limitations include a restricted field of view, and lack of information on flow or filling speed, without the ability to demonstrate exudation or leakage. In the deeper layers, vessels from the superficial vasculature can appear as projection artefacts caused by multiple scattering.[7] Another major issue is related to motion artefacts, which may be corrected using a motion tracking system or on a post-processing using different approaches, but still constitute a problem in clinical applications of this technology.

Currently, commercially available OCTA systems use various proprietary algorithms such as full or split-spectrum amplitude-decorrelation angiography (FSADA or SSADA), optical microangiography (OMAG) and OCT angiography ratio analysis (OCTARA).[8] In addition, many differences exist between OCTA platforms such as scanning speed, acquisition time, processing time, automated segmentation and options of varying the scan area size. Generally, an optimal balance between sampling density, B-scan repetition and field of view needs to be found. Oversampling (repeated scans within one spot size of the laser beam) increases quality but also increases risk of bulk motion artefacts. Typical measurement times are currently between 3 and 6 seconds, a period during which most subjects are able to fixate a target. Other devices, with eye-tracking system, have longer acquisition times allowing for accurate follow-up comparison. The area that can be scanned within this time frame depends on the A-scan rate of the system. With commercially available OCT machines (up to 70 kHz for spectrometer-based systems and up to 100 kHz for swept-source based

systems), areas of either 3x3 mm, 6x6 mm, and 9x9 mm are typically scanned with decreasing oversampling rates.

The purpose of this review is to summarize the current clinical applications of OCTA from the posterior segment to the optic nerve and the anterior segment. We also include potential future clinical applications and developments in the OCTA technology arena.

OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY FOR THE POSTERIOR SEGMENT

To date, most OCTA technology and algorithms have been optimized for the posterior segment and a wide range of potential clinical applications have emerged.[4] Interpretation of posterior segment OCTA images, however, involves a significant learning curve and is not always straightforward. OCTA systems generate both cross-sectional "flow" images (B-scans) and *en face* sections (figure 1-3, Supplementary figure 2-4). For accurate interpretation, each of these should be viewed in a dynamic fashion and closely correlated. Manual manipulation of the images is often required to optimise the vascular details of interest. Awareness of potential sources of artefacts due to suboptimal image acquisition, patient factors, poor segmentation, projection (figure 2, supplementary figure 4) and unmasking artefacts (figure 2) is also required to ensure optimal OCTA interpretation.[9-11]

OCTA imaging is particularly useful in retinal vascular diseases, such as diabetic retinopathy and retinal venous occlusion, where it allows delineation and quantification of the foveal avascular zone (FAZ),[12, 13] (figure 1) detection of macular ischaemia, and some assessment of mid-peripheral retinal non-perfusion (figure 1, supplementary figure 1).[14] Interestingly, previous studies have suggested that increases in FAZ area may precede the development of clinically evident diabetic retinopathy – this has significant potential implications for the screening of this condition.[15, 16] Posterior segment OCTA also allows improved visualisation of retinal vascular abnormalities such as micro- and macroaneurysms,[12, 17] telangiectasia,[18] vascular loops,[19] and venous beading (figure 1, supplementary figure 1).[20] Through the correlation of cross-sectional and *en face* OCTA images, it is now possible to easily distinguish between pre-retinal neovascularisation and intraretinal microvascular abnormalities (IRMAs) or collateral vessels (figure 1).[21] OCTA may also provide new insights into diseases such as macular telangiectasia (MacTel) type 2 (supplementary figure 2). Recent studies suggest that the characteristic stellate arrangement of "telangiectatic" vessels seen in the temporal macula may be caused by contraction of the surrounding tissue (supplementary figure 2).[22] These findings cannot be elucidated using either conventional angiography or structural OCT. OCTA also provides improved visualisation of the subretinal neovascularisation that sometimes develops in this condition.[23]

OCTA imaging has huge potential for the diagnosis of choroidal neovascularization (CNV) in patients with age-related macular degeneration (AMD) (figure 2).[24] In many cases, direct visualisation of the choroidal neovascular membrane is possible, whether it be in the subretinal (type 2) or sub-RPE space (type 1), and patients may be spared the need for invasive angiography (figure 2).[25, 26], Retinal angiomatous proliferation (RAP) lesions, also known as type 3 neovascularisation, may also be seen on OCTA as a small, high-flow, tuft of abnormal vessels on *en face* OCTA images (figure 2).[27] These lesions are often subtle and close correlation between cross-sectional images and superimposed flow is recommended (figure 2). The role of OCTA in polypoidal choroidal vasculopathy (PCV) is less well defined (supplementary figure 3). OCTA is readily capable of highlighting the branching vascular networks (BVNs) in this condition but is not as reliable as ICG in the detection of polyps (supplementary figure 3).[28-30] On cross-sectional OCTA, polyps show patchy flow signals with the lumen being largely devoid of flow (supplementary figure 3). [30] OCTA may be of particular use in the diagnosis of CNV that is not related to AMD (e.g. myopic CNV),[31] and in situations where accurate interpretation of conventional angiography is likely to be challenging (e.g., in CNV secondary to central serous chorioretinopathy (CSCR),[32] or CNV secondary to inflammatory conditions such as multifocal choroiditis (supplementary figure 4).[33] OCTA has also been suggested for the monitoring of patients with known CNV, with attempts to characterise CNV morphology in clinically active versus inactive disease (figure 3). In this regard, active lesions have been described with a "medusa" or "sea-fan" appearance, while chronic, inactive lesions have been described as having a "dead tree" aspect (figure 3).[34] In real world clinical practice, use of OCTA in this manner is challenging and further effort will be required to validate such an approach.

OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY FOR THE OPTIC NERVE

As primary open angle glaucoma (POAG) is an optic neuropathy with a possible vascular component in its multifactorial etiology,[35] OCTA imaging suggests attenuation of the vasculature associated with the optic nerve microvasculature.[36, 37] Moreover, combining conventional OCT with OCTA may allow for the simultaneous evaluation of the retinal nerve fiber layer (RNFL) structure and optic disc sector perfusion, which may correlate with glaucoma severity and the associated visual field loss.[38] Further studies are required to study the temporal association between vascular and structural changes of the retinal ganglion cells and the vascular supply captured by OCTA imaging. However, effects on visual function such as reduced visual field sensitivity may only appear after subsequent damage occurs. Thus, there is a potential for OCTA to detect pre-perimetric POAG even in the presence of RNFL thinning.[39] OCTA may also be helpful for exploring vascular changes in secondary glaucomatous optic neuropathies.[40]

The role of OCTA in detecting optic neuropathies directly associated with vascular pathology, should in theory, be even more promising. Studies have demonstrated delineation of changes in peripapillary microvasculature in acute non-arteritic anterior ischemic optic neuropathy (NAION), and after resolution of the optic disc swelling.[41] One of the proposed mechanisms underlying NAION is a transient hypoperfusion in the deeper capillary beds of the optic nerve head. Vascular congestion is also seen in OCTA images from tortuous capillaries within or surrounding the optic disc in NAION.[42] A potential clinical application of OCTA in NAION is monitoring recovery, as an early OCTA study revealed partial recovery of peripapillary vascular flow was associated with a modest improvement in visual function.[41] Moreover, OCTA may also have the ability to evaluate progression of NAION from a pre-clinical to a full clinical presentation.[41] On the other hand, disc-swelling secondary to conditions such as idiopathic intracranial hypertension may show vessel tortuosity without associated vascular dropout and relatively preserved peripapillary microvasculature in the early stage.[42] However, current limitations of OCTA technology include the reduction of the flow density at different layers in NAION is confounded by imaging artefacts from edema or the presence of blood (figure 4). Nonetheless, further studies on this application of OCTA in optic neuropathies with a vascular etiology could have great implications on clinical practice. Another role of OCTA in evaluating the optic nerve is in optic neuritis, where previous episodes of inflammation were associated with reduction in peripapillary vascular flow index.[43, 44] The OCTA may also demonstrate some residual microvascular abnormalities of the optic nerve even after treatment and recovery of visual function.[44]

OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY FOR THE ANTERIOR SEGMENT

Currently, angiography for the anterior segment is not commonly performed, due its invasive nature and the risk of complications.[45] The main advantage of anterior OCTA is that images are rapidly acquired using a non-contact technique.[46] However, it is important to note that current commercial OCTA systems are not specifically designed for the anterior segment but may be adapted to assess the cornea, iris or scleral vessels.[46] While the SSADA system has been most commonly described for the anterior segment, other spectral domain and swept source OCTA systems have also been successfully adapted for the anterior segment as prototypes in development.[47]

Similar to the OCTA for the posterior segment, one must recognize the limitations and caveats to interpretation of anterior OCTA scans. For example, the OCTA is unable to demonstrate vessel leakage, and has a limited field of view compared to the FA and ICGA.[48] However, leakage of dye tends to hinder images of microvasculature in the cornea, while OCTA has been found to be comparable to ICGA for visualization of corneal vascularisation.[49] It is also important to

recognize image artifacts from saccadic eye movements, projection artifacts and loss of signal in areas of corneal opacities. Future improvements to motion correction and image processing may reduce these artifacts and improve image quality.[50, 51] Lastly, anterior OCTA is currently unable to perform registration and localization required for comparisons in follow-up scans – though it has been found to be potentially useful for serial scans with adjunctive software.[52]

Notwithstanding the current drawbacks of anterior OCTA, it is recognized that this technology has great potential for clinical impact. Pre-operative anterior OCTA provides information on the depth of the corneal lesion with the associated vessels when planning for fine-needle diathermy with lamellar keratoplasty.[53] Further understanding of corneal and scleral inflammatory conditions may be achieved with OCTA which reveals vaso-occlusion without blockage for extravasated dyes.[54] Anterior OCTA may be performed serially to study the extent of corneal thinning and vessel constriction with active disease, as well as new capillary formation or recanalization that may indicate response to treatment.[55] Other future applications include assessment of limbal stem cell deficiency, corneal vascularisation for risk of graft rejection, evaluation of anti-angiogenic treatments, glaucoma bleb vascularity and risk of scarring and study of abnormal or new iris vessels in anterior segment ischemia or neovascular glaucoma (figure 5).

FUTURE APPLICATIONS OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

In parallel with rapid advances in OCTA hardware, OCTA image analysis software is becoming increasing sophisticated. Commercially available OCTA software from multiple vendors now allows for automated measurements of both abnormal flow and non-perfusion areas (figure 1, supplementary figure 1). Further work is required to generate normative databases for comparison with retinal disease and to validate the clinical utility – if any – of these measurements in prospective clinical trials.[56] With the proliferation of commercial OCTA systems from multiple vendors, it will be increasingly important to understand variations in both hardware and software. For example, segmentation of the superficial and deep retinal vascular layers has been shown to differ between the various OCTA systems.[57] It will also be important to characterize the reproducibility and repeatability of measurements from the different systems in a robust manner. A number of advances in the underlying OCTA technology are also underway, including the introduction of commercially available swept source OCTA systems, and the development of variable inter-scan time acquisition protocols (VISTA).[58] These latter protocols are of particular interest because they may allow evaluation of variable flow rates (both slow and fast) to be performed in future OCTA platforms. Improved wide-field imaging OCTA imaging with retention of detail and resolution, obtained with automated montage functions will become increasingly more feasible with improvements in OCTA scanning speeds (supplementary figure 1). Finally, posterior segment OCTA is

starting to be incorporated into the protocols of large, interventional clinical trials and features such as depth resolved colour coded images (figure 3) have the potential for both qualitative and quantitative disease progression monitoring and response to treatment. As the results of these trials are reported, they will undoubtedly drive even greater adoption of posterior segment OCTA in routine clinical practice.

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References

1. Drexler W, Liu M, Kumar A, Kamali T, Unterhuber A, Leitgeb RA (2014) Optical coherence tomography today: speed, contrast, and multimodality. J Biomed Opt 19: 071412 DOI 10.1117/1.JBO.19.7.071412
2. Leitgeb RA, Werkmeister RM, Blatter C, Schmetterer L (2014) Doppler optical coherence tomography. Prog Retin Eye Res 41: 26-43 DOI S1350-9462(14)00017-2 [pii]
10.1016/j.preteyeres.2014.03.004
3. Chen CL, Wang RK (2017) Optical coherence tomography based angiography [Invited]. Biomed Opt Express 8: 1056-1082 DOI 10.1364/BOE.8.001056
4. Gao SS, Jia Y, Zhang M, Su JP, Liu G, Hwang TS, Bailey ST, Huang D (2016) Optical Coherence Tomography Angiography. Investigative ophthalmology & visual science 57: OCT27-36 DOI 10.1167/iovs.15-19043
5. Zhang A, Zhang Q, Chen CL, Wang RK (2015) Methods and algorithms for optical coherence tomography-based angiography: a review and comparison. Journal of biomedical optics 20: 100901 DOI 10.1117/1.JBO.20.10.100901
6. Keane PA, Sadda SR (2014) Retinal imaging in the twenty-first century: state of the art and future directions. Ophthalmology 121: 2489-2500 DOI 10.1016/j.ophtha.2014.07.054

7. Zhang M, Hwang TS, Campbell JP, Bailey ST, Wilson DJ, Huang D, Jia Y (2016) Projection-resolved optical coherence tomographic angiography. Biomed Opt Express 7: 816-828 DOI 10.1364/BOE.7.000816

8. Wylegala A, Teper S, Dobrowolski D, Wylegala E (2016) Optical coherence angiography: A review. Medicine (Baltimore) 95: e4907 DOI 10.1097/MD.0000000000004907

9. Ferrara D (2016) Image artifacts in optical coherence tomography angiography. Clinical & experimental ophthalmology 44: 367-368 DOI 10.1111/ceo.12781

10. Spaide RF, Fujimoto JG, Waheed NK (2015) Image Artifacts in Optical Coherence Tomography Angiography. Retina 35: 2163-2180 DOI 10.1097/IAE.0000000000000765

11. Dolz-Marco R, Freund KB (2017) Directional Changes in Tissue Reflectivity May Influence Flow Detection on Optical Coherence Tomography Angiography. Retina DOI 10.1097/IAE.0000000000001656

12. Soares M, Neves C, Marques IP, Pires I, Schwartz C, Costa MA, Santos T, Durbin M, Cunha-Vaz J (2017) Comparison of diabetic retinopathy classification using fluorescein angiography and optical coherence tomography angiography. The British journal of ophthalmology 101: 62-68 DOI 10.1136/bjophthalmol-2016-309424

13. Balaratnasingam C, Inoue M, Ahn S, McCann J, Dhrami-Gavazi E, Yannuzzi LA, Freund KB (2016) Visual Acuity Is Correlated with the Area of the Foveal Avascular Zone in Diabetic Retinopathy and Retinal Vein Occlusion. Ophthalmology 123: 2352-2367 DOI 10.1016/j.ophtha.2016.07.008

14. Samara WA, Shahlaee A, Adam MK, Khan MA, Chiang A, Maguire JI, Hsu J, Ho AC (2017) Quantification of Diabetic Macular Ischemia Using Optical Coherence Tomography Angiography and Its Relationship with Visual Acuity. Ophthalmology 124: 235-244 DOI 10.1016/j.ophtha.2016.10.008

15. de Carlo TE, Chin AT, Bonini Filho MA, Adhi M, Branchini L, Salz DA, Baumal CR, Crawford C, Reichel E, Witkin AJ, Duker JS, Waheed NK (2015) Detection of Microvascular Changes in Eyes of Patients with Diabetes but Not Clinical Diabetic Retinopathy Using Optical Coherence Tomography Angiography. Retina 35: 2364-2370 DOI 10.1097/IAE.0000000000000882

16. Takase N, Nozaki M, Kato A, Ozeki H, Yoshida M, Ogura Y (2015) Enlargement of Foveal Avascular Zone in Diabetic Eyes Evaluated by En Face Optical Coherence Tomography Angiography. Retina 35: 2377-2383 DOI 10.1097/IAE.0000000000000849

17. Parravano M, De Geronimo D, Scarinci F, Querques L, Virgili G, Simonett JM, Varano M, Bandello F, Querques G (2017) Diabetic Microaneurysms Internal Reflectivity on Spectral-Domain Optical Coherence Tomography and Optical Coherence Tomography Angiography Detection. Am J Ophthalmol 179: 90-96 DOI 10.1016/j.ajo.2017.04.021

18. Matet A, Daruich A, Dirani A, Ambresin A, Behar-Cohen F (2016) Macular Telangiectasia Type 1: Capillary Density and Microvascular Abnormalities

Assessed by Optical Coherence Tomography Angiography. Am J Ophthalmol 167: 18-30 DOI 10.1016/j.ajo.2016.04.005

19. Giuffre C, Carnevali A, Cicinelli MV, Querques L, Querques G, Bandello F (2017) Optical Coherence Tomography Angiography of Venous Loops in Diabetic Retinopathy. Ophthalmic Surg Lasers Imaging Retina 48: 518-520 DOI 10.3928/23258160-20170601-13

20. Hwang TS, Jia Y, Gao SS, Bailey ST, Lauer AK, Flaxel CJ, Wilson DJ, Huang D (2015) Optical Coherence Tomography Angiography Features of Diabetic Retinopathy. Retina 35: 2371-2376 DOI 10.1097/IAE.0000000000000716

21. de Carlo TE, Bonini Filho MA, Baumal CR, Reichel E, Rogers A, Witkin AJ, Duker JS, Waheed NK (2016) Evaluation of Preretinal Neovascularization in Proliferative Diabetic Retinopathy Using Optical Coherence Tomography Angiography. Ophthalmic Surg Lasers Imaging Retina 47: 115-119 DOI 10.3928/23258160-20160126-03

22. Spaide RF, Marco RD, Yannuzzi LA (2017) Vascular Distortion and Dragging Related to Apparent Tissue Contraction in Macular Telangiectasis Type 2. Retina DOI 10.1097/IAE.0000000000001694

23. Zhang Q, Wang RK, Chen CL, Legarreta AD, Durbin MK, An L, Sharma U, Stetson PF, Legarreta JE, Roisman L, Gregori G, Rosenfeld PJ (2015) Swept Source Optical Coherence Tomography Angiography of Neovascular Macular Telangiectasia Type 2. Retina 35: 2285-2299 DOI 10.1097/IAE.0000000000000840

24. Sulzbacher F, Pollreisz A, Kaider A, Kickinger S, Sacu S, Schmidt-Erfurth U, Vienna Eye Study C (2017) Identification and clinical role of choroidal neovascularization characteristics based on optical coherence tomography angiography. Acta Ophthalmol 95: 414-420 DOI 10.1111/aos.13364

25. Inoue M, Jung JJ, Balaratnasingam C, Dansingani KK, Dhrami-Gavazi E, Suzuki M, de Carlo TE, Shahlaee A, Klufas MA, El Maftouhi A, Duker JS, Ho AC, Maftouhi MQ, Sarraf D, Freund KB, Group C-S (2016) A Comparison Between Optical Coherence Tomography Angiography and Fluorescein Angiography for the Imaging of Type 1 Neovascularization. Investigative ophthalmology & visual science 57: OCT314-323 DOI 10.1167/iovs.15-18900

26. Kuehlewein L, Bansal M, Lenis TL, Iafe NA, Sadda SR, Bonini Filho MA, De Carlo TE, Waheed NK, Duker JS, Sarraf D (2015) Optical Coherence Tomography Angiography of Type 1 Neovascularization in Age-Related Macular Degeneration. American journal of ophthalmology 160: 739-748 e732 DOI 10.1016/j.ajo.2015.06.030

27. Tan AC, Dansingani KK, Yannuzzi LA, Sarraf D, Freund KB (2017) Type 3 Neovascularization Imaged with Cross-Sectional and En Face Optical Coherence Tomography Angiography. Retina 37: 234-246 DOI 10.1097/IAE.0000000000001343

28. Cheung CM, Yanagi Y, Mohla A, Lee SY, Mathur R, Chan CM, Yeo I, Wong TY (2016) Characterization and Differentiation of Polypoidal

Choroidal Vasculopathy Using Swept Source Optical Coherence Tomography Angiography. Retina DOI 10.1097/IAE.0000000000001391

29. Tanaka K, Mori R, Kawamura A, Nakashizuka H, Wakatsuki Y, Yuzawa M (2017) Comparison of OCT angiography and indocyanine green angiographic findings with subtypes of polypoidal choroidal vasculopathy. The British journal of ophthalmology 101: 51-55 DOI 10.1136/bjophthalmol-2016-309264

30. Srour M, Querques G, Souied EH (2016) Optical Coherence Tomography Angiography of Idiopathic Polypoidal Choroidal Vasculopathy. Developments in ophthalmology 56: 71-76 DOI 10.1159/000442781

31. Querques L, Giuffre C, Corvi F, Zucchiatti I, Carnevali A, De Vitis LA, Querques G, Bandello F (2017) Optical coherence tomography angiography of myopic choroidal neovascularisation. Br J Ophthalmol 101: 609-615 DOI 10.1136/bjophthalmol-2016-309162

32. Bousquet E, Bonnin S, Mrejen S, Krivosic V, Tadayoni R, Gaudric A (2017) Optical Coherence Tomography Angiography of Flat Irregular Pigment Epithelium Detachment in Chronic Central Serous Chorioretinopathy. Retina DOI 10.1097/IAE.0000000000001580

33. Levison AL, Baynes KM, Lowder CY, Kaiser PK, Srivastava SK (2017) Choroidal neovascularisation on optical coherence tomography angiography in punctate inner choroidopathy and multifocal choroiditis. Br J Ophthalmol 101: 616-622 DOI 10.1136/bjophthalmol-2016-308806

34. Takayama K, Ito Y, Kaneko H, Kataoka K, Sugita T, Maruko R, Hattori K, Ra E, Haga F, Terasaki H (2017) Comparison of indocyanine green angiography and optical coherence tomographic angiography in polypoidal choroidal vasculopathy. Eye 31: 45-52 DOI 10.1038/eye.2016.232

35. Cherecheanu AP, Garhofer G, Schmidl D, Werkmeister R, Schmetterer L (2013) Ocular perfusion pressure and ocular blood flow in glaucoma. Curr Opin Pharmacol 13: 36-42 DOI 10.1016/j.coph.2012.09.003

36. Jia Y, Wei E, Wang X, Zhang X, Morrison JC, Parikh M, Lombardi LH, Gattey DM, Armour RL, Edmunds B, Kraus MF, Fujimoto JG, Huang D (2014) Optical coherence tomography angiography of optic disc perfusion in glaucoma. Ophthalmology 121: 1322-1332 DOI 10.1016/j.ophtha.2014.01.021

37. Liu L, Jia Y, Takusagawa HL, Pechauer AD, Edmunds B, Lombardi L, Davis E, Morrison JC, Huang D (2015) Optical Coherence Tomography Angiography of the Peripapillary Retina in Glaucoma. JAMA ophthalmology 133: 1045-1052 DOI 10.1001/jamaophthalmol.2015.2225

38. Yarmohammadi A, Zangwill LM, Diniz-Filho A, Suh MH, Yousefi S, Saunders LJ, Belghith A, Manalastas PI, Medeiros FA, Weinreb RN (2016) Relationship between Optical Coherence Tomography Angiography Vessel Density and Severity of Visual Field Loss in Glaucoma. Ophthalmology 123: 2498-2508 DOI S0161-6420(16)31087-9 [pii] 10.1016/j.ophtha.2016.08.041

39. Akil H, Huang AS, Francis BA, Sadda SR, Chopra V (2017) Retinal vessel density from optical coherence tomography angiography to differentiate

early glaucoma, pre-perimetric glaucoma and normal eyes. PLoS One 12: e0170476 DOI 10.1371/journal.pone.0170476

PONE-D-16-21744 [pii]

40. Ang M, Sng C, Milea D (2016) Optical coherence tomography angiography in dural carotid-cavernous sinus fistula. BMC Ophthalmol 16: 93 DOI 10.1186/s12886-016-0278-1

10.1186/s12886-016-0278-1 [pii]

41. Sharma S, Ang M, Najjar RP, Sng C, Cheung CY, Rukmini AV, Schmetterer L, Milea D (2017) Optical coherence tomography angiography in acute non-arteritic anterior ischaemic optic neuropathy. The British journal of ophthalmology DOI 10.1136/bjophthalmol-2016-309245

42. Ghasemi Falavarjani K, Tian JJ, Akil H, Garcia GA, Sadda SR, Sadun AA (2016) Swept-Source Optical Coherence Tomography Angiography of the Optic Disk in Optic Neuropathy. Retina 36 Suppl 1: S168-S177 DOI 10.1097/IAE.0000000000001259

43. Wang X, Jia Y, Spain R, Potsaid B, Liu JJ, Baumann B, Hornegger J, Fujimoto JG, Wu Q, Huang D (2014) Optical coherence tomography angiography of optic nerve head and parafovea in multiple sclerosis. The British journal of ophthalmology 98: 1368-1373 DOI 10.1136/bjophthalmol-2013-304547

44. Higashiyama T, Nishida Y, Ohji M (2017) Optical coherence tomography angiography in eyes with good visual acuity recovery after treatment for optic neuritis. PloS one 12: e0172168 DOI 10.1371/journal.pone.0172168

45. Ang M, Cai Y, Shahipasand S, Sim DA, Keane PA, Sng CC, Egan CA, Tufail A, Wilkins MR (2015) En face optical coherence tomography angiography for corneal neovascularisation. Br J Ophthalmol DOI bjophthalmol-2015-307338 [pii]

10.1136/bjophthalmol-2015-307338

46. Ang M, Sim DA, Keane PA, Sng CC, Egan CA, Tufail A, Wilkins MR (2015) Optical Coherence Tomography Angiography for Anterior Segment Vasculature Imaging. Ophthalmology 122: 1740-1747 DOI 10.1016/j.ophtha.2015.05.017

47. Ang M, Cai Y, Tan AC (2016) Swept Source Optical Coherence Tomography Angiography for Contact Lens-Related Corneal Vascularization. J Ophthalmol 2016: 9685297 DOI 10.1155/2016/9685297

48. Ang M, Cai Y, MacPhee B, Sim DA, Keane PA, Sng CC, Egan CA, Tufail A, Larkin DF, Wilkins MR (2016) Optical coherence tomography angiography and indocyanine green angiography for corneal vascularisation. Br J Ophthalmol DOI 10.1136/bjophthalmol-2015-307706

49. Ang M, Cai Y, Shahipasand S, Sim DA, Keane PA, Sng CC, Egan CA, Tufail A, Wilkins MR (2016) En face optical coherence tomography angiography for corneal neovascularisation. Br J Ophthalmol 100: 616-621 DOI 10.1136/bjophthalmol-2015-307338

50. Girard MJ, Ang M, Chung CW, Farook M, Strouthidis N, Mehta JS, Mari JM (2015) Enhancement of Corneal Visibility in Optical Coherence

Tomography Images Using Corneal Adaptive Compensation. Transl Vis Sci Technol 4: 3 DOI 10.1167/tvst.4.3.3

51.   Chung CW, Ang M, Farook M, Strouthidis NG, Mehta JS, Mari JM, Girard MJ (2016) Enhancement of Corneal Visibility in Optical Coherence Tomography Images with Corneal Opacification. Transl Vis Sci Technol 5: 3 DOI 10.1167/tvst.5.5.3

52.   Cai Y, Alio Del Barrio JL, Wilkins MR, Ang M (2017) Serial optical coherence tomography angiography for corneal vascularization. Graefes Arch Clin Exp Ophthalmol 255: 135-139 DOI 10.1007/s00417-016-3505-9

53.   Spiteri N, Romano V, Zheng Y, Yadav S, Dwivedi R, Chen J, Ahmad S, Willoughby CE, Kaye SB (2015) Corneal angiography for guiding and evaluating fine-needle diathermy treatment of corneal neovascularization. Ophthalmology 122: 1079-1084 DOI S0161-6420(15)00127-X [pii]

10.1016/j.ophtha.2015.02.012

54.   Guex-Crosier Y, Durig J (2003) Anterior segment indocyanine green angiography in anterior scleritis and episcleritis. Ophthalmology 110: 1756-1763 DOI S0161-6420(03)00567-0 [pii]

10.1016/S0161-6420(03)00567-0

55.   Watson PG (1987) Anterior segment fluorescein angiography in the surgery of immunologically induced corneal and scleral destructive disorders. Ophthalmology 94: 1452-1464

56.   Cole ED, Ferrara D, Novais EA, Louzada RN, Waheed NK (2016) Clinical Trial Endpoints for Optical Coherence Tomography Angiography in Neovascular Age-Related Macular Degeneration. Retina 36 Suppl 1: S83-S92 DOI 10.1097/IAE.0000000000001338

57.   Spaide RF, Curcio CA (2017) Evaluation of Segmentation of the Superficial and Deep Vascular Layers of the Retina by Optical Coherence Tomography Angiography Instruments in Normal Eyes. JAMA Ophthalmol 135: 259-262 DOI 10.1001/jamaophthalmol.2016.5327

58.   Ploner SB, Moult EM, Choi W, Waheed NK, Lee B, Novais EA, Cole ED, Potsaid B, Husvogt L, Schottenhamml J, Maier A, Rosenfeld PJ, Duker JS, Hornegger J, Fujimoto JG (2016) TOWARD QUANTITATIVE OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY: Visualizing Blood Flow Speeds in Ocular Pathology Using Variable Interscan Time Analysis. Retina 36 Suppl 1: S118-S126 DOI 10.1097/IAE.0000000000001328

Figure Legend

Figure 1. Optical coherence tomography angiography of a 45-year-old diabetic patient with proliferative diabetic retinopathy. A. Fluorescein angiography showed multiple areas of ischemia with small neovascular proliferation in the supero-temporal vascular arcade. The superficial (B) and deep (C) retinal capillary plexus showed the areas of flow signal voids with a mild temporal enlargement of the foveal avascular zone. D. Near-infrared reflectance showed the scanned area

on panel E (green line). E. Structural OCT at the level of the supero-temporal arcade showed an area of vitreous proliferation (arrowhead). F. OCT angiography segmented at the level of the posterior hyaloid showed an area of abnormal flow signal corresponding with the area of neovascularization (arrowhead).

Figure 2: Optical coherence tomography angiography (OCTA) images of eyes with age-related macular degeneration (AMD). En face OCTA (top row) and corresponding cross-sectional OCTA (bottom row). Left column: Neovascular AMD with type 1 neovascularisation (NV) with flow seen below the retinal pigment epithelium (RPE) on cross –sectional OCTA and a corresponding flow signal on en face OCTA. Second from left column: Neovascular AMD with type 2 NV with flow noted above the RPE on cross sectional OCTA in the region of sub-retinal hyperreflective material and a corresponding flow signal seen on en face OCTA. Third from left column: Neovascular AMD with type 3 NV (yellow circle) seen as a abnormal linear flow signal within the retina extending deep towards a small pigment epithelial detachment on cross sectional OCTA (bottom row) and corresponding tuft of vessels seen on en face OCTA (top row). Right column: Non-neovascular AMD with geographic atrophy (GA) atrophy seen on cross-sectional OCTA with boundaries marked by a hyper-transmission signal in the choroid that contains a flow signal, which resulted in a corresponding unmasking artifact seen on en face OCTA in the area of GA. No flow signal was seen within the retinal layers in this case.

Figure 3: Optical coherence tomography angiography (OCTA) images of the outer retinal segmented layer (top row) with the projection artifact removed, depth encoded colour images (middle row) and cross sectional OCTA (bottom row) showed a type 1 neovascularization at baseline (left column), after treatment with 2 doses of intravitreal ranibizumab (middle column) and after an additional injection of ranibizumab and 3 additional injections of bevacizumab, the last given 6 months before this image was taken (right column). The type 1 NV showed a decrease in size and vessel density, with pruning of the more peripheral anastomotic vessels in response to treatment. In addition, there was a gradual decrease in subretinal fluid as seen on cross sectional OCTA however despite the achieving stability with no exudation (right column), the type 1 vessel complex still persisted.

Figure 4. Optical coherence tomography angiography of optic disc in acute stage of non-arteritic ischemic optic neuropathy (top left). Early images reveal sectoral areas of vascular changes (top right), with suggestion of sectors of reduced microvascular signal in the inferior quadrants after several days (bottom left) and eventually, unmasking of vessels with retinal nerve fiber layer loss and optic disc pallor in late stage of disease (bottom right).

Figure 5. Top: Optical coherence tomography angiography of the iris in an eye with neovascular glaucoma and new vessels at the iris along the pupillary

margin. Optimisation and improvements are required to detect normal and abnormal iris vessels especially in pigmented irides. Optical coherence tomography angiography of the anterior segment have been previously described for corneal vascularisation, but this technique also allows for evaluation of failed or scarred blebs after trabeculectomy and may provide more information on bleb function to guide decisions on intervention.

Supplementary Figure 1. Wide-field optical coherence tomography angiography images of the case of ischemic branch retinal vein occlusion showed areas of flow signal voids superior temporal to the macula corresponding to areas of ischemia. The image was obtained with full-retinal segmentation and a montage of multiple smaller-field en face optical coherence tomography angiography images to create a wide-field image without sacrificing resolution and detail. The foveal avascular zone in this case was not enlarged and did not show any macular ischemia.

Supplementary Figure 2: Cross sectional (bottom left) and en face optical coherence tomography (top left) of an eye with macular telangiectasia type 2 showing the presence of intra-retinal cystic changes. En face (top right) and cross-sectional optical coherence tomography angiography (bottom right) showed stellate arrangement of perifoveal telangectatic vessels temporal to the fovea that may be due to contraction of the tissue due to degenerative changes.

Supplementary Figure 3: Indocyanine green angiography (ICGA) (top left), structural optical coherence tomography (OCT) image (bottom left), en face (top right) and cross sectional OCT angiography (OCTA) images of eyes with polypoidal choroidal vasculopathy. Polyps (yellow circle) showed hyper-reflectivity within a peaked pigment epithelial detachment (PED) with a corresponding focal abnormal flow signal seen on cross sectional OCTA, on ICGA the polyps show extensive hyper-cyanescence but have only the patchy corresponding high flow signals on en face OCTA. The adjacent branching vascular network (blue arrows) is seen as a shallow, irregular PED with abnormal flow signal on cross sectional OCTA and a corresponding high flow network of vessels seen on en face OCTA similar to the appearance on ICGA. Supplementary Figure 4. Optical coherence tomography angiography (OCTA) images of secondary causes of neovascularization (NV). Left column: Type 1 NV related to chronic central serous chorioretinopathy, seen on cross sectional OCTA (bottom row) as flow signal within a shallow irregular pigment epithelial detachment, with a thick choroid, and corresponding abnormal flow signal seen on en face OCTA (top row) with projection artifact removed, and imaged on a depth colour encoded en face OCTA image with the NV seen in blue (middle row). Middle column: Myopic NV seen as an abnormal flow signal on cross-sectional OCTA (bottom row), with a corresponding abnormal flow signal on en face OCTA (top row) with the projection artifact removed and depth colour encoded en face OCTA with the NV appearing blue-green. Right column: Type 2 NV secondary to inflammatory diseases seen as abnormal flow signal in areas of

subretinal hyper-reflective material on cross-sectional OCTA (bottom row), and a corresponding flow signal on a 6x6 mm en face OCTA image (top row) showed a larger imaged area with less detail while a magnified view of the NV on a 3x3mm en face OCTA image (middle row) showed greater detail of the NV.