

Review article

Optical Coherence Tomography Angiography – A New Insight Into Macular Vasculature

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Abstract

Optical coherence tomography angiography (OCT-A) is a new non-invasive technology for imaging of retinal and choroidal vasculature of the macular area with resolution comparable to histological sections. OCT-A does not require usage of intravenous dye, contrary to fluorescein angiography, the current gold standard for imaging of retinal vessels, and indocyanine-green angiography, which is important for imaging of choroidal vessels. With the advancements in optical coherence tomography (OCT) scanning speeds and creation of powerful algorithms for improvement of image quality in recent years, OCT-A imaging of macular vasculature, superficial, deep and avascular retinal complex, as well as choriocapillaris and deep choroid has become available in everyday clinical practice. This review covers aspects important for understanding choroidal and retinal blood supply, as well as the development, mechanisms and clinical application of OCT and OCT-A technology.

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Introduction

Optical coherence tomography angiography (OCT-A) is a novel non-invasive technology for detailed imaging of retinal and choroidal vasculature of the macular area. It utilizes laser light reflectance off moving erythrocytes, generating information about volumetric blood flow in all retinal layers and the choroid (1). The resolution of OCT-A is comparable to the resolution of histological sections (2). Unlike fluorescein angiography (FA) or indocyanine-green angiography (ICG), OCT-A does not require the use of dye (1).

Dye-based angiography has been the gold standard for imaging macular and choroidal vasculature for decades. Because of the risk of adverse reactions, particularly vomiting, nausea, allergic reaction and anaphylaxis, coupled with the time-consuming nature of the examination (10 to 30 minutes), dye-based angiography is not frequently used for monitoring the course of retinal vascular diseases. While FA can only delineate superficial retinal vasculature, ICG imaging is restricted to visualization of the choroidal circulation. Moreover, FA is not capable of imaging the radial peripapillary capillary network (RPC), which is very important for monitoring of glaucoma (3).

FA is still the gold standard for detecting choroidal (CNV), retinal (NVE, neovascularization elsewhere), disc (NVD), neovascularization of the disc) and irideal (NVI, neovascularization of the iris) neovascularization (4).

Optical coherence tomography angiography- creating an image

Optical coherence tomography

Optical coherence tomography (OCT) is a diagnostic technique that enables in vivo cross-sectional visualization of the tissue in focus. It is currently used for imaging in cardiology, ophthalmology, oncology and dermatology (5). In ophthalmology, it was first introduced in 1991 by Huang et al. (6). OCT uses interferometry to measure the amplitude and delay of reflected or backscattered near-infrared light from ocular

structures. The depth of structure measured in this fashion is known as axial scan (A-scan). By sequential arranging of multiple A-scans in the transverse direction, a B-scan or cross-sectional image is generated (7).

OCT is based on two techniques: time-domain (TD-OCT), introduced in 1996 (8), and frequency-domain (FD-OCT), devised as spectral-domain (SD-OCT) and swept-source (SS-OCT). The importance of the advent of FD-OCT technology is the acceleration of slow scan so that artefacts caused by motion in earlier TD-OCT devices are no longer an impediment for better imaging of small vessels (9).

Doppler OCT (DOCT) was first introduced concurrently by Izatt et al. (10) and Chen et al. (11) in 1997. DOCT provides quantitative volumetric information about blood flow, together with vascular and structural anatomy. However, it is limited to larger vessels (12). In clinical practice, DOCT is not widely used (12, 13).

Optical coherence tomography angiography (OCT-A)

OCT-A is a three-dimensional functional extension of OCT which uses repeated B-scans of the same retinal location to detect blood flow. In 2012, OCT-A was introduced as a method for imaging the retinal microvasculature (14). OCT-A signals are primarily used to detect the presence or absence of vessels, rather than to provide information about blood flow speed, enabling three-dimensional en face imaging (15). If retinal location is stationary (i.e. if there is no blood flow), the repeated B-scans will be identical. However, if the tissue's optical scattering is time-dependent because of the blood flow through the region, the repeated B-scans will vary. The most important vascular component that can induce backscattering of light is red blood cells. Areas of faster blood flow will show greater change over a unit of time. The exact relationship of this change in regard to flow speed depends on many parameters, such as OCT beam size and blood vessel size, and is not necessarily linear (16).

By using different algorithms, OCT-A can monitor flow even in transverse motion, while the other form of monitoring the motion of RBCs, Doppler shift (used in DOCT), can monitor flow only in axial motion. This enables OCT-A to monitor flow in microvasculature, while DOCT can monitor flow only in larger vessels (17). Optical resolution of commercially available OCT-A systems ranges between 5-10 μ m in the axial, and averages \sim 20 μ m in the transverse direction (16). Smaller resolution improves the differentiation of retinal vasculature but increases sensitivity to eye motion. If the signal is below a threshold, a mask is generated. Errors in imaging caused by bulk tissue motion are reduced by using different eye tracking modalities (15). OCT-A quantification of blood flow, namely flow index and vessel density, has great clinical importance. Flow index is the average flow signal in the area of interest. Vascular density is the percentage of the area occupied by vessels (18).

Image artefact is an anomaly in the visual presentation of information derived from an object. Projection artefact, one of the most important types of artefacts, represents the appearance of the object at a deeper location than where it exists in reality due to disturbance of the signal. Shadowing is the attenuation of a signal behind a scattering opacity or obstruction that absorbs the signal. Displacement artefact is caused by eye motion where one part of the image is from one retinal location, while the remaining part of the image is from a different retinal location. Stretch artefact is related to software correction of eye motion in which part of the image appears to be stretched. White line artefact is a white line seen due to eye movement (19).

One of the most important limitations of OCT-A is a fixed area of the central field of view measuring 3 \times 3, 6 \times 6 and 12 \times 12 mm. Visualization of the peripheral retina is thus not possible (19). OCT-A can detect blood flow above the minimum threshold only. Areas with flow under the threshold remain invisible (20, 21).

For example, in case of branch retinal vascular occlusion, slow-flow areas may be perceived as areas of non-perfusion (21). Moreover, OCT-A is incapable of accurately determining vascular leakage, which is especially important in neovascular age-related macular degeneration (nAMD), diabetic macular oedema, and retinal vein occlusion (22). Because of the need for steady fixation, it is difficult to obtain images of children's retina.

Clinical use of OCT-A

In OCT-A, vascular abnormalities manifest as abnormal vessel density (dry age-related macular degeneration, AMD), anomalous vessel geometry (dilated vessels, aneurysms in diabetic retinopathy, DR), abnormal flow (CNV) and absent flow (nonperfusion/capillary dropout in retinal artery or vein occlusion). Therefore, OCT-A is currently extensively useful for patients with variable retinal diseases (15). OCT-A concurrently obtains images of both retinal and choroidal macular vasculature divided into different layers based on their depth. Moreover, OCT-A enables the imaging of RPC, originating from choroidal vessels, which is particularly vulnerable to glaucoma and retinal vascular occlusion (23). Retinal capillary plexuses are divided into (a) superficial vascular plexus (SVP), located in the retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL), and (b) deep vascular plexus (DVP) that extends down to the inner nuclear layer (24). DVP is subdivided into intermediate (ICP) and deep capillary plexus (DCP) (25). Additionally, OCT-A is the only method capable of visualizing CC separately from the deeper choroid (15).

Foveal avascular zone (FAZ)

The capability of OCT-A to image capillaries with high resolution has enabled researchers to study the foveolar avascular zone (FAZ) in greater detail than it had been possible in the past with FA. On an OCT-A scan, FAZ is presented as a discoid zone within the macula that is devoid of capillaries (Figure 1).

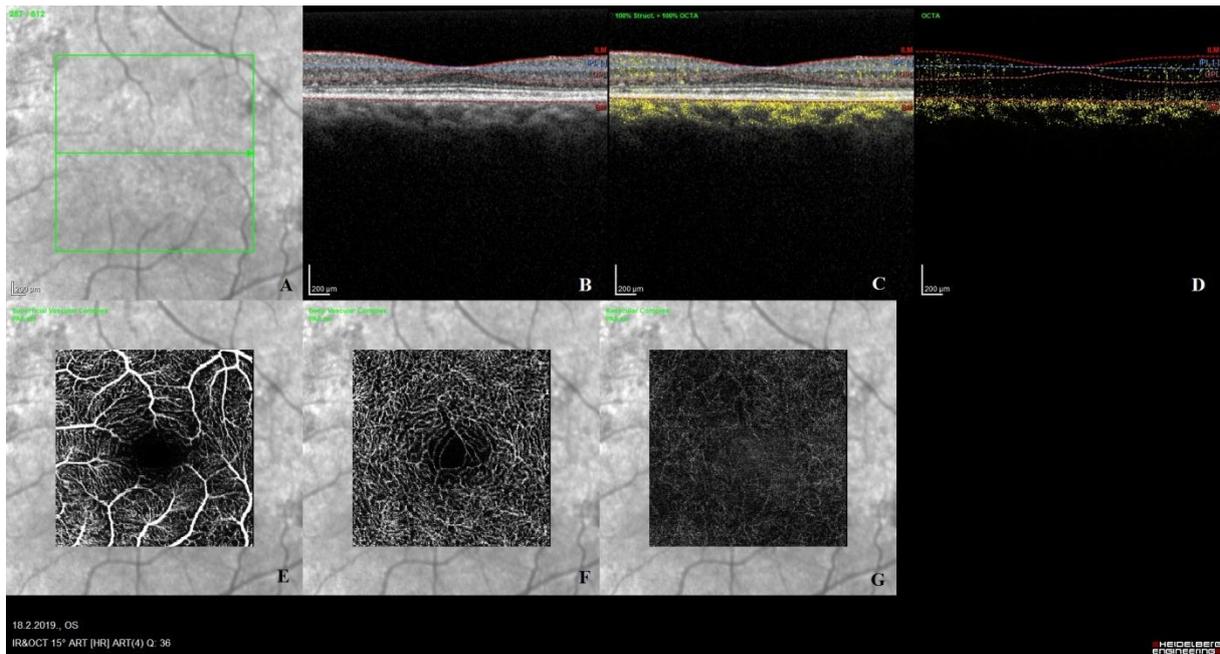


Figure 1. OCT-A image of the left eye of a healthy 60-year-old female patient. (A) Photography of the macula. (B) Foveal anatomy. (C) Foveal layers with depicted red blood cells (yellow). (D) Red blood cells (yellow) in the foveal area. Clear distinction is visible between (E) SVP, (F) DVP and (G) avascular complex of the retina. Images obtained from Spectralis® OCT (Heidelberg Engineering, Heidelberg, Germany). OCT-A-optical coherence angiography, OCT-optical coherence tomography, SVP-superficial vascular plexus, DVP-deep vascular plexus

FAZ borders are manually drawn on a certain capillary plexus level. Parameters defining FAZ are divided into two groups. Area (in mm²), perimeter (length of the FAZ borders, in mm) and Feret's diameter (maximum diameter of FAZ, in mm) assess the size, while circularity, axial ratio, roundness and solidity represent the shape of FAZ. FAZ circularity is the degree of resemblance to a perfect circle ($4\pi \times \text{area}/\text{perimeter}^2$). Axial ratio is obtained from a best-fit ellipse of the FAZ (length of major axis/length of minor axis of a best-fit ellipse). Roundness uses the best-fit ellipse and is similar to circularity, but is insensitive to irregular borders along the perimeter of the FAZ ($4\pi \times \text{area}/(\text{length of major axis})^2$). Solidity describes the extent to which a shape is convex or concave ($\text{area}/\text{convex area}$). These parameters are calculated using computer software (26). Most studies that investigated FAZ parameters in healthy individuals reported a larger deep area compared to the superficial area of FAZ (27, 28, 29, 30). Superficial and deep FAZ area are larger in females (26, 31, 32), and this is possibly related to thinner fovea (32). The FAZ area and foveal

thickness at both the SVP and DVP levels exhibited significant inverse correlation (26, 29, 30). This could be explained by an association between higher metabolic demand of a thicker retina and a reduction of the FAZ area (30).

Previous studies using FA observed an increase in the FAZ size with advancing age. However, FA as a diagnostic method is limited when it comes to SVP imaging and should not be correlated with OCT-A (32, 33). The studies that examined changes that occur in FAZ with aging are inconclusive. Some studies reported significant (34, 35), while others observed insignificant changes in the FAZ area with aging (27, 28, 29, 36). Yu et al. found an increase in the FAZ size by 1.48% annually, with a decrease in vascular density by 0.4% (35). In studies using FA, it was proposed that in patients aged 40 or older, age was positively correlated with the FAZ area (32); however, studies using OCT-A did not support this conclusion (36). Coscas et al. divided their participants by age into three groups: 20–39 years old, 40–59 years old, and 60 years old or older (37). The FAZ size was smaller in the oldest group compared to the two younger

groups at the level of SVP. No statistically significant difference was found for the level of DVP among the groups (37).

A single study evaluated the FAZ shape in healthy eyes and demonstrated that none of

these parameters was significantly correlated with age, sex and refractive error (26). There are no homogenous studies about FAZ parameters in children (Figure 2).

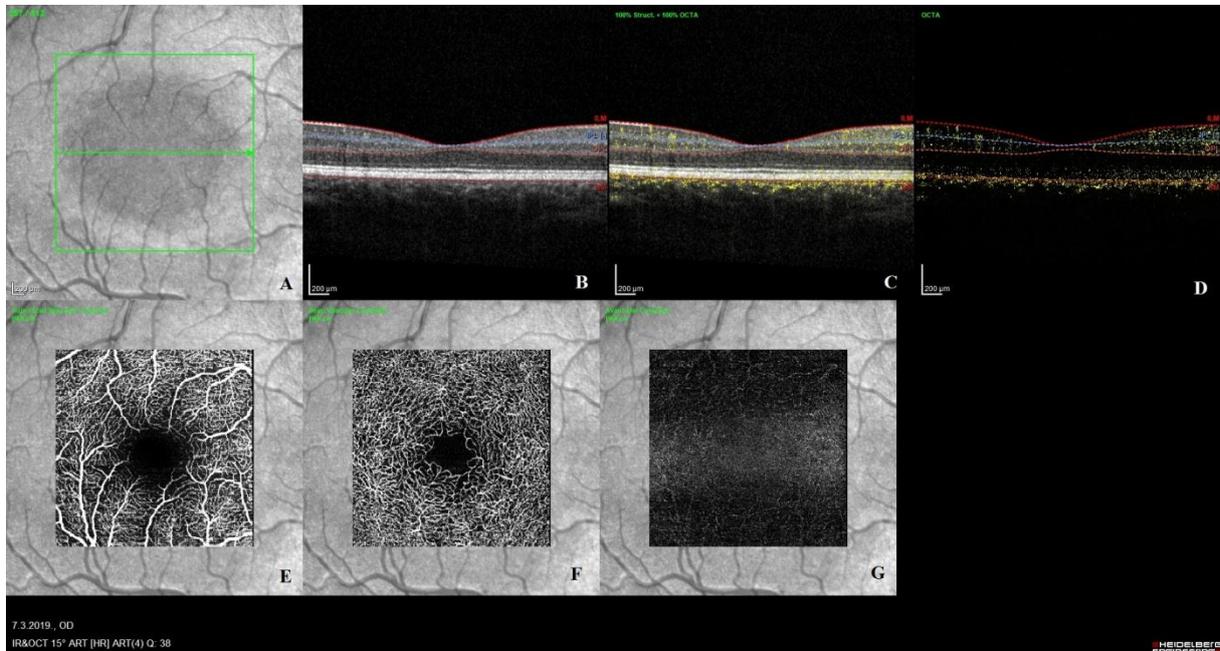


Figure 2. OCT-A image of the right eye of a healthy 4-year-old female patient. (A) Photograph of the macula. (B) Foveal anatomy. (C) Foveal layers with depicted red blood cells (yellow). (D) Red blood cells (yellow) in the foveal area. Clear distinction is visible between (E) SVP, (F) DVP and (G) avascular complex of the retina. Images obtained from Spectralis® OCT (Heidelberg Engineering, Heidelberg, Germany). OCT-A-optical coherence angiography, OCT-optical coherence tomography, SVP-superficial vascular plexus, DVP-deep vascular plexus

Choroidal neovascularization (CNV)

The advent of OCT has enabled new classification of CNV: type 1 (beneath the RPE), which is the most common type, type 2 (above the RPE) (Figure 3) and type 3 (intra-retinal).

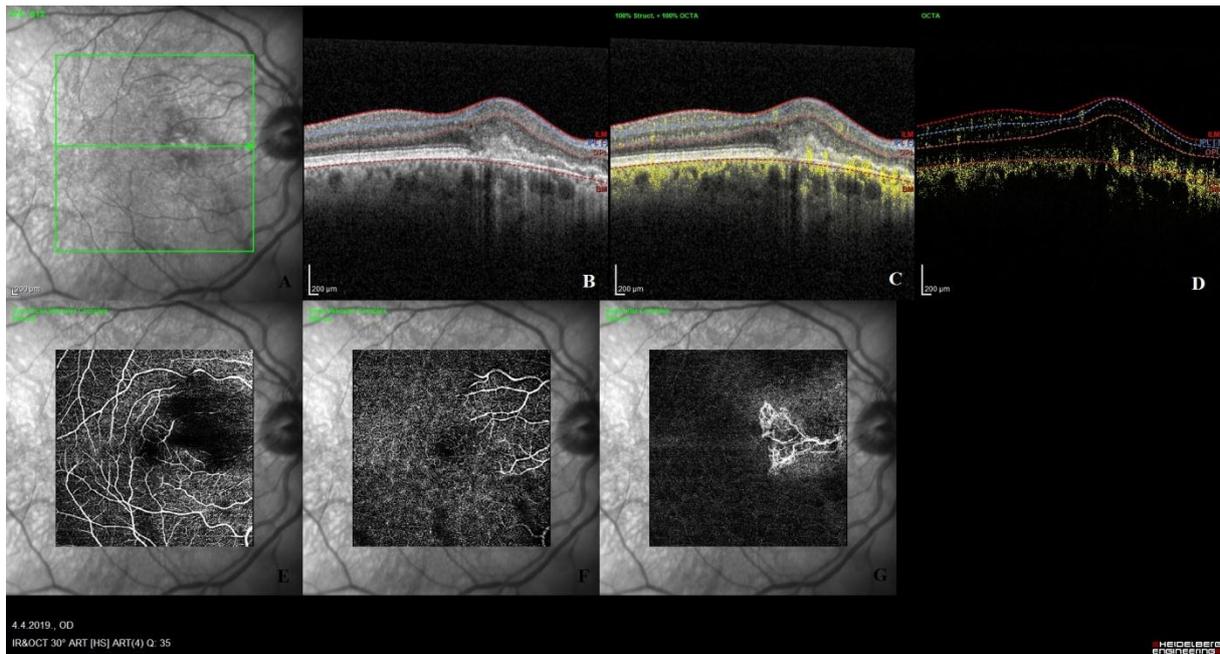


Figure 3. OCT-A image of the right eye of a 71-year-old male patient with type 2 CNV. (A) Photography of the macula with oedema of the papillomacular area. (B) Foveal anatomy. (C) Foveal layers with depicted red blood cells (yellow). (D) Red blood cells (yellow) in the foveal area. OCT images demonstrate mild oedema of retinal layers and Bruch's membrane rupture with NV emerging from the choroid. (E) SVP devoid of vessels in the area of the pathologic process. (F) DVP with NV. (G) NV emerging from the choroid. Images obtained from Spectralis® OCT (Heidelberg Engineering, Heidelberg, Germany). OCT-A-optical coherence angiography, CNV-choroidal neovascularization, OCT-optical coherence tomography, SVP-superficial vascular plexus, DVP-deep vascular plexus, NV-neovascularization

Type 1 is the most common type of CNV in AMD. FA is incapable of determining whether CNV is above or beneath the RPE and thus of defining the type of CNV or of detecting a polyp in polypoidal choroidal vasculopathy, a subtype of type 1 CNV. CNV therefore requires multimodal imaging (OCT, FA, ICG) (38). OCT-A can vastly improve the definition of exact CNV dimensions compared to FA (39, 40, 41, 42). This is of high importance as larger CNVs have poorer visual outcome (39).

OCT-A introduced new biomarkers for predicting disease activity and duration. Greater vessel calibres are fairly unresponsive to treatment due to excessive covering with pericytes (39). Encouraged by these insights, the greatest vascular calibre (GVC) was proposed as the marker of long-standing disease. The GVC could reveal the duration of CNV, which is important due to excessive damage caused by long-standing type 1 CNV, which remains

asymptomatic longer than type 2 (39). More mature vessels are found in type 1 CNV compared to type 2 (43). As a biomarker for active CNV, tiny branching vessels (TBV) can be used due to their presence in 82% of active lesions and only 30% of quiescent ones (44). The peripheral arcade is also present in 82% of active lesions compared to 40% of quiescent ones (44, 45). TBVs are important because they are more vulnerable to treatment due to their lack of pericytes compared to prominent vessels. In addition, pericytes appear later than angiogenesis, which means that TBVs could be related to the exudative status of the lesion; they could enable prompt treatment in order to preserve the macular architecture and thus, visual acuity (45). In light of these findings, it seems reasonable to include OCT-A imaging in the monitoring of all patients with CNV (45).

Nonexudative (subclinical) CNV was first described in post-mortem eyes by Green et al.

(46) and Sarks et al. (47) as abnormal choroidal vessels passing through breaks in Bruch's membrane in the absence of overlying haemorrhage or exudation. These lesions, which presented as plaques on ICG (48), can now be diagnosed more accurately using OCT-A (49). Compared with ICGA, the sensitivity and specificity of OCT-A in detecting subclinical CNV was reported as 81.8% and 100 %, respectively (50). It would be beneficial to determine the presence of subclinical CNV in fellow eyes of patients with unilateral exudative AMD, which ranges from 6.25% to 27%, respectively (49). The progression rate of subclinical CNV to exudative form is 20% and the existence of a possible protective effect of subclinical CNV against geographic atrophy progression has been suggested (51). Reduction in CC flow adjacent to CNV could be a marker of imminent exudation in subclinical CNV, as new evidence demonstrates (49, 51). Exudation may be triggered by the underlying progression of CC nonperfusion. Hypoxia of the retinal pigment epithelium causes the release of abnormal vascular endothelial growth factor (VEGF) signalling with growth and eventual exudations of a CNV (49).

Glaucoma

Pathophysiology of glaucoma and the onset of changes in macular vasculature are yet to be elucidated. Recent studies have suggested that macular vascular changes in glaucoma may be related to mechanisms other than intraocular pressure (IOP) (52, 53). In early glaucoma, OCT-A revealed focal loss of RPC (54) and decreased parafoveal vascular density (52). In eyes with central visual field defects, FAZ perimeter could be used as a biomarker for detecting glaucoma (55). In a recent study, eyes with open-angle glaucoma demonstrating central visual field defects (CVFDs) confined to a single hemifield exhibited a larger FAZ area and a less circular FAZ than those with peripheral visual field defects (55). Loss of FAZ circularity and increased size of the FAZ area were significantly correlated with the presence and severity of CVFD at initial presentation (55).

Parafoveal and peripapillary vascular density decrease in primary open-angle glaucoma compared to normal tension glaucoma (52, 53) is inconsistent with the earlier described mechanism of normal tension glaucoma development through its association with vascular compromise as a contrast to primary open-angle glaucoma, where the pathophysiology is mostly correlated with intraocular pressure (56). It is unclear whether vascular density changes in glaucoma antedate ganglion cell loss or are a direct result of loss of neural tissue and thus a marker for both primary open-angle glaucoma and normal tension glaucoma (53).

Diabetic retinopathy

Optical coherence tomography angiography offers a non-invasive alternative in the investigation of diabetic retinopathy. FAZ has been one of the most extensively investigated areas in diabetic retinopathy (57). In eyes with diabetic retinopathy, the circularity and axial ratio of the FAZ are significantly different from normal eyes. These metrics could be predictors of disease progression and response to therapy (58). However, even without retinopathy, OCT-A demonstrated significantly enlarged FAZ areas compared to controls – in both the SCP and DCP (57).

In eyes with diabetic retinopathy, OCT-A can identify microaneurysms (MA), microvascular abnormalities associated with diabetic macular oedema (DMO), and areas of capillary non-perfusion associated with neovascularization, allowing enhanced analysis compared to FA in that their intraretinal location beyond SVP can be identified (59). However, the sensitivity for MA detection and small field of view are currently the major limitations of OCT-A technology (57). A lower number of MA visible on OCT-A as compared to FA may be due to slower flow speeds in MA that are beyond the OCT-A detection threshold (60) or due to focal staining of vessel walls allowing superior identification by FA (61).

In eyes with proliferative diabetic retinopathy, OCT-A can visualize preretinal

neovascularization. Compared to FA, OCT-A has demonstrated moderate agreement for grading of diabetic macular ischemia (59).

By enabling three-dimensional visualization of the individual retinal vascular networks, OCT-A is enhancing our understanding of the role of deeper vasculature in the pathogenesis of diabetic retinopathy and maculopathy. OCT-A can differentiate between different subgroups of diabetic retinopathy severity by measuring perfusion indices in eyes with DR and branching complexity of vessels (57). The decrease in vascular density with the progression of the disease has already been established (62, 63). Reduction of vascular density in DVP occurs earlier in the course of the disease and this finding gives rise to possible new studies concerning vascular density in DVP as a marker of disease severity in earlier stages of diabetic retinopathy (60). FAZ enlargement and reduction of parafoveal deep and superficial vascular density can be beneficial as a marker of increased disease severity in diabetic retinopathy (60).

Central serous chorioretinopathy

Diagnosing CNV as a complication of chronic central serous chorioretinopathy (CSCR) using FA is difficult due to the confusing signs of the primary disease, such as choroidal hyperpermeability, retinal pigment epithelium leakage, or atrophy and cystic macular oedema (64). OCT-A has the advantage of identifying only the flow, without the exudative component, and it allows for depth-correlated visualization of flow with separation of the signal generated from the pathologic area between RPE and the Bruch membrane from the CC. These advantages of OCT-A are more prominent for type 1 CNV (65). CNV locations correspond to slightly irregular and hyperreflective RPE areas (66), which is consistent with earlier observations (67).

With OCT-A, a higher detection rate of CNV (mainly type 1) in chronic CSCR is achieved compared to ICG and FA (65). Thus, in case of

CSCR, using OCT-A B-scan and en-face mode is always recommended in order to define the area of flat irregular pigment epithelial detachment, which is claimed to be imperative for the CNV diagnosis (65).

Ocular oncology

A significant enlargement of the deep FAZ and a decrease in the superficial and deep vascular density in eyes with choroidal melanoma were observed compared to healthy eyes (68). These changes are correlated with larger tumour size and presence of subretinal fluid, which could elucidate the pathogenesis of vision loss in patients with melanoma (68). One possible mechanism behind these changes is VEGF-induced microvascular compromise preceding macular oedema (68). These features are absent in eyes with choroidal nevi, giving rise to easier differentiation of small melanoma from choroidal nevi (68).

Early vascular changes in radiation retinopathy that can be detected by OCT-A as irregular widening of FAZ, discontinuity of retinal vasculature and retinal MA have been used as a part of a new grading scheme and treatment decisions for radiation retinopathy (69).

Conclusion

OCT-A is an important new non-invasive tool for imaging of the chorioretinal vasculature. It has provided new insights into the pathogenesis of multiple retinal and choroidal diseases, but its full contribution is yet to come. Regarding the paediatric population, the normal values have to be defined first in order for us to accurately elucidate the pathology.

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