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Optical coherence angiography
A review

Adam Wylęgała, MD, PhD[a,*], Sławomir Teper, MD, PhD[b], Dariusz Dobrowolski, MD, PhD[a,b], Edward Wylęgała, MD, PhD[b]

Abstract

Background: Retinal vascular diseases are one of the most common causes of blindness in the developed world. Optical Coherence Tomography Angiography (OCT-A) is a new noninvasive method that uses several algorithms to detect blood movement. This enables the creation of high-resolution vascular images with contrast depicting motionless tissue.

Methods: This review presents the results of articles relevant to age-related macular degeneration (AMD), diabetic retinopathy (DR), and OCT-A. The OCT-A technique can successfully be used in the diagnosis of neovascularization, retinal vein occlusion (RVO) and retinal artery occlusion (RAO), vessel abnormalities and even anterior segment neovascularization. OCT-A can also be applied to compute data such as vessel density, and flow index in both superficial and deep plexuses.

Results: Many studies have compared fluorescein angiography with OCT-A. Other studies have reported differences in vascular density in AMD patients and have compared them with people having healthy eyes. Although OCT-A offers rapid picture acquisition, high repeatability and resolution, it also has many drawbacks. The most common are: motion artifacts, projections from overlying vessels and limited field of view.

An interesting new application is the possibility to assess changes during antivascular endothelial growth factor (anti-VEGF) therapy. Another function of OCT-A is the possible application in the study of choriocapillaries in many fields of ocular pathology.

Conclusion: OCT-A is a new promising method that allows the visualization of the retinal vascular network and the counting of blood flow parameters. This technique provides reliable images useful in clinical routines.

Abbreviations: AMD = age-related macular degeneration, anti-VEGF = retinal artery antivascular endothelial growth factor, CNV = choroidal neovascularization, DL = deep layer, DR = diabetic retinopathy, FA = fluorescein angiography, FAZ = foveal avascular zone, MS = multiple sclerosis, NPA = nonperfusion areas, OCT-A = Optical Coherence Tomography Angiography, PV = phase variance, RAO = retinal artery occlusion, RVO = retinal vein occlusion, SL = superficial, SSAD = split spectrum amplitude decorrelation, SS-OCT = swept source OCT, SV = speckle variance.

Keywords: AMD, anti-VEGF, CNV, diabetic retinopathy, optical coherence tomography, Optical Coherence Tomography Angiography (OCT-A)

1. Introduction

OCT is a noninvasive, noncontact method that enables in vivo visualization of cross sections. This technique was introduced in 1991 and since then it has revolutionized ophthalmology in both clinical and research area. Today it enables the visualization of both anterior and posterior segments, the production of 3D models of internal parts of the eye, measurement of the velocity of blood flow as well as vascular density.[1]

One of the new inventions is Optical Coherence Tomography Angiography (OCT-A). It allows visualization of retinal vasculature without the need to inject dye.[2,3] Almost 55 years ago, Novotny and Alvis injected fluorescein dye and used a fundus camera modified with several filters to take images of retinal vasculature. Before taking a vasculature image 5 mL of fluorescein were injected into a patient's vein.[4] This technique was later called fluorescein angiography (FA). Doppler-OCT, that allows visualization of blood velocity, was introduced later.[5] However, it only allows the measurement of axial speed and it should be adjust to heart rate.[6] Another technique to study retinal blood flow is laser speckle imaging.[7] As light produced by lasers is a coherent wave, when it strikes an object it creates a secondary wave front. When superpositioned, these reflected waves create small regions when the waves interfere. This constructive interference can be seen as speckles.[8] Motion in tissue produces a signal that differs over time, while stationary tissue only produces a constant reflection. Movement detection leads to the possible encoding of pixels. When change in the signal of one area has been detected in B-scan (Fig. 1), the system encodes it as bright pixels, assuming that this is blood flow, whereas no change in signal is encoded as dark color.[9]

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[a] Departament of Ophthalmology, Santa Barbara Hospital, Sosnowiec,
[b] Ophthalmology Clinic, Railway Hospital Katowice, II School of Medicine with the Division of Dentistry in Zabrze, Silesian Medical University, Katowice, Poland.

[*] Correspondence: Adam Wylęgała, Department of Ophthalmology, Santa Barbara Hospital, Sosnowiec, Plac Medyków 1, Sosonwiec 41-200, Poland (e-mail: adam.wylegala@gmail.com).

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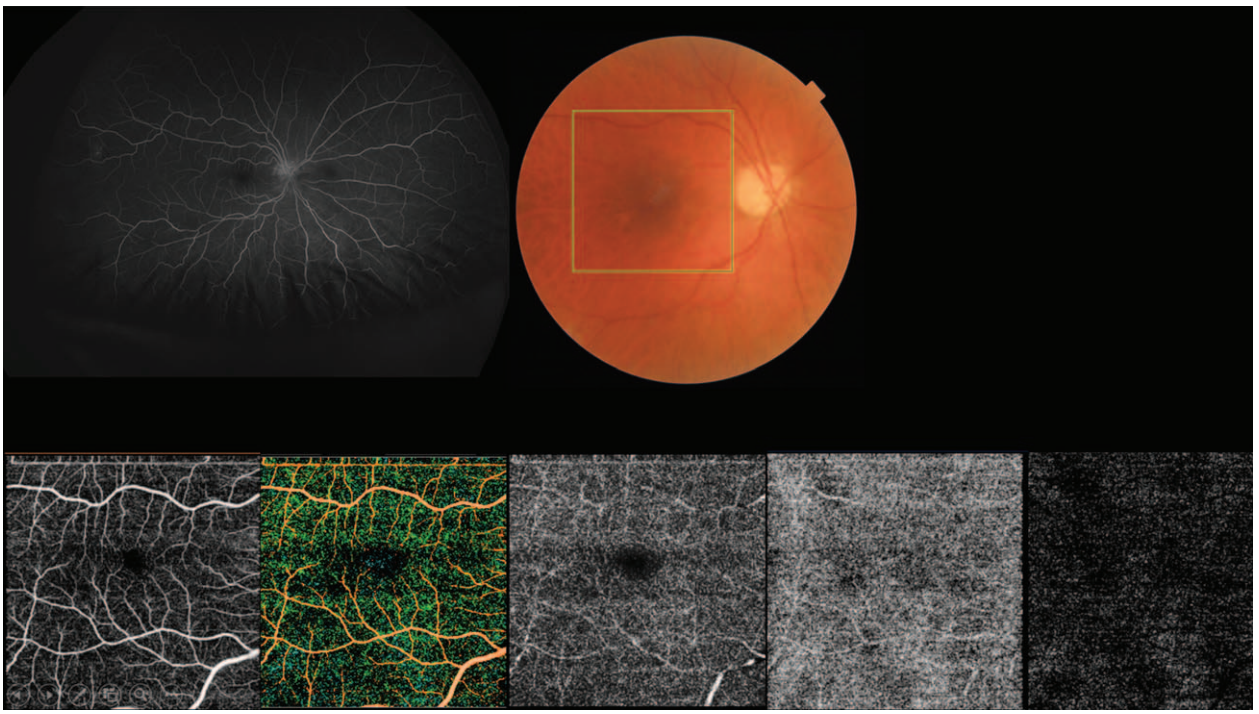

Figure 1. Comparison of wide field FA and 6 mm × 6 mm OCT-A. OCT-A is able to visualize only a small fragment of retina. From right to left top: FA image, Fundus photo with a 6 mm × 6 mm square. Bottom: superficial layer, merged images, deep layer, outer retina, and choriocapilaries. Topcon Triton. Optos California.

In 2006, Makita et al[10] constructed a modified SD-OCT and applied it to make scans of retinal vasculature. One year later, Yasuno et al[11] demonstrated that it is possible to visualize choriocapillaris and choroidal microvasculature using modified swept source OCT (SS-OCT). SS-OCT uses a high frequency laser around 100 kHz,[12] which allows up to 400,000 A-scans per second to be made. This procedure also uses a complementary metal–oxide–semiconductor camera as opposed to the Charge-coupled device sensor used in SD-OCT. The aforementioned changes allow a 5.3 μm axial resolution to be achieved. Moreover, use of infrared light improves tissue penetration.[13] Visualizing choroid might play a crucial role in understanding pathology of retinal disease as it plays major role in nourishing both Retinal pigment epithelium (RPE) and photoreceptors.[14]

OCT-A reveals more details in the superficial and, especially, in the deep retinal layer than FA.[15] Many studies have shown that OCT-A is useful for diagnosing choroidal neovascularization (CNV) age-related macular degeneration (AMD),[16] retinal vein occlusion (RVO),[15] abnormal retinal vessels,[17] and even nonexudative AMD[18] and melanocytic tumors.[19] However in contrast to FA, OCT-A will not detect pooling staining or leakage.[16] As OCT-A is a motion detection technique, structures with very slow motion (flow) will be poorly visible. Moreover, change in the thickness of the retina may lead to visual reposition of the vessels.[20]

Currently, several devices are equipped with OCT-A functions: XR-Avanti (Optovue, Inc., Fremont, CA. USA), Triton and Atlantis (Topcon, Tokyo. Japan), Cirrus HD (Carl Zeiss Meditec, Inc., Dublin, CA. USA), Spectralis (Heidelberg Engineering, Heidelberg. Germany), and RS-3000 (Nidek Co, Gamagori. Japan).

2. Methods

This systematic review did not require ethical comity approval.

2.1. Database search

PubMed, Google scholar, and Mendeley literature search were utilized as a source of literature up to January 2016. Studies for this review were identified using an advanced search with the combined keywords: OCT, optical coherence angiography, angiography, AngioVue, and fluorescein angiography. Results are shown in a flow chart. It is important to note that all the articles discussed here observed changes ex post. Only English language manuscripts were considered. Studies describing OCT-A in animal models were excluded as well as studies discussing physical principles of OCT-A.

2.2. Technical principles

OCT-A is able to visualize any flow of fluids within the vessels. This modality may distinguish flow within the vessels from motionless tissue. This unique feature is possible thanks to several protocols such as split spectrum amplitude decorrelation (SSAD),[12] phase variance (PV), and speckle variance (SV).[14] All imagining methods can be defined as the amount of change in a region from 1 sequentially repeated image to the next.[8] Both SSAD and SV analyze amplitude alterations of the OCT signal, while PV analyzes the phase.[14] The OCT wave spectrum is divided into many narrow bands, which are then used to compute reflectance amplitude decorrelations in a single voxel over time. Splitting the spectrum reduces noise in axial dimensions associated with liquid flow. SSAD is used in Avanti (Optovue, Inc.) device.[21] Several algorithms have been developed to create

motion contrast.[22,23] One of these is optical microangiography, OMAG used in Cirrus (Carl Zeiss), that compares absolute differences between linear intensities of the repeated B-scans.[24] Another method of motion detection is OCT-A ratio analysis, where, rather than splitting the spectrum into narrower bands, the intensity-based ratio is analyzed. According to Topcon this should lead to better visualization of low intensity capillary networks.[25] Another approaches include dual beam-scanning OCT and phase-variance OCT.[26] An acquisition of high-quality images is not possible without reducing all movements such as saccade. This was overcome by introducing eye tracking software. Heildelber Spectralis obtains B-scans simultaneously with infrared images. After algorithm choses the reference image, all B-scans will be compared to it.[27]

There are three sizes for field of view—3 mm × 3 mm, 6 mm × 6 mm, and 12 mm × 12 mm. The first provides more detailed images due to its higher sampling density, while the latter offers wider retinal coverage.[28]

3. Results

3.1. Fluorescein angiography

The clinical relevance of OCT-A has been compared with regular angiography. OCT-A is fast and has no limited time window for imaging. However, due to large number of scans necessary for creating an image processing time may be long. Moreover, OCT-A enables the delineation of selected parts of the membrane, including choriocapillaris.[28]

Spaide compared FA with OCT-A in 12 patients, in none of the eyes was it possible to fully visualize radial peripheral capillary networks around the nerve head. In contrast, OCT-A provided reliable images from this region.[29]

Use of OCT-A might be advantageous in patients with history of allergic sensitivity to fluorescein.[30] In 1 study[31] the quality of images obtained by FA and OCT-A was compared. As many as 57% and 44% of images acquired using FA and OCT-A, respectively, were considered sufficient for quantitative and qualitative analysis. Foveal avascular zone (FAZ) was also better delineated and detected in OCT-A than in FA. The detection of microaneurysms was significantly lower than in FA.[31] OCT-A is superior to FA in detecting chronic intraretinal edema associated with hard exudates.[32] OCT-A provides little information about low flow structures such as polyps.[33] Miere et al showed a high rate of original CNV detection in OCT-A compared with FA (Table 1). The authors concluded that it was easier to visualize vascular plexus under a fibrotic scar.[34] In 1 patient, OCT-A could not detect a microaneurysm seen in FA.[35]

Another study examined scans of 29 eyes using AngioVue. The study concluded that OCT-A might be superior to FA due to smaller changes being detected by OCT-A. OCT-A is also useful when seeking to assess changes in neovascular complexes during type 3 neovascularization of AMD.[36] Bailey et al[37] concluded that OCT-A is superior to FA in visualizing occult CNV and subretinal hemorrhage.

OCT-A offers a rapid and noninvasive technique to discriminate the vascularized from the nonvascularized type of pigment epithelial detachment.[38]

One of the biggest limitations of OCT-A is image size. However, it is possible to visualize both the macula and the disk using FA. OCT-A only produces 6 mm × 6 mm images and this makes it almost impossible to capture those anatomical structures.[16]

3.2. Studies in normal subjects

Savastano et al described visual features of vessels localized in both DL (deep layer) and SL (superficial) in healthy eyes. SL

Table 1

Different studies comparing OCT-A and FA.

Refs.	Machine	FA	OCT-A	Disease
Suzuki,[45] 28 eyes	AngioVue (Avanti)	Telangiectasia 11/0 Veno-venous shunts 16 NPA 18 microaneurysm	Telangiectasia –13/11 Veno-venous shunts 18 NPA 28 microaneurysm	BRVO
Spaide,[31] 12 eyes	Avanti	14 mean proportion Inner plexus vs 95.3%	13 mean proportion Outer plexus 4.7%	Healthy eyes
Couturier,[33] 20 eyes	Avanti	11.7 ± 7.1 mean number of microaneurysm	7.3 ± 3.9 (62%)	Diabetic retinopathy
Mierie,[36] 49 eyes	Avanti	62% detection of CNV	93.8%	AMD
Coscas,[47] 54 RVO patients	Avanti	Perifoveal arcade 52 eyes Intraretinal cystoid space 49	 45 eyes 34	RVO
Dansingani et al,[54] 22 eyes of patients with irregular pigment epithelial detachment	Avanti	4/19 eyes with type 1 neovascularization	21/22 eyes with type 1 neovascularization	Pachychoroid spectrum disease and shallow irregular pigment epithelial detachment
Gong,[93] 86 eyes with suspected wet AMD	Avanti	52 cases of CNV	56 cases of CNV 11 false positive 7 false negative	Exudative AMD
Moult et al,[75] 19 eyes with exudative AMD	Swept source OCT– (prototype)	19 eyes including 1 with severe subretinal hemorrhage 2 with inactive lesions	16 of 17	Exudative AMD

AMD = age-related macular degeneration, CNV = choroidal neovascularization, FA = fluorescein angiography, NPA = nonperfusion areas, OCT-A = Optical Coherence Tomography Angiography, RVO = retinal vein occlusion.

showed a continuous and linear shape with a homogenous wall. Vessels were evenly distributed and resembled a spider's web. The deep network in healthy eyes had a regular distribution around the FAZ with more complex minute interconnections. Many anastomoses were observed between SL and DL. By following the superficial flow, it is possible to detect the deep network.[39]

It is difficult to quantify vascular density accurately and compare it with results obtained by OCT-A. Most studies have measured pixel intensity which correlate with the presence of vascular structure. However, this method may not be so precise. Vascular density is usually defined as % of space occupied by vessels. There are a number of studies showing a change of vascular density during ocular pathologies and in healthy group. One of these described a decrease in the parafoveal flow index, vascular density, and capillary-free zone correlating with age using Avanti OCT. The authors also reported that the capillary-free zone is larger in females than in males. They studied 76 eyes.[40]

However, Samara et al[41] using similarly sized group did not show any significant correlation in FAZ area and sex or age. The former study was conducted in China on a group aged 24 to 59 while later on racially mixed aged 12 to 76.

3.3. Retinal vascular occlusion and vascular abnormalities

One of the most promising applications of OCT-A might be as a diagnostic technique for both retinal and venous occlusions. Several studies emphasize that it provides better visualization of abnormal vessels than FA. However, most groups have consisted of only a very limited number of patients.

Bonini Filho et al compared the images of 7 patients with retinal artery occlusion acquired by FA with Avanti. Decreased vascular perfusion in both deep and superficial plexus was detected in all seven eyes. Radial peripapillary capillary assessment was performed in all but 1 patient, and this was due to the poor image quality.[42]

Suzuki et al compared OCT-A images of 28 eyes with FA. Patients with macular edema associated with Branch retinal vein occlusion (BRVO) were enrolled. It was possible to visualize NPA (nonperfusion areas) using OCT-A in all eyes compared with only 18 detected with FA. The first method was also more sensitive in identifying veno-venous shunts, and both superficial and deep capillary telangiectasia. FA detected microaneurysms in 14 eyes, while OCT-A only identified 13. The authors concluded that microaneurysms without flow are hard to detect with OCT-A.[43] Another group clearly visualized all microaneurysms from 3 eyes that were also observed in FA.[44] Rispoli et al evaluated 10 eyes with branch RVO. The authors demonstrated capillary abnormalities around FAZ, general FAZ enlargement, and vascular congestion in deep vascular network and capillary nonperfusion zones. However, the authors did not measure FAZ area or conduct any other measurements.[45]

Coscas et al compared images from OCT-A scans with FA scans (Table 1). Generally, OCT-A had a better rate of detection of macular edema than FA or SD-OCT. Moreover, the authors reported that nonperfusion zones in RVO are more common in deep than in superficial plexus.[46] It is hard to distinguish vascular abnormalities in BRVO associated with macular edema due to many artifacts.[43]

3.4. CNV

CNV is a process in which new blood vessels grow and penetrate through the Bruch membrane into the subretinal pigment epithelial and subretinal space (Fig. 2). Type 1 CNV refers to neovascularization confined to sub-RPE space, while type 2 to proliferation above RPE into subsensory space. Type 3 also known as retinal angiomatous proliferation (RAP) can be characterized as intraretinal neovascularization.[47] This process leads to destruction of photoreceptors and vision loss.[48]

New devices are able to automatically delineate the vascular membrane, which enables both qualitative and quantitative evaluation. De Carlo et al studied 72 eyes using OCT-A. However, only 30 eyes were examined using both FA and OCT-A, out of which 8 were determined to have CNV. The authors concluded that OCT-A has 50% sensitivity and 91% specificity.[49] Using a prototype, Jia et al[50] compared 5 eyes with CNV and determined that OCT-A is a useful method to assess CNV.

Another group enrolled 34 participants in their study, they reported high CNV flow area measurement repeatability and reproducibility. The authors detected 2 cases of nonexudative CNV type 1 which were impossible to detect using FA or in standard OCT.[51] However, the method of choice for the detection of inactive CNV type 1 is Indocyanine Green (ICG).

Roisman et al compared different imaging modalities SS OCT-A was able to detect type 1 CNV corresponding to ICG plaques. However, only 3 eyes were included with central macular plaques.[52]

Deep choroid plexus might only selectively be visualized using OCT-A. Another study[29] compared 80 eyes of patients with different types of AMD-related CNV using FA and OCT-A. CNV type I was identified in 58 and 59 eyes using FA and OCT-A, respectively. The authors concluded that OCT-A is a highly reliable method for reproducing vascular imaging.[53] According to Dansingani et al,[54] the mean size of neovascularization was 2.1 mm^2 for eyes without polypoidal lesions and 8.1 mm^2 for eyes with polypoidal choroidal vasculopathy. CNV area may also be counted automatically, which saves time and is more accurate than manual delineation methods.[55]

In an earlier study performed using standard en-face scans from SD-OCT, Sohrab et al[56] described choroid vascular density to be $75.4 \pm 2.3\%$ in controls, and $71.7 \pm 3.6\%$ and $74.4 \pm 2.8\%$ in early and advanced AMD, respectively. El Ameen et al described an anomaly, while observing lesions in an eye with type 2 CNV. After detection in OCT-A, the authors tried to visualize it in exact same level of the choriocapillaris using SD-OCT. However, SD-OCT did not show any of them. The authors speculate that such a discrepancy might be an artifact resulting from a neovascular flow from the outer retina into choriocapillary layers. Furthermore, the authors spotted external borders of the lesions that appeared as a dark ring. This dark area authors speculate might be a result of turbulent flow rather than a no flow area.[57]

3.5. Anti-VEGF therapy

During anti-VEGF treatment of a patient with type 1 and 2 CNV, lesions apparently decreased from 2.03 to 1.8 mm^2 and 0.25 to 0.19 mm^2, respectively.[58] Such effect might be attributed either to decrease of flow velocity or a CNV size depletion. Spaide used AngioVue to determine changes in eyes after anti-VEGF treatment. In his retrospective case series, he observed signs of vascular abnormalization in 17 eyes, for example, enlarged diameter of vessels, as well as many anastomotic connections. His conclusion undermined the hypothesis of choroidal normalization after antiangiogenic factor treatment.[59] Huang et al observed cyclical changes in CNV flow area in response to

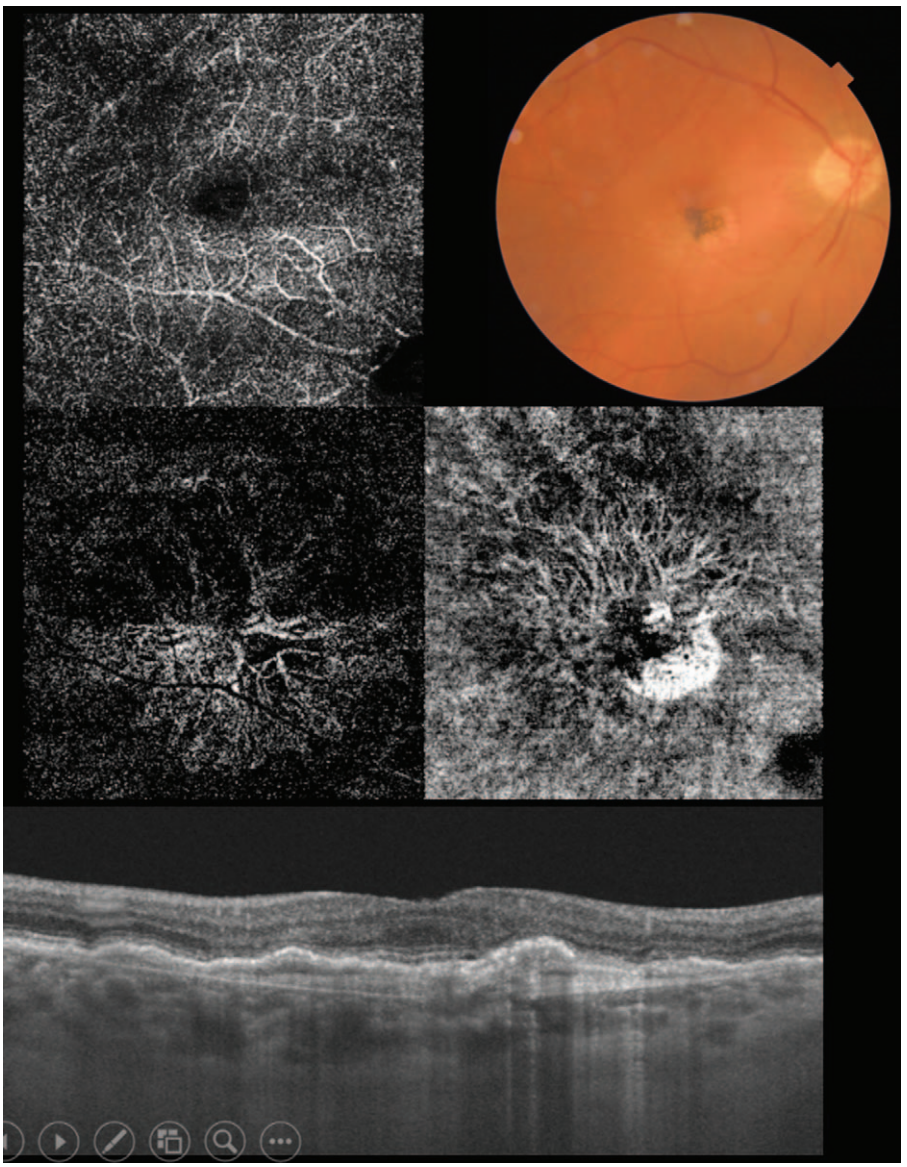

Figure 2. From stylistic point of view it should rather be written: Neovascularization at the level of choriocapilaries. Topcon Triton.

anti-VEGF treatment. Within 2 weeks of Aflibercept injection, a rapid decrease in CNV was followed by reappearance of channels in 4 weeks and accumulation of fluid was observed at 6 weeks.[60] Another group observed a CNV area decrease in 5 out of 6 eyes after VEGF treatment. The mean area decreased by about 23.6%.[61]

3.6. Diabetic retinopathy

Neovascularization around disks in diabetic retinopathy (DR) was measured in another study. Before treatment, the area was 1.2 mm^2, while 2 and 4 weeks postinjection the area size dropped to 0.5 and 0.3 mm^2, respectively. However, after 8 weeks the area increased again to 0.5 mm^2.[62]

Diabetic retinopathy can increase the FAZ as compared with healthy patients. One study[63] included 24 eyes with diabetes mellitus, 20 eyes with diabetic retinopathy, and 19 healthy eyes. FAZ area was 0.25, 0.37, and 0.38 mm^2 in control, diabetic mellitus, and diabetic retinopathy groups, respectively. The results were significant compared with the control group.[63] The results in this[63] study group are similar to those produced by Di et al[64] (Table 2) and de Carlo[65]; however, FAZ was far bigger in the control group.[64] Another group not only measured FAZ diameter but also the angle of the maximum diameter in healthy eyes. This was either 0 or 90, whereas in DR it was atypical.[66] Hwang et al detected FAZ area to be between 0.282 and 0.785 mm^2 in 4 eyes.[35] FAZ was not correlated with age, diabetes mellitus duration and HbA1c.[63] Ishibazawa et al[62] presented far greater number of results, but they measured the nonperfusion zone and did not compare results with a control group.

3.7. Glaucoma and other ocular pathologies

Liu et al described the mean vascular density of glaucomatous eyes versus healthy ones to be 80.55% to 93%, respectively. They also measured the peripapillary flow index in those groups and determined it to be 0.082 and 0.066 while optic disc perfusion was 0.09 and 0.088, respectively.[67] One of the first studies in

Table 2

Measurement of FAZ in different studies.

Refs.	Control	N-PDR	PDR	Device
Di et al[64]	85 eyes 0.36 ± 0.11	53 0.4 ± 0.16	60 0.42 ± 0.13	Avanti
Takase et al[63]	19 SL 0.25 ± 0.06 mm^2 DL 0.38 ± 0.11 mm^2	24 SL 0.37 ± 0.07 mm^2 DL 0.54 ± 0.13	20 0.38 ± 0.11 mm^2 DL 0.56 ± 0.12	Avanti
Freiberg et al[66]	25 0.26 ± 0.02		29 0.424 ± 0.06	Avanti
Ishibazawa et al[62]			42 3.67 ± 0.69 mm^2	Avanti
de Carlo et al[65]	0.288 ± 0.1364 mm^2	0.348 ± 0.1008 mm^2		Avanti
Hwang[37]	n/a		0.282–0.785 mm^2	Avanti
Samara[43]	70 eyes SL 0.266 ± 0.097 mm^2 DL 0.495 ± 0.227 mm^2			Avanti
Carpineto et al[92]	60 eyes SL 1st observer 0.251 ± 0.096 mm^2 2nd observer 0.252 ± 0.096 mm^2			Avanti
Shahlaee[94]	17 eyes SL 0.27 ± 0.101 mm^2 DL 0.34 ± 0.116 mm^2			Avanti

DL = deep layer, FAZ = foveal avascular zone, PDR = proliferative diabetic retinopathy, SL = superficial.

this field showed different results: a normal density of 74%, while in preperimetric glaucoma density was only 49.1%.[68] In another series of studies,[69] the authors measured density in normal eyes which was from 74% to 87%, while in mild, moderate, and severe glaucoma density was 81.6%, 77.06%, 72.5%, respectively.[69] Huang[70] described vascular density to be lower in glaucomatous eyes than in healthy eyes.

Wang et al measured the optic disc flow index in 3 groups of patients: Multiple sclerosis (MS) only, (MS) with optical neuritis and a control group. The results that they showed are higher than those of Liu et al 0.156, 0.140, and 0.160.[71]

It is possible to use AngioVue to detect changes in vascular structure in eyes with birdshot retinopathy. A study was conducted[72] in which the authors examined 8 eyes and observed changes such as vessel telangiectasia, increased intercapillary space, and retinal thinning. Capillary dilatations and loops were seen in 7 eyes. The authors concluded that OCT-A may provide new insights and information about vascular structure in retinal diseases.[72]

OCT-A can be used in diagnosis of central serous retinopathy (CSR). Images of CSR revealed dark areas and dark spots. Furthermore choroidal vessels were described as abnormally dilated, high-flow, tangled pattern areas in the choriocapillaris layer.[73]

3.8. SD-OCT and SS-OCT

Visualizing choriocapillaries using SD-OCT is a challenge due to the absorption of light by tissue and projections artifacts. SS-OCT may overcome this limitation. Choi et al[74] compared OCT-A images of the choriocapillaris with established histological images from electron microphotography and found general consistency. Using SS-OCT-A it was possible to visualize AMD related CNV choroidal lesions in 16 of 17 eyes. The prototype also created choroidal images in 63 healthy eyes.[75] SS-OCT compared to SD-OCT is able to better visualize CNV lesions. In this study[76] the mean CNV area measured using SS-OCT was almost 3 times bigger.[76]

3.9. Anterior segment

OCT-A can also be used to determine changes in the anterior segment. Although this area is easy to examine using a standard slit-lamp, the use of OCT-A may be advantageous. Ang et al were able to visualize corneal vessels invading a corneal graft and corneal neovascularization in a postherpes scar and in pterygium. The system was able to outline abnormal feeder vessels obscured by deposits in an eye with lipid keratopathy. It must be noted that the OCT-A system is able to measure simultaneously the depth of the lesion as well as the blood vessels. The authors reported good image quality and a high level of reproducibility.[77] Poddar et al[78] generated microcapillary perfusion maps of the anterior segment with deep-color coding. OCT-A that the authors created has a potential to detect changes in aqueous outflow leading to faster diagnosis and better understanding of the potential mechanisms leading to glaucoma. It is also possible to image an iris angiography, but only in light-colored eyes, because in dark irises there is a pigment layer produced by multiple artifacts as well as shadowing of the vasculature.[79]

Ang et al used OCT-A to determine corneal neovascularization in 20 patients after herpetic keratitis, corneal graft, bacterial keratitis, and limbal steam cell deficiency. The mean area of corneal neovascularization was 0.57 ± 0.30 mm^2.[80]

4. Discussion

OCT-A is a new technique which requires further study. Most articles cited in this review have used only one device—Avanti AngioVue, some Spectralis HR II, one Zeiss Plex 9000, or custom-built systems.[59]

Many articles have been published with a limited number of subjects; other studies are designed to give a general impression of the possibilities that this method can bring rather than testing a hypothesis. This is because OCT-A has only recently been invented and many more detailed studies will subsequently be published. The main limitations of the above-mentioned studies are their small study group.

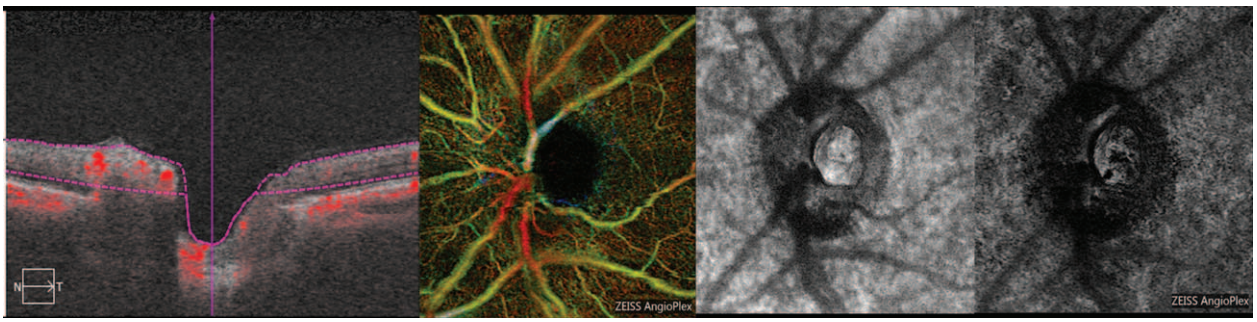

Figure 3. Images optic nerve disc in 68-year-old male with DR. Zeiss Cirrus HD 5000.

OCT-A is a noncontact noninvasive technique which can be performed at each clinical visit which enables rapid image acquisition as well as isolation of specific vessels.[33] While FA provides only information about the structure, OCT-A can bring information about the flow and structure of the vessel.[81]

The leaking fluorescein from vessels may mask NPA due to hyperfluorescence, but this problem is overcome in OCT-A.[43,50] It is difficult to discern areas of type 1 CNV on Indocyanine Green Angiography, in contrast to OCT-A which gives a clear and distinctive image.[82]

In choroidermia, OCT-A can visualize both retinal and choroidal dysfunctions.[83] The opacities of layer might be decreased in order to allow visualization of underlying vessels. Thanks to volume rendering, it is possible to create 3D images that can be rotated in space and retain a sense of depth.[84] It allows the visualization of 3D relationships between the vessels.[85] Liu et al[86] developed a method to automatically detect CNV zones.

The images of the SL often interfere with the images of the DL, making it very challenging to discriminate one from the other.[87] One of the greatest limitations is the relatively small field of view.[32] However, rapid developments will make it possible to overcome this problem in a few years.

Extensive macular edema as well as fluid in the subretina space might prevent acquisition of high quality images.[88] As motion decorrelation is speed dependent, velocity over and under a certain limit will not be displayed as a fluid flow. This means that structures such as polyps or type 3 neovascularization may not be depicted.[89] However, the use of variable interscan time analysis (VISTA) allows to calculate the relative flow velocity, by analyzing the reflectance between every other B-scan.[26] Large pigment epithelial detachment as well as exudates may obscure images.[90]

The biggest problem with OCT-A image acquisition are motion artifacts that appear in the background. Steady fixation is necessary in order to present high quality pictures. This affects patients with poor visual acuity due to fixation problems or low compliance (Fig. 3).[91]

Another aspect is the huge discrepancy of results, for example, the density of the glaucomatous eyes is determined to be from 49.1%[67] to 80.55%.[68] It is important to note that those studies were conducted on different devices. The same problems occur with the issue of the flow index (e.g., Wang et al[71] and Liu et al[67]). Although OCT-A is a new and beneficial technique, because of the limited image size (Figs. 1 and 4), in future

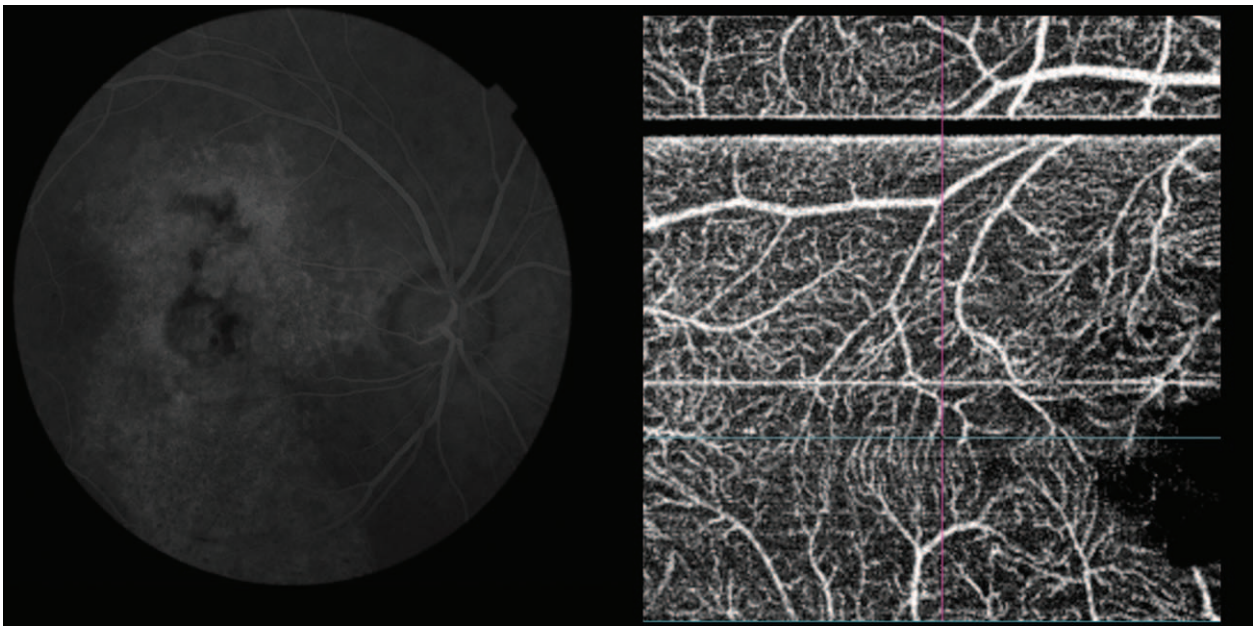

Figure 4. Comparison of FA and 3×3 image in a AMD patients who received 7 Bevacizumab injections. Many spots of anastomosis are visible, dark places near fovea are considered avascular zones. This image was acquired before introduction of motion eye tracking. Topcon Triton.

clinicians will use combined multimodal techniques with OCT OCT-A and FA.

4.1. Repeatability

Liu et al[67] showed repeatability regarding the flow index and vascular density to be from 1.9% to 5.7%, while Wang et al[69] reported 2.8 and 3.5%. Ang et al[80] determined repeatability to be ($\kappa = 0.84$). Carpineto et al[92] measured FAZ in 60 healthy eyes and they observed a repeatability of 1.83% between 2 observers.

4.2. Future studies

OCT-A opens a new and exciting field of studies and the authors believe that research on the choriocapillaris might provide new insights into the pathology of retinal diseases. It is worth comparing different devices. Another form of application is a search for CNV type 3 and understanding vascular responses of the eye during treatment of new drugs such as Platelet-derived growth factor inhibitors. As new versions of software will probably be able to automatically perform measurements such as density and flow index, it will be necessary to create studies on how this parameter change in standard and pathological conditions. A large retrospective study might reveal discrepancies between different devices.

5. Conclusion

OCT-A is able to visualize only moving structures is promising and has already proved to have many applications. It is able to monitor changes in vascular architecture after treatment, diagnose vascular pathologies and perform quantitative analysis. Despite its many limitations which are not fully described, it might be a very good addition to routinely used clinical tools.

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