Optical-Coherence Tomography Angiography in AMD

Optical coherence tomography angiography (OCTA) is a non-invasive diagnostic instrument that has become indispensable for the management of age-related macular degeneration (AMD). OCTA allows quickly visualizing retinal and choroidal microvasculature, and in the last years, its use has increased in clinical practice as well as for research into the pathophysiology of AMD.

1. Introduction

Age-related macular degeneration (AMD) is the third leading cause of severe irreversible vision loss worldwide, and it represents the major cause of central blindness in developed countries, especially among people older than 60 years [1][2][3]. Prevalence data suggest that about 200 million of people are nowadays affected by AMD, and this value is expected to increase to nearly 300 million by 2040 [4].

The advancement of imaging technology, in particular the use of optical coherence tomography (OCT) and OCT angiography (OCTA), has improved scientific knowledge on AMD, making mandatory a multimodal imaging approach for retinal and choroidal conditions. OCTA allows a clear and detailed visualization of retinal and choroidal microvasculature, and it is useful either for reaching the diagnosis or for guiding treatment choice and monitoring AMD patients [5][6].

In 2013, Ferris proposed a five-stage AMD clinical classification based on the risk of progression [7]. According to this classification, the presence of only small drusen ≤ 63 μm without pigmentary abnormalities is considered normal aging change; early AMD is characterized of medium drusen > 63 μm and ≤125 μm, while intermediate AMD (iAMD) is defined with the presence of large drusen > 125 μm and/or pigmentary abnormalities. Late AMD develops when macular neovascularization (MNV) or geographic atrophy (GA) occur [7].

MNVs are a growth of abnormal vessel and associated tissues into the outer retina, subretinal space, or subretinal pigmentary epithelium (RPE) space. They are classified according to the anatomic location determined by OCT imaging into three types: type 1 is a growth of vessels from choriocapillaris that proliferates into and within the sub-RPE space; type 2 originates from the choroid, and it passes through the Bruch's membrane and the RPE monolayer proliferating in the subretinal space; type 3 develops from the retinal circulation, usually in the deep capillary plexus, and it grows toward the outer retina [8][9].

MNV are usually characterized by intraretinal or subretinal fluid within the macula, but recent studies demonstrated that type 1 MNV can present without exudation on OCT, but it can be well visualized by means of fluorescein angiography (FA), indocyanine green angiography (ICGA), and OCTA [10][11]. The Consensus on Neovascular AMD Nomenclature (CONAN) group stated that this form of MNV could be identified more commonly with the improvement of imaging technology, but there is still not a consensus on which term to use [9]. In this article, we will use the term nonexudative MNV, even if there is a substantial difference between the term "treatment-naïve quiescent neovascularization" used by Querques and colleagues [10][11] and "asymptomatic, nonexudative or subclinical MNV" used by other authors [12][13][14][15]. Treatment-naïve quiescent neovascularization are MNVs without sign of activity for at least 6 months from baseline, while all the other terms refer to new diagnosis MNVs without exudation [12][13][14][15].

2. AMD Diagnosis

In the last decades, new multimodal imaging techniques have been incorporated to study AMD. They have led to a remarkable improvement in both understanding of the pathophysiology of macular diseases and its progression, but most importantly, to monitor treatment response [16].

FA is an irreplaceable dye-based invasive diagnostic tool to detect subtle neovascularization, monitor leaks, and compare them with staining and window defects. In the era of photodynamic therapy, FA has been considered the gold standard method for detecting and classifying subtle choroidal neovascularization as classic, occult, or combination subtypes [16] [17]. Nowadays, it is still a useful method for the detection of "active" neovascularization and geographic atrophy [16]. However, fluorescein dye leaks from blood vessels, making it less ideal for visualization of details in the choroidal circulation [18]. Although FA is useful for the visualization of MNV, retinal–choroidal anastomoses and other choroidal vascular abnormalities are better visualized using ICGA [18]. In contrast to FA, it uses a dye that is 98% protein bound, providing more detailed images of the choroid and thus identifying the entire extension of the MNV [16]. However, both modalities have many drawbacks: they are time consuming and invasive, requiring intravenous dye injection, which can cause some side effects such as nausea and anaphylaxis [19].

In last two decades, OCT has emerged as a new non-invasive diagnostic tool for the diagnosis and follow-up treatment of macular diseases. Particularly in AMD, OCT facilitates in vivo high-resolution evaluation of the retina [20], so detecting the presence of drusen, RPE atrophy, fibrovascular complex, sub and intraretinal fluid, among other features [18].

More recently, OCTA has become available to retinal specialists. Unlike traditional angiography and ICGA, OCTA is a quick and non-invasive 3D imaging modality that does not require the use of a contrast agent [21]. OCTA detects the erythrocyte movement by analyzing the signal decorrelation within multiple B-scans performed repeatedly at the same location of the retina [21]. Changes in temporal contrast at a specific location indicate movement (erythrocyte motion) and hence vessel location [21].

OCTA allows the direct visualization and measurement of the foveal avascular zone (FAZ) area and provides morphologic and quantitative vascular information on macular microcirculation, including the deep and superficial capillary plexus, with good reproducibility and repeatability, in vivo and without dye leakage and staining that may obscure the limits and anatomy of pathologies [22].

However, as with any other imaging methods, several image artifacts also occur in OCTA, such as the shadow effect or those due to algorithms for data acquisition and image processing and motion-related artifacts [21].

3. Current OCTA Devices

OCTA represents an emerging non-invasive imaging technology that provides detailed visualization of the retinal and choroidal vascular networks. This technique employs the principle of motion contrast in order to generate blood flow and thereby images the vasculature without the need for a contrast agent [23]. Since its introduction, OCTA has allowed a deep characterization of several retinal pathologies, including AMD, diabetic retinopathy, vascular diseases, and also different inherited retinal diseases such as Stargardt macular dystrophy, Best disease, and choroideremia [24][25]. OCTA is able to compare the signals of sequential OCT B-scans from the same cross-section and distinguish the moving scatters from the tissue in the background in order to provide an image of retinal and choroidal networks [23]. In this way, it allows acquiring angiograms in a short time (<5 min), without the use of dye.

OCTA technology is constantly evolving to improve image quality, acquisition time, and the automatic interpretation of scans. Table 1 shows the comparison of different commercially available OCTA devices: Zeiss AngioPlex, Cirrus HD-OCT 6000; Optovue AngioVue, RTVue XR AVANTI; Topcon Triton, DRI Triton; Heidelberg Spectralis, OCT2, Angiography; Nidek AngioScan RS-3000 Advance 2 and Canon Angio Xephilio OCT-S1. Table 1 compares the main characteristics provided by the manufacturer, including central wavelength, scanning speed, resolution, imaging depth, and imaging size.

Table 1. different main features provided by the manufacturer of the different OCTA devices.

OCTA System	Central Wavelength (nm)	Scanning Speed (scans/s)	Resolution (Axial × Transverse, μm)	Imaging Depth (mm)	Imaging Size (mm)	OCTA Approach
Zeiss AngioPlex, Cirrus HD-OCT 6000	840	100,000	5 × 15	2.0–2.9	3 × 3, 6 × 6, 8 × 8, 12 × 12	Combined intensity and phase variance

Device	Wavelength (nm)	Scans/sec		Depth (mm)	Scan sizes	Algorithm
Optovue AngioVue, RTVue XR AVANTI	840	70,000	5 × 15	2.0–3.0	3 × 3, 6 × 6, 8 × 8	Intensity decorrelation
Topcon Triton, DRI Triton	1050	100,000	8 × 20	2.6	3 × 3, 6 × 6	Intensity ratio analysis
Heidelberg Spectralis, OCT2, Angiography	870	85,000	5 × 6	2	3 × 3	Intensity decorrelation
Nidek AngioScan RS-3000 Advance 2	880	85,000	7 × 20	2.1	3 × 3, 4.5 × 4.5, 6 × 6, 9 × 9	Combined intensity and phase decorrelation
Canon Angio, Xephilio OCT-S1	855	100,000	NA	5.3	3 × 3, 6 × 6, 10 × 10, 20 × 23	NA

The OCTA devices available at the present can do 70,000 to 100,000 scans per seconds. The scanning speed is related to the presence of motion artifact and to the image resolution. In particular, the higher the scanning speed, the lower the motion artifacts that would be present in the final image. This feature plays a fundamental role in the clinical practice, where it is often necessary to optimize exam times. Recently, Topcon, Zeiss, and Canon developed novel systems that allow a scanning speed of 100,000 scans per second.

In addition, imaging depth has been improved compared to the first models. In particular, in current available devices, the imaging depth ranges from 2.0 to 5.3 mm.

The software for the visualization of volumetric data, and segmentation algorithms, is different between the devices and hardly comparable. Different approaches, such as the amplitude decorrelation algorithm and the combined intensity and phase decorrelation, have been developed to improve image quality and to reduce the motion artifacts [26][27][28].

Finally, the image size has been significantly increased over the years. In fact, in the first models, only 3 × 3 or 6 × 6 scans were possible. Recently, 12 × 12 by Zeiss and even 20 × 23 by Canon have also been introduced.

Moreover, two main Fourier domain detection systems of OCTA are available: the spectral domain (SD-OCTA) and the swept source OCTA (SS-OCTA) [16].

The SD-OCT employs a broadband near-infrared superluminescent diode that has a wavelength of 840 nm, with a spectrometer to measure wavelengths of light. The SS-OCT instead employs a tunable swept laser that has a wavelength of 1050 nm and uses a single photodiode detector [29][30].

The main advantages of SS-OCTA imaging over SD-OCTA are (i) the faster scanning speed, which allows for denser scan patterns and larger scan areas compared with SD-OCT scans for a given acquisition time, it presents a faster scanning speed, resulting in a higher number of scans for a given acquisition time compared with SD-OCT, (ii) its reduced sensitivity roll-off, resulting in enhanced light penetration through the RPE, as well as a better detection of signals from the sub- RPE layer due to its reduced sensitivity roll-off, which allows a better light penetration through the RPE and thus a greater detection of signals from the sub-RPE layer [31], which is particularly important in case of drusen or RPE thickening (iii). Since that resolution depends mainly on the wavelength, increasing this parameter allowed a better axial resolution, resulting in a better characterization of the different layers even in the presence of obstacles such as the presence of cataracts or vitreous opacities.

The higher wavelength in combination with the reduced sensitivity roll-off improves the detection the weaker signals from the deeper layer, resulting in a better detection of type 1 MNV compared with SD-OCTA imaging [30][31].

4. OCTA in Intermediate AMD

AMD may present at different stages, and the "intermediate AMD" stage is clinically characterized by the presence of pigmentary abnormalities and/or large drusen [7]. Of note, eyes with subretinal fluid may be also characterized by the absence of neovascularization and thus classified as iAMD [32].

Although the AMD pathogenesis is intricated and related to several systemic and lifestyle factors that may have a role in the development and progression of this disorder [33][34], a growing body of evidence suggests that this disorder is ultimately characterized by damage of the unit comprised of photoreceptors, RPE, Bruch's membrane, and choriocapillaris (CC) complex [35][36][37]. Importantly, several pieces of evidence suggest that this may be considered as a tightly knit, integrated unit [38][39][40]. In AMD, this impairment causes the development of drusen and progressive photoreceptor, RPE, and CC degeneration [41][42][43][44].

Previous studies have fully characterized the CC perfusion in eyes with iAMD [45][46][47][48]. In detail, using both spectral domain and swept source technologies, Borrelli and colleagues demonstrated that the CC is impaired (i.e., CC ischemia) in these eyes [45][46]. Importantly, they provided a topographical analysis revealing that the CC impairment is mainly confined to the CC beneath and surrounding drusen [46]. Moreover, the CC perfusion was more affected in iAMD eyes with neovascular AMD in the fellow eyes [45], especially in those with type 3 MNV [47]. In two studies employing OCTA in iAMD eyes [49][50], the authors showed that the CC perfusion is strictly correlated with macular function in these eyes, further highlighting the association between CC ischemia and outer retina dysfunction in iAMD.

Although the CC is known to be the vascular plexus most affected in AMD, also retinal vessels were demonstrated to be impaired in these eyes [51][52]. Toto et al. demonstrated that eyes with iAMD are characterized by a lower retinal perfusion as compared with normal eyes [51]. Of note, iAMD eyes with OCT signs of nascent GA are featured by a greater reduction in retinal vessels perfusion [52].

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