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Review

Imaging in retinal vascular disease: A review

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ABSTRACT

Retinal vascular diseases represent a broad field of ocular pathologies. Retinal imaging is an important tool for diagnosis, prognosis and follow up of retinal vascular diseases. It includes a wide variety of imaging techniques ranging from colour fundus photography and optical coherence tomography to dynamic diagnostic options such as fluorescein angiography, and optical coherence tomography angiography. The newest developments in respective imaging techniques include widefield imaging to assess the retinal periphery, which is of especial interest in retinal vascular diseases. Automatic image analysis and artificial intelligence may support the image analysis and may prove valuable for prognostic purposes. This review provides a broad overview of the imaging techniques that have been used in the past, today and maybe in the future to stage and monitor retinal vascular disease with focus on the main disease entities including diabetic retinopathy, retinal vein occlusion, and retinal artery occlusion.

Keywords: Diabetic Retinopathy; Retinal Vein Occlusion; Retinal Artery Occlusion; Fluorescein Angiography; Optical Coherence Tomography

1. INTRODUCTION

The eyes are the window to the heart!

While this popular saying is frequently used to describe the eye as a spiritual window to a (wo)man's soul, it is also valid in a medical sense. Nowhere else in the body can the blood vessels and, even more importantly, the health of the capillary beds be better observed than within the retina. The invention of the ophthalmoscope by H. Helmholtz in 1850[1] marks the beginning of retinoscopy as an important technique to monitor the severity of cardiovascular diseases, in particular diabetes mellitus and arterial hypertension. The first description of a central retinal vein occlusion (R. Liebreich) and diabetic retinopathy (E. Jäger) dates back to 1855. Four years later, the first description of an embolus of the central retinal artery was described (A. von Graefe)[2]. The usefulness of ophthalmoscopy in this context was first documented by photos of the retina in 1886[3]. Since then, methods have significantly improved. Today, new imaging techniques and artificial intelligence (AI) based interpretation aids are of special interest. With the introduction of fluorescein angiography (FA) in 1961[4], imaging of the functionality and integrity of the retinal vasculature was enabled. It still is the most sensitive imaging tool to assess retinal perfusion in retinal vascular diseases. More recently, the advent of optical coherence tomography angiography (OCT-A) propelled imaging of the retinal vasculature to a next level by enabling non-invasive high-resolution imaging of retinal vessels and capillary beds. OCT-A provides access to a wide range of data like vessel density, perfusion density, fractal dimensions and much more. The full clinical value and interpretation of all the information provided by OCT-A is just being realized. Its further use and exploration will not only improve clinical diagnostics but also open up new fields of research.

2. IMAGING IN RETINAL VASCULAR DISEASE

2.1 Historic Background

2.1.1 Fundus photography

W. Jackman and J. Webster managed to take the first photo of the retina in a living human eye in 1886 with an exposure time of 2.5 seconds, showing a black and white image of the optic disc and some barely visible retinal vessels[3]. This milestone marked the starting point of an exponentially growing development of specialized fundus cameras. Forty years later - in 1926 - the first commercially available fundus camera was produced by the Carl Zeiss Company with a 20° field of view (FOV)[5] (Figure 1). Years later, Carl Zeiss expanded the FOV to 30°, which became the standard for the traditional fundus camera. The *Early Treatment Diabetic Retinopathy Study (ETDRS) group* defined seven standard images in 1991 with a total FOV of approximately 75° (about 30% of the entire retina)[6]. Later, the set of seven standard images was extended to nine to document changes attributed to cytomegalovirus retinitis[7]. This nicely illustrates the need for a wider viewing angle, which resulted in the development of today's variety of widefield cameras. In 1975, Pomerantzeff introduced a contact lens-based camera (Equator-plus camera) with a FOV of 148°. He used a fiber optic system for transpupillary and trans-scleral illumination[8]. The first commercially available widefield (WF) camera was the Retcam (Clarity Medical Systems, Inc., Pleasanton, CA, USA) with a field of view of 130° launched in 1997. It utilizes a contact lens with a fiber optic cable light source[9]. In 2005, Staurenghi et al. presented a special multi-element contact lens-based system with two biconvex aspheric lenses and a two-element convex-concave contact lens[10]. With this Staurenghi lens, the standard field of view could be extended five-fold up to 150°. The lens is adapted to a confocal scanning laser ophthalmoscope (SLO) to perform fundus fluorescein angiography (FA) and indocyanine green angiography (ICG) for peripheral chorioretinal structures.

2.1.2 Fluorescein Angiography (FA)

Fundus photography was the earliest imaging technique to depict retinal vasculature. However, the introduction of fundus FA by H. Novotny and D. Alvis in 1961[4] represented a crucial improvement since it enabled the assessment of the integrity and perfusion status of the retinal vessels in the living eye. Even now, fundus FA is still the only option to directly display leakage of retinal vessels and, thus, the integrity of the blood-retina barrier. In addition, the assessment of

the dynamics of the retinal perfusion allows the identification of delayed arterial and venous retinal perfusion. This often helps to identify the underlying cause of the retinal pathology. Additionally, fundus FA allows the precise definition of areas of low or no perfusion, which is critical for the further management and treatment of the patient.

2.1.3 Optical coherence tomography (OCT)

F. Fercher was the first to present a two dimensional image of the fundus using light interferometry in 1990[11]. J. G. Fujimoto, D. Huang and their group illustrated for the first time the potential of this method to depict cross-sectional pictures of light scattering tissue and termed it optical coherence tomography (OCT) in 1991[12]. In 1996 Humphrey Instruments launched the first commercially available OCT device. Today, OCT is one of the most important imaging tools in ophthalmology and allows for a deeper understanding of many ophthalmic pathologies. A report from 2016 assumed that about 30 million OCT imaging procedures were performed worldwide each year[13]. Technically, OCT can be divided into the two groups: time-domain OCT (TD-OCT) and Fourier-domain OCT (FD-OCT). TD-OCT was the earlier and slower OCT system due to the mechanical speed limit of the moving reference mirror, which is needed to obtain information of different depth of the sample. To overcome this limitation, in FD-OCT systems the reference mirror is fixed and Fourier transformation is used to obtain the image, thus making it 100x faster, more quiet while achieving a threefold better resolution. That is the reason why FD-OCT remains the most commonly used OCT. The FD-OCT group can be subdivided into spectral-domain OCT (SD-OCT) using a broadband light source like the TD-OCT, and swept-source OCT (SS-OCT) using a swept laser light source and photodetector[14]. The usage of this swept laser source makes SS-OCT twice as fast as spectral domain OCT and is therefore the choice for obtaining widefield OCT and widefield OCT-A images. The latest OCT system is the full-field OCT (FF-OCT). By using an incoherent light source and an area array camera, it is capable of not only obtaining submicrometer spatial resolution and millisecond temporal resolution, but also allowing a larger field of view[15].

2.1.4 OCT-Angiography (OCT-A)

OCT-A is based on conventional OCT imaging. Instead of imaging a certain area once via multiple individual A-scans which form a single cross-sectional B-scan, the area is repeatedly scanned and the acquired images are subtracted. Therefore, the final image contains only the information that has changed over time, thus any particles in motion such as blood cells. A three dimensional volume scan can be reconstructed out of the gained data, and an en-face view is possible for every single layer. A superficial as well as a deep capillary plexus are differentiated. Qualitative as well as quantitative image analysis can be performed. Vascular metrics include analysis of the foveal avascular zone, vessel density, and branching of the vascular network. This allows assessment of the retinal microvasculature in much more detail than with conventional techniques. A main advantage of OCT-A is that it is non-invasive, and no injection of dye is needed in contrast to fundus FA.

3. WIDEFIELD IMAGING

The words *widefield (WF)* and *ultra widefield (UWF)* were used very heterogeneously. In 2019, the *International Widefield Imaging Study Group* agreed that a widefield image needs to cover all four quadrants of the retina posterior to the vortex vein ampulla[16]. Larger image angles including the anterior part of the vortex vein ampulla in all four retinal quadrants are classified "ultra-widefield"[16]. The terminology of widefield OCT is somewhat different and consists of the size (in degrees or millimeter), the location (posterior pole, mid peripheral, far peripheral), and the scan type. The definition of "widefield" corresponds to an OCT in the mid periphery (60-100°, covering the retina up to the posterior edge of vortex vein ampulla) and an "ultra-widefield" OCT in the far periphery (110-220°, covering the anterior edge of vortex vein ampullae and beyond to pars plana)[16].

Because of the limited FOV of today's OCT-A models, the consensus-based recommendations for OCT-A reporting in uveitis suggested , that a FOV ≥ 70° is considered "widefield" for OCT-A (corresponding to a composite of two 15x9 mm OCT-A scans)[17]. Larger FOV such as 90° (composite of five 12x12 mm scans) or 120° (experimental) may be reserved to define "ultra-widefield" OCT-A in the future.

However, in a similar Delphi based approach to report OCT-A findings in retinal vascular diseases no consensus was achieved how to define WF and UWF OCT-A[18].

WF and UWF imaging have several advantages compared to the standard fundus image. It enables a larger FOV and therefore adds more information. The impact of this will be discussed in the following chapters. In addition, the time of acquisition is much shorter. While it takes about 15 minutes to create a 7 field color fundus (CF) image, WF and UWF images can be obtained in a fraction of this time. Additionally, no pupil dilatation is necessary.

Limitations include a lower resolution when compared to conventional CF photography, as resolution is dependent on imaging width. However, the development of today's cameras have limited this disadvantage and allow nowadays WF images up to a resolution of 7 microns per pixel. A recent study by the DRCR net compared the DRSS levels assessed via conventional seven ETDRS CF imaging and UWF images obtained by the Optos camera, masking the retinal areas beyond the 75 degree. After adjudication, a difference within one DRSS step was found in 38% of the cases, while a ≥ 2 step difference was only found in 1% (DRSS ≥ 2 steps worse in 7 fields) and 2% (DRSS ≥ 2 steps worse in UWF), respectively[19]. This highlights that the information obtained by WF and UWF imaging are comparable to the high resolution CF images, which are still gold standard in many retinal vascular diseases.

Nonetheless, technical limitations of widefield imaging remains. An optimal focus is only possible in a field of view of 30°. Beyond that, a considerable focus error can occur. Every 0.3mm of depth difference equals 1 diopter of focus error. Furthermore, distortion and decreased resolution of the periphery is a phenomenon that is hard to address. Not only the lens induced barrel or pincushion distortion, but more importantly the spherical 3-dimensional aspect of the retina that is mapped on a flat 2-dimensional image contribute to this effect of an enlarged peripheral retina and stretched vessel. The latter is called a stereographic projection. This needs to be considered, especially for example when the retina is evaluated for non-perfusion area[20]. As the imaging systems do not standardize the images to a particular axis of the eye, the distance and area will probably not correspond to the actual dimension[5].

Figure 1: Schematic illustration of field of view corresponding to imaged area on the retina. From Emmett T. Cunningham et al. Ultra-Widefield Imaging in Uveitis. Ocul Immun and Inflammation. 2019, p345-348

3.1 The main widefield and ultra widefield cameras of today

Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany): The Heidelberg Spectralis lens is a ten-lens-system that is able to take retinal pictures with a FOV of 105° and a resolution of 10 µm/pixel. The modalities are infrared (IR), FA, ICG, FAF and red free (RF) fundus images.

Optos 200Tx camera (Optos PLC, Dunfermline, United Kingdom): The combination of an SLO with an ellipsoid mirror creates an image covering a FOV of 200° in a single picture corresponding to 82% of the entire retina. The calculation of the FOV is based on several assumptions, which may lead to a smaller FOV as advertised[5]. The resolution of 11-14 µm/pixel is a little bit less than the Heidelberg Spectralis or Clarus 700. With the ability to capture red and green reflectance image simultaneously, it can create "pseudo" CF images, which look similar to a CF but does not show the real appearance of a traditional fundus picture. Additionally, FAF, FA and ICG image can be captured with the Optos 200Tx.

Clarus 700 (Carl Zeiss Meditec, Jena, Germany): The Clarus 700 is the succeeding model of the Clarus 500. With a FOV of 133°, true color WF images with a resolution of 7 µm/pixel can be taken in a single picture. The combination of two images covers 200° of the retina. With the montage of up to 6 images, a FOV of up to 267° can be reached. With the Clarus 700 CF, FAF, FA, ICG and IR can be obtained.

4. CLINICAL IMPORTANCE OF IMAGING IN RETINAL VASCULAR DISEASES

4.1 Diabetic retinopathy (DR)

Diabetic retinopathy remains the leading cause of vision loss globally[21]. Microaneurysms are the earliest stage of diabetic retinopathy and progress from mild non-proliferative diabetic retinopathy (NPDR) in a natural course of an uncontrolled diabetes mellitus (DM) to proliferative diabetic retinopathy (PDR) with retinal neovascularization (NV) and vitreous hemorrhage. Untreated it may result in a

tractional retinal detachment. Hyperglycemia induced oxidative stress, hypoxia, pericyte and endothelial cell loss, leucostasis and inflammation lead to a breakdown of the blood retina barrier, leakage of the retinal vessels and the formation of diabetic macular edema (DME) as another complication of diabetes in the eye (Figure 2).

Figure 2: Diabetic retinopathy (DR). Wide field fundus photography in DR is very useful in identifying and documenting diabetic findings such haemorrhages, neovascularization and cotton wool spots. In the fundus fluorescein angiogram (FA 1 early phase, FA 2 late phase), neovascularization as well as ischaemic retinal areas are clearly evident. OCT imaging is used as the gold standard technique to monitor and follow up diabetic macula oedema and the effect of therapy.

In order to assess the risk of progression in eyes with DR, the ETDRS group defined the seven standard imaging fields in 1991. It remains the gold standard for the assessment and grading of DR severity[22, 6]. In 2012, Silva et al. reported in their study of 206 eyes with DR, that 30% of all haemorrhages and MAs, 13% of areas of venous beading (VB), 27% of intraretinal microvascular abnormalities (IRMAs) and 34% of new vessels elsewhere (NVE) were found outside the seven standard ETDRS fields [23]. Based on these peripheral lesions, around 10% of all eyes with DR have more severe DR than expected when only assessing the seven ETDRS fields[23]. Other groups have reported that the presence of peripheral retinal lesions is associated with increased DR severity in 9-15% of eyes[24-26]. Predominantly peripheral lesions (PPL), defined as over 50% of the lesions found outside the ETDRS standard images, are present in up to 10% of eyes examined with CF photographs[27]. These PPL may be associated with an increased risk of DR progression over 4 years, independent of baseline DR severity and HbA1c levels [27]. These findings highlight the importance of WF and UWF imaging in DR.

The ETDRS study research group also assessed the potential value of fluorescein angiography to predict the progression of DR. FA increased the power to predict progression to PDR, but the study group concluded that it was not of great clinical value and that CF imaging alone was enough to provide valid guidelines. However,

following the development of WF and UWF-FA, evaluation of the retinal non-perfusion area (NPA) showed a high correlation between NPA and the presence of PPLs and the severity of DR[29]. Therefore, the identification of PPLs may reflect the extent of non-perfusion and ischaemia accounting for the increased risk of disease severity progression. Just recently, this suggestion was supported by a prospective 4-year longitudinal study by the DRCR.net, which showed that both greater baseline retinal non-perfusion on FA and PPL on UWF-FA were associated with a higher risk of disease worsening (9x in mild NPDR and 4x in moderate NPDR), even after adjusting for baseline Diabetic Retinopathy Severity Scale (DRSS) score and known systemic risk [22]. However, no association between PPL found in CF photographs and a higher risk of disease worsening could be detected[30]. This highlights the importance of UWF FA imaging in DR and the need to include it in future DR staging systems and clinical care to determine prognosis more accurately in NPDR eyes[30].

OCT-A is also a valuable imaging modality in the assessment of DR. It allows the individual assessment of the retinal plexi: the superficial capillary plexus (SCP), the middle capillary plexus (MCP) and the deep capillary plexus (DCP). This is advantageous compared to FA, which only depicts the SCP. Conventional macular 3x3, 6x6 and 9x9 mm scans allow the assessment of multiple metrics including vessel density, perfusion density, vessel morphology parameters such as fractal dimension, vessel diameter index, and areas of non-perfusion. Foveal avascular zone (FAZ) metrics such as size, raw lengths and circularity can be evaluated as well[31-33]. When these parameters are combined, the accuracy of DR assessment is even greater. Combining information from the SCP FAZ area, the DCP vessel density and the circularity of the FAZ has proven to best distinguish between DR severity groups[34]. Many studies have shown that the different plexi display distinct changes in DR progression[35] as they are differently affected at different stages of DR. An initial increase in the flow index and a higher perfusion capillary density can be observed in patients with diabetes, without DR, which may represent an auto regulatory response to the increased oxygen demand[36]. The importance of OCT-A is also noticeable in a recent Delphi method-based proposal of an OCT-A and retinal vascular disease expert consortium. This consortium recommended the

implementation of OCT-A for the identification and staging of DR by including the assessment of the foveolar avascular zone metrics, the presence and amount of no flow areas, IRMAs, NVs, and the vessel density of the superficial and deep capillary plexus[37]. WF imaging in OCT-A can be particularly useful in assessing DR. In some cases, the WF or UWF CF photographs can appear normal, while WF OCT-A demonstrates large NPAs and even neovascularization[38] (Figure 3). Furthermore, the repeatability of WF OCT-A is reasonable not only for qualitative image analysis but also for quantitative measurements. The intraclass correlation (ICC) varies between 0.67 to 0.84 depending on the assessed quantitative parameter[39]. Actually, the ICCs were lower in the macular region (central 6x6 mm) compared to the peripheral region, which underlines the usefulness of assessing the retina beyond the macular area for retinal vascular diseases[40]. Future research may show that the assessment of mid-peripheral non perfusion reveals a higher sensitivity to determine DR compared to the macular area[41].

Figure 3: Comparison of montage wide field OCT-A on the right and colour fundus (CF) photography (Clarus 500) on the left. While diabetic changes are hardly detectable in the CF photograph, capillary dropouts and neovascularization can be seen at a glance in widefield OCT-A.

Imaging can also help to identify neurodegenerative changes attributed to diabetes. Peripapillary OCT ring scans and macular ganglion cell layer (GCL) and retinal nerve fibre layer (RNFL) thickness is decreased in eyes of patients with diabetes compared to healthy age matched controls, even with only minimal or even no DR. These neurodegenerative changes correlate with microvascular changes in eyes with DR. Early foveal microcirculatory alterations in diabetic eyes and FAZ circularity for example correlate with GCL thinning[42, 43].

Considering all these important findings, it becomes evident that a new DR staging system is warranted. A current large initiative, the so-called *Restoring vision moonshot diabetic retinal disease staging system initiative* aims to address the limitation of the current staging system by implementing a holistic 3 dimensional model which not only includes different image modalities but addresses all aspects

of diabetes such as quality of life, worsening of vascular, neural and visual function and changes at the biochemical level[44].

4.2 Retinal vein occlusion (RVO)

RVOs are the second most common retinal vascular disease worldwide affecting 16.4 million people in 2008[45]. It is the obstruction of the normal retinal venous system. RVO can be broadly divided into branch RVO (BRVO) and central RVO (CRVO). Whereas BRVO usually occur at an arteriovenous intersection, CRVO most often develops near the level of the lamina cribrosa at the optic nerve[46]. RVOs are an important cause of visual loss and need to be treated in a timely manner to avoid serious complications[47]. BRVO and CRVO can be further classified into ischemic and non-ischemic types, based on the extent of capillary non-perfusion. Retinal non-perfusion is a risk factor for iris and retinal neovascularization with a broad range of complications resulting from it. Furthermore, retinal non-perfusion is believed to be a source of vascular endothelial growth factor (VEGF). Elevated VEGF levels not only contribute to the above-mentioned complications but also may induce macular edema[48]. Presumably, higher intraocular VEGF levels are positively associated with the total retinal NPA[49]. Thus, the evaluation of peripheral retinal non-perfusion is crucial for the management of RVO.

The cheapest and fastest way for a clinician to differentiate an ischemic from a non-ischemic RVO is by testing for a relative afferent papillary defect (RAPD). Other clinical features are the presence of multiple dark, deep intraretinal haemorrhages, the presence of multiple cotton wool spots, and the degree of retinal vein dilatation and tortuosity found on fundoscopy or in CF images[47]. However, even using all these parameters, it is still hard to determine the exact extent of retinal non-perfusion. A recent study found that perivascular and peripapillary RNFL haemorrhage at baseline corresponded with more severe forms of CRVO and greater risk of ischemia and neovascularization[50].

The differentiation between ischaemic and non-ischaemic CRVOs was first proposed by Hayreh when he described large non-perfusion areas seen in fundus FA in 1983[51]. Fluorescein angiography is still the gold standard imaging tool to assess the extent of NPA in RVO. Although there is no homogenous definition, ischemic RVO

is most often defined by the evidence of NPA larger than 10 disc areas that are found in the seven field fundus fluorescein angiography[47] (Figure 4).

Figure 4: Central retinal vein occlusion (CRVO). The classical appearance of a CRVO includes intraretinal haemorrhages, congested and tortuous veins, and swelling of the optic nerve head as shown in the colour fundus (CF) image. Substantial macular oedema is visible in the OCT and infrared (IR) images IR 1 and OCT 1. In the follow up examinations (IR 2, OCT 2) following treatment with anti-VEGF agents, the amount of macular oedema has reduced. Fundus fluorescein angiogram shows diffuse vascular leakage and disc swelling. It is useful to identify avascular retinal areas.

Figure 5: Colour coded whole retina wide field montage OCT-A of a patient with a superior hemi-RVO. Decrease in the SCP and DCP vessel density as well as tortuous venous vessels are evident. Anastomotic collaterals can be visualized at the junction of affected and unaffected retina.

With the wider adoption of WF and UWF imaging, this definition may require revision. Keeping in mind, that Optos 200Tx is capable to cover 82% of the entire retina in one image. With today's UWF FA we can define the extent of the NPAs better than ever before. However, image distortion towards the periphery as mentioned earlier is an important factor to consider. This means that non-perfusion areas in the peripheral retina can be easily overestimated. As illustrated by Tan et al., the same amount of pixel in the central area and peripheral area correspond to an area of 30.9 mm^2 and 17.2 mm^2 respectively[20]. Only after the images are represented in a stereographic projection, accurate area, distance and angle measurements can be estimated using widely known mathematic formulas. Fortunately, these calculations are incorporated in the DICOM standards[20].

Like in DR, further non-invasive techniques such as OCT-A and WF OCT-A might play an increasingly important role in the assessment of RVOs[52] (Figure 5). A Delphi based expert round on OCT-A and retinal vascular

diseases recommended defining ischemic CRVO based on ≥ 30% of decreased flow area of absolute imaged area of the WF OCT-A image[18]. The vascular density in the superficial and deep vascular network as well as the FAZ appear to correlate with visual function[53]. The periarterial capillary-free zone (paCFZ) could be of additional special interest. The paCFZ, first described by His in 1880, is a physiological avascular zone surrounding the retinal arteries mainly in the SCP and derives from a higher oxygen concentration in this area during embryonic development[54]. Vasoobliteration of the periarterial capillaries can be induced upon exposure to hyperoxia[55]. Arthur et al. described a larger paCFZ in patients with DR imaged with OCT-A[56]. Likewise, enlarged paCFZ can be found along unaffected major retinal arteries in eyes with BRVO[57]. Thus, paCFZ might be a useful biomarker for monitoring retinal diseases associated with change in retinal microvasculature[54]. Perivenous retinal whitening may be another related finding in RVO. It occurs secondary to hypoperfusion induced middle retinal ischemia and can be best visualized with en-face OCT scans[58, 59].

4.3 Retinal artery occlusion (RAO)

RAOs can be classified as transient monocular vision loss (TMVL), branch retinal arterial occlusion (BRAO), central retinal arterial occlusion (CRAO), and ophthalmic arterial occlusion (OAO). They are associated with an elevated risk of stroke and cardiac events and need to be addressed immediately and accurately. In an acute situation, time-consuming imaging is not advisable, especially in the first 4.5 hours after initial symptoms because of reasonable chance of reperfusion when treated with intravenous tissue plasminogen activator. Also after the initial critical hours, patients with RAO need immediate referral to the stroke unit or neurologic examination within the first days and up to 1-2 weeks, depending on the acuteness of the event and after exclusion of arteritic causes[60].

There are several typical features seen on a CF image in eyes with RAO. The most common sign is the cherry-red spot appearance caused by an unchanged red coloured fovea surrounded by ischaemic, swollen and whitened inner retinal layers (Figure 6). In about 25% of all patients, a cilioretinal artery may still be perfused and preserve the maculopapillary bundle in a variable amount. In

embolic cases, an intra-arterial embolus may be found [52]. Sometimes the embolus may present as hyperautofluorescent on fundus autofluorescence (FAF), which may help to identify it more easily[61].

OCT in RAO shows thickening and swelling of the ischemic inner retinal layers in the acute phase and thinning of these layers due to atrophy over time. Correspondingly, hyperreflectivity on infrared imaging and hypoautofluorescence on FAF can be seen in the acute stage[62, 63]. Later the affected retinal areas may be easily identified using WF en-face thickness maps (Figure 7), revealing significant thinning and a so called "blue retina" in respective areas.

Fundus FA can show arterial occlusion and delayed retinal arterial profusion. It can determine the extent of the non-perfused retinal area. In contrast to RVO, where about 60% of all eyes with CRVO develop neovascularization, only about 20% of all eyes with CRAO do so. Sometimes, CF images and fundus FA may show normal results while vision is severely decreased. In these cases, quick degradation and transportation of the emboli far into the retinal periphery is suggested[64].

In contrast to fundus FA, where perfusion of the SCP and DCP cannot be distinguished, OCT-A gives a deeper understanding of the microvascular changes in RAO. Bonini et al. showed that reduced vascular perfusion in both, the SCP and DCP could be quantified on OCT-A. According to the underlying pathology of the disease, the decrease of vessel density in the SCP is more pronounced than in the DCP[65]. Furthermore, a correlation between reduced vascular perfusion in OCT-A and delayed dye perfusion in FA was demonstrated[66]. Interestingly, Yang et al. revealed that in RAO patients the SCP of the fellow eye was also reduced, implying that chronic microvascular changes may exist already before the onset of RAO[67]. Thereby, OCT-A could be further explored regarding possible predictive value for cardiovascular events or stroke which illustrates the potential of ultrastructural imaging techniques such as OCT-A.

Figure 6: Central retinal artery occlusion (CRAO). 1) Acute CRAO with swelling of the inner retinal layer with cherry-red spot appearance of the fovea (CF 1). Retinal arteries are barely visible or just remarkable as segmented vessels. Corresponding

OCT shows swelling of the inner retinal layers (OCT 1). 2) Long term follow up after CRAO in the same subject. The macula has a blunt appearance and the optic nerve head is pale (CF 2). Retinal vessels are very thin or not visible. The corresponding OCT shows significantly reduced inner retinal layers (OCT 2).

Figure 7: wide field montage en-face thickness map of a case with retinal artery occlusion. The blue areas indicate precisely the previously affected retina. Also, appreciate the relative foveal sparing with normal retinal thickness values.

5. ARTIFICIAL INTELLIGENCE (AI)

It is generally accepted that artificial intelligence (AI) started with intervention of robots. The term "robot" was introduced into literature by the writer Karel Capek in 1921 to describe biosynthetic machines in a factory that were used as forced labor[68]. Therefore, the concept of AI is not new; however with recent advancement in computer power, data availability and refined algorithms, AI experiences a renaissance with a growing field of research. The term AI is generally used to describe "the use of a computer to model intelligent behaviour with minimal human intervention"[68]. However, in medicine, AI is mostly used to describe deep learning (DL) algorithms that are trained by processing patient data. This virtual intelligence can be used in daily practice to analyse clinical data for active guidance of physicians in their diagnostic or treatment decision as an example.
Several commercial imaging software implement AI for fundus image processing and evaluation[69]. Studies showed that predicting the risk of myocardial infarction through retinal scans and minimal personal information might be possible[70]. AI showed good performance when recognizing RVO and therefore can assist the physician in diagnosing RVO[71]. AI is also being used and evaluated in other ophthalmologic fields such as age-related macular degeneration, retinopathy of prematurity, glaucoma, keratoconus and cataracts[69, 72].

6. CONCLUSION

With the ever-growing progress in imaging techniques, computer power and refined processing algorithms, retinal imaging has advanced in the last decades. Since the first fundus photo in 1886 until today, retinal imaging has led to the better understanding of many retinal diseases. In this review, we focused on DR, RVO, and RAO as representative entities of retinal vascular diseases. Nowadays, retinal imaging represents an important tool for diagnosis, prognosis, therapeutic decisions, and follow up of patients with retinal vascular diseases. It has facilitated the daily business in the clinical practice tremendously. Regarding the steadily growing population development in the next decades, support of retinal imaging and automatic image analysis will become more relevant than ever. Some of the available imaging tools such as colour fundus photography provide an easy and effective tool for population screening. Automatic screening programs and image analysis are likely to be based on artificial intelligence approaches in future. This will assist early disease detection and may help to guide ocular as well as systemic treatment. The broad range of imaging possibilities supports greater understanding of the pathophysiology of retinal vascular diseases. Developments towards higher resolution, wider field of view, and dynamic imaging of retinal changes will additionally promote our understanding and future research addressing retinal vascular diseases.

"*The eyes are the window to the heart"* will probably keep its importance forever, thus let us take a snapshot from the eye!

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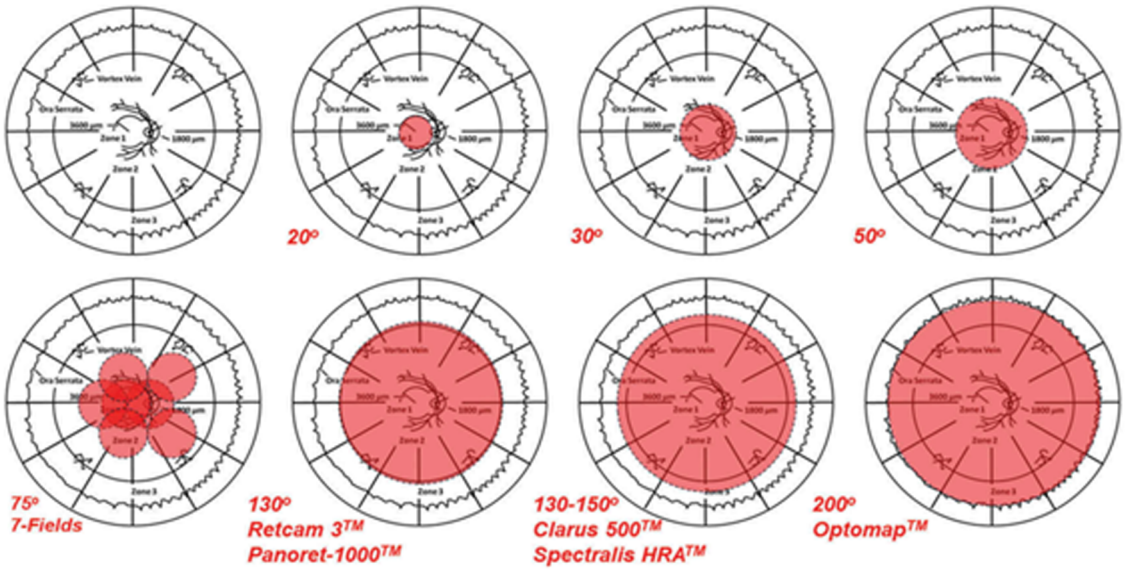

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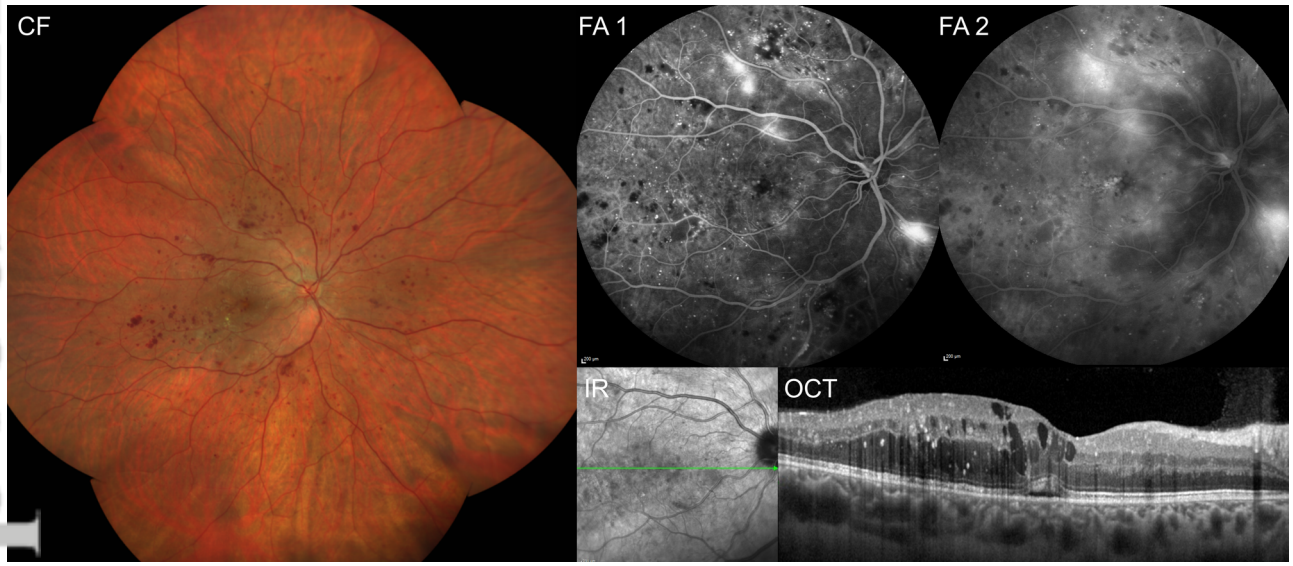

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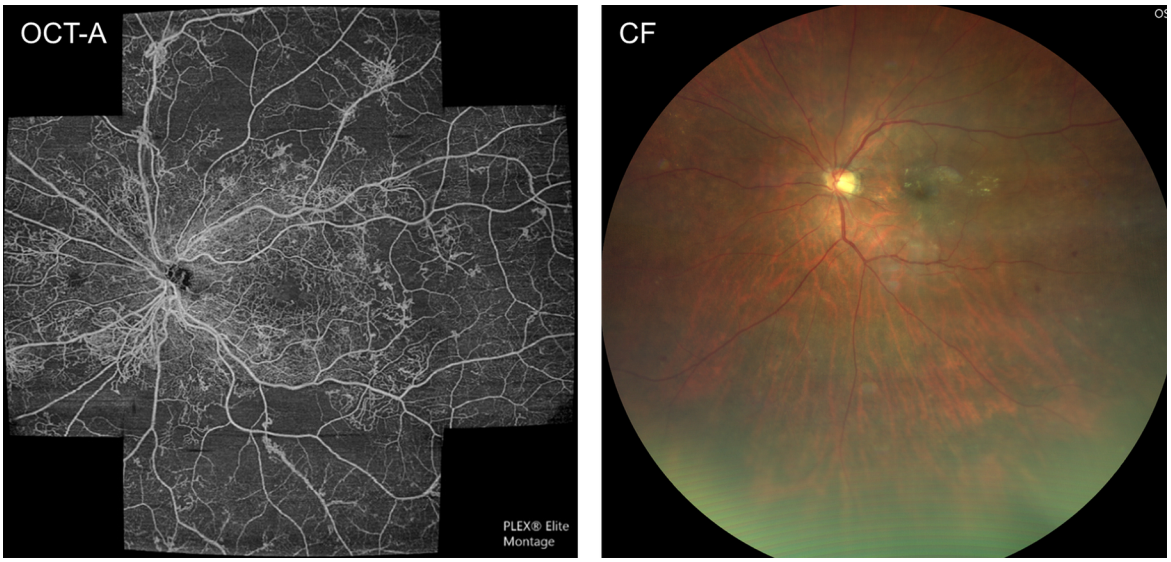

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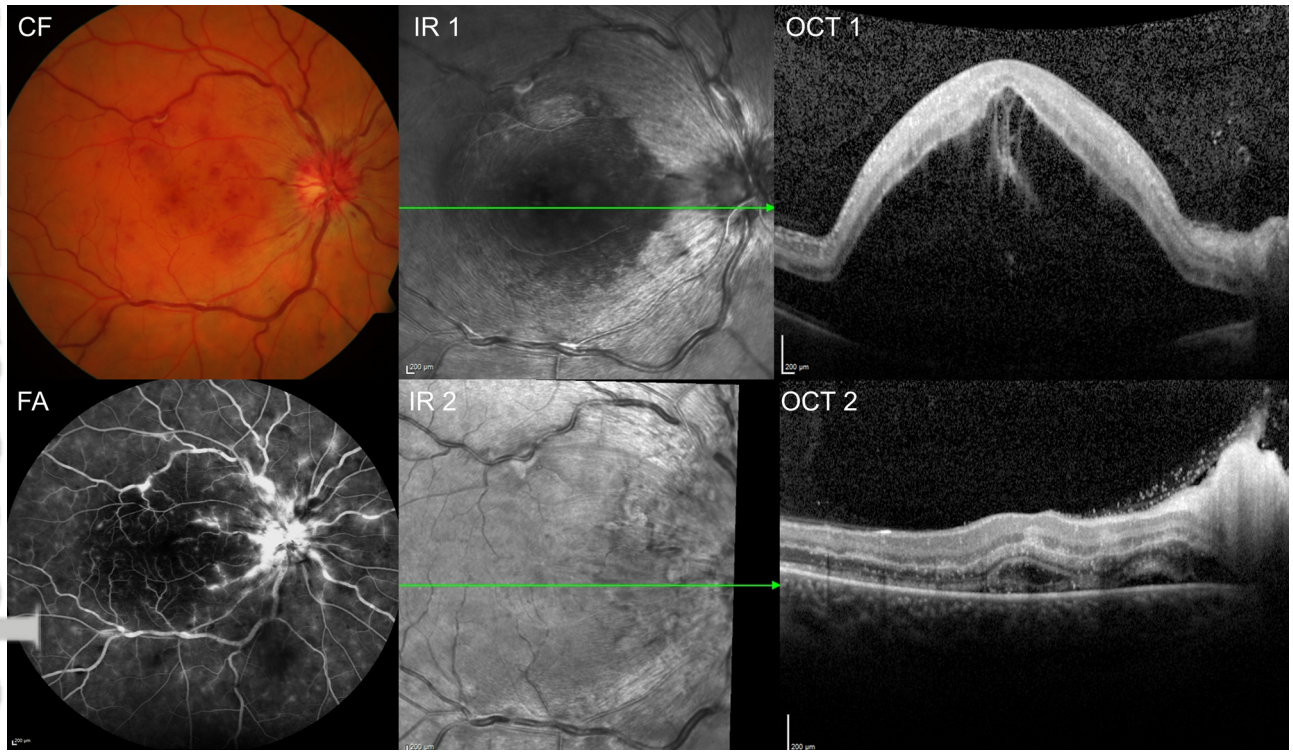

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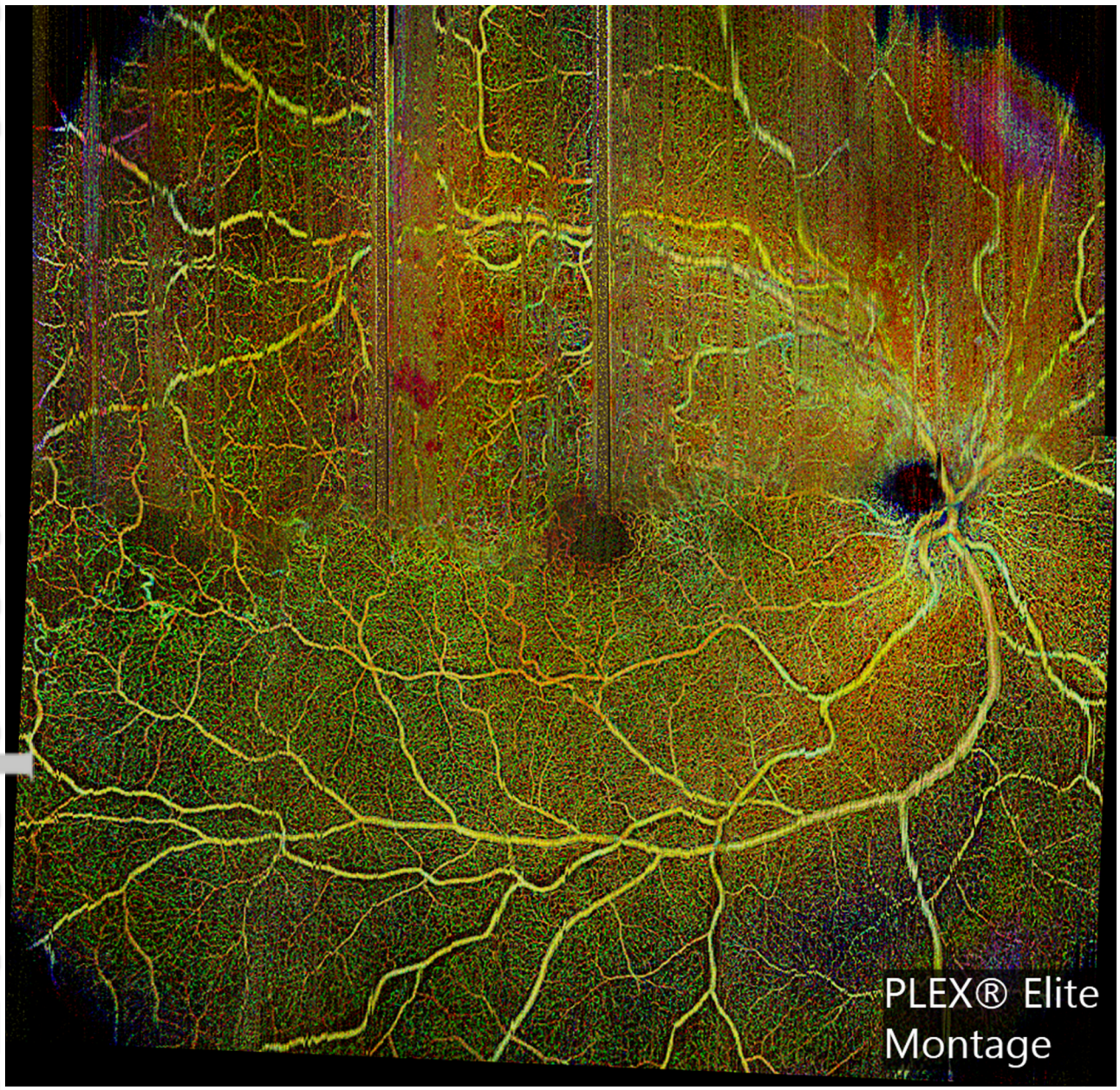

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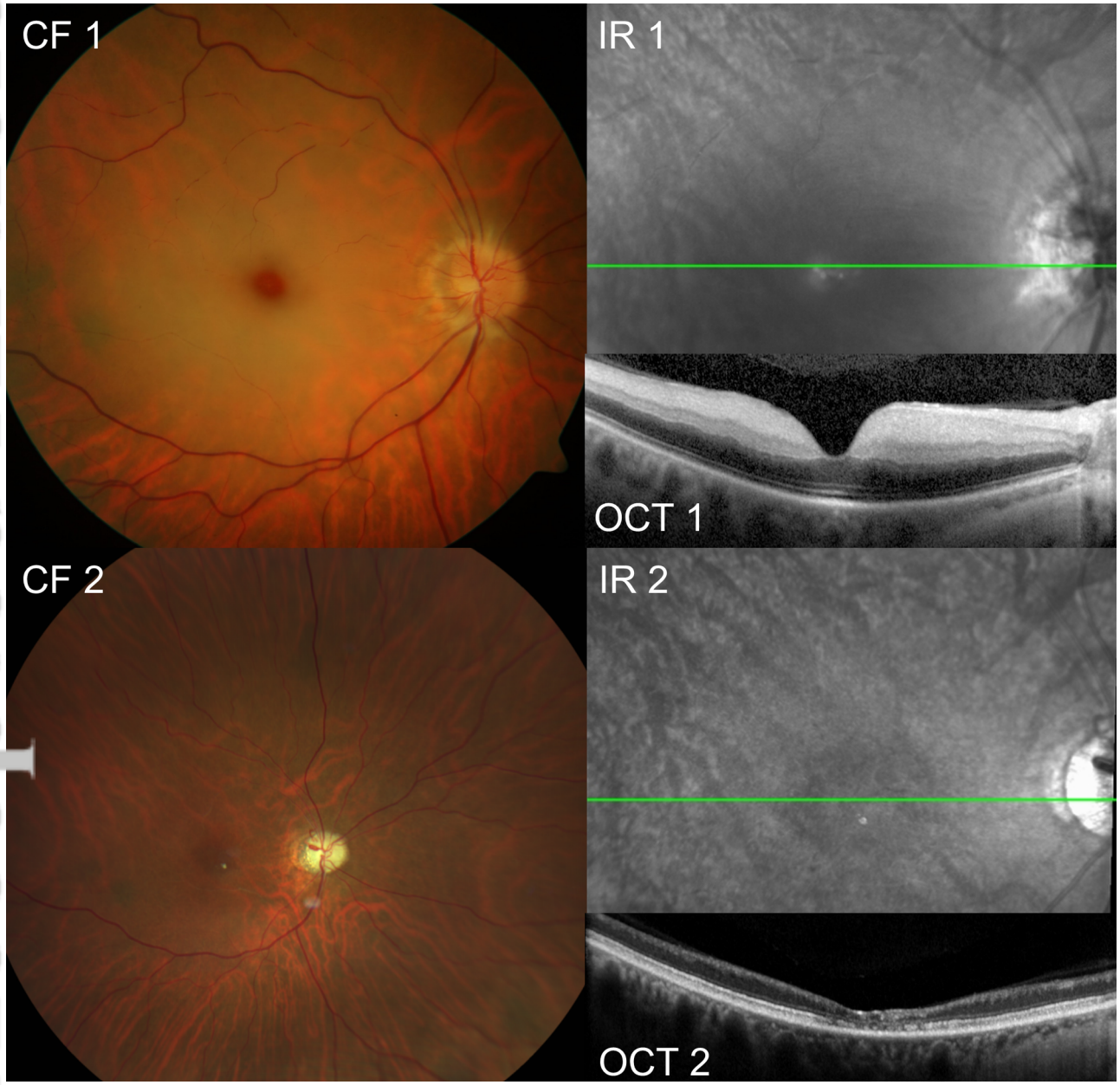

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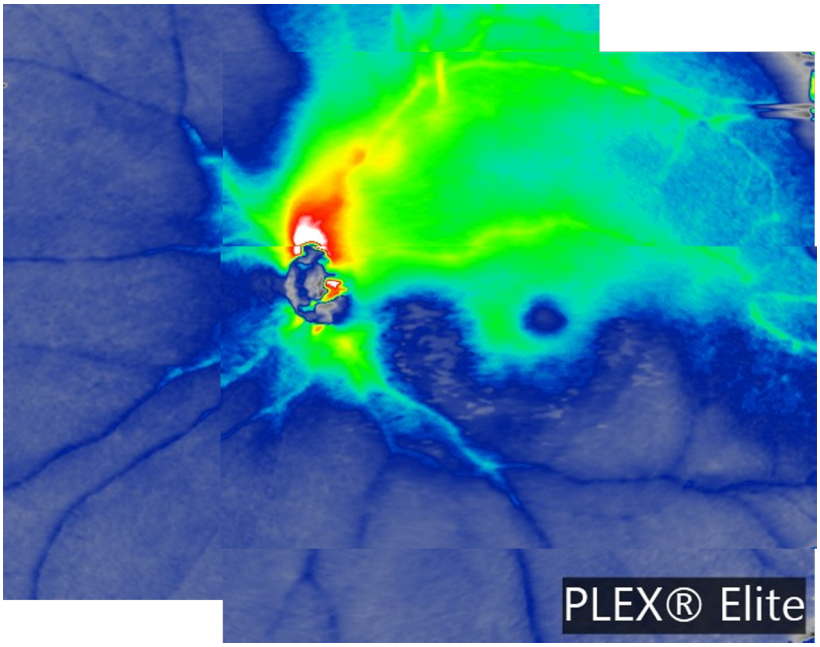

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