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Optical coherence tomography angiography in glaucoma

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Abstract

Optical coherence tomography angiography (OCTA) is a relatively new, non-invasive, dye-free imaging modality that provides a qualitative and quantitative assessment of the vasculature in the retina and optic nerve head. OCTA also enables visualization of the choriocapillaris, but only in areas of parapapillary atrophy. With OCTA, movement of red blood cells is used as a contrast to delineate blood vessels from static tissues. The features seen with OCTA in eyes with glaucoma are reduction in the superficial vessel density in the peripapillary and macular areas, and complete loss of choriocapillaris in localized regions of parapapillary atrophy (called deep-layer microvascular dropout). These OCTA changes correlate well topographically with the functional changes seen on visual field examination and structural changes seen on OCT (i.e., parapapillary retinal nerve fiber layer changes and inner retinal layer thickness changes at macula). The OCTA measurements also have acceptable test-retest variability and well differentiate glaucomatous from normal eyes. OCTA measurements can be affected by various subject-related, eye-related and disease-related factors. Vessel density reduction on OCTA reaches a base level (floor) at a more advanced disease stage than the structural changes on OCT and therefore has the potential to monitor progression in eyes with advanced glaucomatous damage. OCTA also adds information about glaucoma patients at risk of faster progression. OCTA, therefore, complements visual field and OCT examinations to diagnose glaucoma, detect progression and assess risk of progression.

Glaucoma is a chronic optic neuropathy characterized by progressive loss of retinal ganglion cells (RGCs).[1] Although the exact pathogenesis of glaucoma is not fully understood, two main theories have been proposed to explain the death of RGCs in glaucoma.[2] The “mechanical theory” postulates RGC death to be a consequence of raised intraocular pressure (IOP). It proposes that increased IOP causes a blockade of axoplasmic flow within the RGCs at the lamina cribrosa. As a result, there is a failure to deliver target-derived neurotrophic growth factors and this leads to RGC death.[3] IOP is a leading risk factor for

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glaucoma and multiple studies have reported IOP also to be a major causal factor.[1, 4–10] However, it is well accepted that the mechanical theory alone, fails to explain the entire pathogenic mechanism of glaucoma.[11, 12] The “vascular theory”, an alternative theory to explain glaucoma pathogenesis, postulates RGC death to be a consequence of reduced blood supply.[13]

Measuring ocular blood flow in humans

Although numerous technologies, including fluorescein angiography (FA),[14–18] indocyanine green angiography (ICGA),[19] scanning laser ophthalmoscopy,[20] laser Doppler flowmetry,[21] and laser speckle flowgraphy,[22] have been used to document the impairment of ocular blood flow and alterations of the retinal microvasculature in glaucoma, they have had diverse limitations and only minimal success in elucidating the role of vascular dysregulation in glaucoma.[23] Moreover, many of these technologies have been unable to obtain accurate, reproducible and quantitative measurements.[24]

The search for a simple, non-invasive, reproducible method of evaluating the ocular blood flow led to the development of optical coherence tomography (OCT) angiography.

OCT angiography

OCT angiography (OCTA) is a non-invasive, dye-free technology that can image large vessels as well as microvasculature of the retina, optic nerve head (ONH) and some part of the choriocapillaris by performing multiple OCT scans of the same region. Moving particles, such as red blood cells in blood vessels, resulting in high variance of the OCT signal between scans and this variation in OCT signal is used to identify blood vessels. Several algorithms have been developed to interpret the variance in the OCT signals and to delineate the blood vessels, and these have been incorporated in various commercially available OCTA devices. The split spectrum amplitude decorrelation angiography (SSADA, Angiovue, RTVue-XR SD-OCT, Optovue Inc., Fremont, CA) uses the variation in the intensity of the OCT signal to identify blood vessels.[25, 26] The full spectrum amplitude decorrelation angiography (FS-ADA, Spectralis OCT2 Module, Heidelberg Engineering, Heidelberg, Germany) uses the variation in the entire intensity spectrum of the OCT signal to identify blood vessels.[27] Similarly, OCTA ratio analysis (OCTARA, DRI OCT Triton, Topcon, Japan) is another algorithm that uses the full spectrum of the OCT signal for blood vessel delineation, thereby preserving the axial resolution.[28] The optical microangiography (OMAG), another OCTA algorithm (Angioplex, Cirrus HD-OCT, Carl Zeiss Meditec Inc., Dublin, CA), uses the variation in intensity as well as the phase difference of the OCT signals for vessel delineation.[29–31] In addition to tracing the blood vessels, these algorithms are also designed to reduce motion artifacts and pulsatile bulk motion noise.[26, 32]

The current generation of OCTA can scan the optic disc region and the macula. The optic disc OCTA scan is performed using volumetric scans generally covering an area of 4.5 × 4.5 mm centered around the optic disc. The optic disc scan is divided into several slabs for further analysis. Segmentation of these slabs differs among commercially available OCTA devices mentioned above. Two slabs of the optic disc scan that are found to be useful in

glaucoma are the radial peripapillary capillary (RPC) slab that delineates the vessels within the retinal nerve fiber layer (RNFL) layer and the choroidal slab that delineates the choroidal vessels in the parapapillary region. The RPC slab extends from the internal limiting membrane (ILM) to the posterior boundary of the RNFL (Figure 1a). Reduction in vasculature is reported to be more pronounced on the RPC slab compared to the deep retinal slabs in glaucomatous eyes.[33] The "choroidal" slab is used to assess the deep retinal and choroidal vasculature. The choroidal slab on RTVue-XR SD-OCT extends from 75 μm below the retinal pigment epithelium (RPE, Figure 1b).[34] The choroidal slab on Cirrus HDOCT extends from 64 μm below the RPE-fit line to 115 μm posterior (having a thickness of 51 μm).[31]

The macular OCTA scan is performed using a volumetric scan covering either a 3 × 3 mm (Figure 2a) or a 6 × 6 mm (Figure 2b) area of the macula. A comparative study has shown that the 6 × 6 mm scans better detect glaucomatous changes compared to the 3 × 3 mm scans (as in the example shown in Figure 3).[35] The macular region is also divided into slabs for further analysis. Of these, superficial retinal slab is the one found to be useful in glaucoma. The superficial retinal slab on RTVue-XR SD-OCT extends from 3 μm below the ILM to 15 μm below the inner plexiform layer (IPL, Figure 2).[34] The same slab on Cirrus HDOCT extends from ILM to IPL.[31] Reduction in vasculature is reported to be more pronounced on the superficial retinal slab compared to the deep retinal slabs in glaucomatous eyes.[36] Another important point to note is that segmentation errors are possible in the setting of normal anatomic variation or pathologic changes in the retinal layers due to the fact that fixed boundaries are assigned for the slabs; hence each OCTA B-scan should be reviewed prior to interpretation of the quantitative analysis.

OCTA quantifies the ocular circulation using two parameters: flow index and vessel density. Flow index is defined as the average decorrelation values in the measured area. Vessel density, the most widely used OCTA parameter, is defined as the percentage area occupied by vessels in the measured area.[25] The method of quantification of OCTA vessel density varied among different studies, especially until automated software were available; this might explain some discrepancies among investigations.[37] Also, measurements from different OCTA algorithms (described above) in healthy eyes varied significantly, suggesting that the OCTA measurements from different algorithms cannot be used interchangeably.[38]

OCTA and POAG

(i) OCTA features in POAG

Initial studies with OCTA were performed in eyes with POAG and they showed reduced flow index and vessel density within the ONH (nerve head slab) and in the peripapillary region (RPC slab) of eyes with POAG compared to controls (Figure 3).[25, 39–41] Subsequently, it was shown that OCTA vessel densities measured in the superficial macular regions were also reduced in eyes with glaucoma compared to control eyes (Figure 3).[42, 43] Vessel densities showed a more pronounced decrease as the severity of glaucoma increased.[36, 40, 44–52] More recently, deep-layer microvasculature dropout (MvD, Figure 4), defined as the complete loss of choriocapillaris in localized regions of parapapillary atrophy (PPA), has

been observed on the choroidal slab in POAG eyes.[53, 54] MvD has been shown to be a true perfusion defect using indocyanine green angiography.[55]

(ii) Repeatability and Reproducibility

Intra-visit repeatability and inter-visit reproducibility of OCTA measurements in the peripapillary and macular regions have been investigated by several groups. One study found that intra-visit coefficient of variation (CV) of OCTA peripapillary vessel density measurements (global and sectoral) ranged from 2.5% to 6.6% and that of superficial macular vessel density from 3.4% to 5.6%.[56] Two other studies also showed similar CV for both intra-visit and inter-visit OCTA measurements.[57, 58] Glaucoma eyes showed worse inter-visit repeatability than healthy eyes.[57] In comparison, CV of the OCT measurements (RNFL and ganglion cell complex [GCC] thickness) were found to be less than that of OCTA measurements implying that the OCTA measurements were less reproducible than the OCT measurements.[57] The intra-visit and inter-visit CVs of average RNFL and GCC thickness, for example, were around 1.5%, whereas that of average peripapillary and parafoveal vessel density were close to 4.0% ($P < 0.001$).[57] This is an important consideration when using OCTA measurements to detect glaucoma progression.

(iii) Relationship of OCTA measurements with VF and OCT measurements

The relationship of the OCTA measurements to visual field (VF) and OCT measurements also has been evaluated using linear, quadratic and polynomial fits.[59–69] This relationship was found to be good and non-linear fits described this relation better than linear fits.[60, 62] Additionally, in glaucoma eyes with high myopia[70] and in eyes with advanced glaucoma,[71, 72] the association of VF parameters seemed to be stronger with OCTA compared to OCT thickness measurements. Furthermore, a recent study also found that the measurement floor, the value beyond which further change in the measurement becomes undetectable, was at a lower level for OCTA compared to OCT measurements.[73] In fact, no detectable measurement floor was found for macular vessel density measurements and this showed that OCTA is a promising tool for monitoring progression in advanced disease.[73]

Studies have also reported a topographic association between the location of MvD and structural defects (RNFL thinning and lamina cribrosa defects) as well as functional defects (VF loss) in POAG eyes.[53, 74–76]

It is important to determine the temporal relationship of vessel density reduction on OCTA with respect to RNFL thinning and visual field defects. This would help develop strategies to detect the disease in the earliest stages. However, OCTA is a relatively new technology with only a few, small, longitudinal studies. As an alternative approach, studies have been performed in eyes with established perimetric glaucoma, whose VF defects are limited to one hemifield and the OCTA changes in regions corresponding to the intact hemifield have been examined. These studies have found reduced peripapillary vessel density and RNFL thickness in the hemiretina corresponding to the perimetrically intact hemifield compared to that of healthy eyes.[77–79] One of these studies also found that the temporal sector of the perimetrically intact hemifield (corresponding to the region of papillomacular bundles) showed reduced vessel density in the presence of normal RNFL thickness.[78] This suggested

that there may be regional variations in the alterations of RNFL thickness and vessel density measurements, and OCTA changes may precede RNFL changes in some sectors. Another recent study reported that the OAG eyes with VF defects limited to one hemifield and also having a MvD showed significantly lower RNFL and GCIPL thickness in the hemiretina corresponding to the perimetrically intact hemifield than those without a MvD.[80]

(iv) Comparing OCTA with OCT measurements in diagnosing POAG

The diagnostic abilities of OCTA measurements (peripapillary and superficial macular vessel densities) have been compared with corresponding OCT measurements (RNFL and GCC thickness) in glaucoma.

A few studies comparing the diagnostic abilities (area under the receiver operating characteristic curves [AUC] and sensitivities at high specificities) of peripapillary vessel densities and RNFL thickness in POAG have found them too similar.[40, 41, 61, 81, 82] Depending on the severity of glaucoma patients included in these studies, the AUCs of both peripapillary vessel density and RNFL thickness have ranged between 0.85 to 0.95. A few other studies have reported a better diagnostic ability of RNFL thickness compared to peripapillary vessel density in POAG.[43, 83] In spite of the AUCs being similar, a few studies showed that the sensitivity to detect glaucoma in early stages of severity was better with RNFL thickness compared to peripapillary vessel density measurements.[43, 84] Similar to the peripapillary measurements, diagnostic ability of superficial macular vessel density was found to be similar to that of macular GCC thickness by a few studies,[61, 85] while the same was found to be inferior to GCC thickness in other studies.[35, 43, 86, 87] One of these studies found that despite similar AUCs, more than one-third of early glaucoma eyes showed greater loss of vessel density than GCC thickness.[85]

(v) Factors associated with OCTA parameters

Factors associated with OCTA measurements can be classified into disease-related, subject-related, and eye-related factors. Clinicians evaluating the OCTA scans quantitatively, therefore, should consider all these factors during interpretation.

Disease-related Factors: Variability in OCTA measurements has been reported in different subgroups of patients with POAG. It should be noted that that POAG eyes are not homogenous in terms of vascular density even at similar disease severities and the characteristics of glaucomatous eye might influence the OCTA measurements.

1. Glaucoma severity: Vessel densities showed a more pronounced decrease as the severity of glaucoma increased.[36, 40, 44–52] Prevalence and the size of MvD increased as the severity of disease increased.[53, 74, 75, 88] MvD was also more commonly present when the VF defects were in the parafoveal region.[88–91]

2. Lamina cribrosa (LC) defect: In eyes with similar severity of VF loss, the reduction in OCTA circumpapillary vessel density was greater in those with than those without focal LC defects. Further, reduction of vessel density was spatially correlated with the location of the LC defect.[92] However, macular vessel density was not significantly different in severity-

matched glaucoma eyes with and without focal LC defects.[93] The presence of MvD is also reported to be strongly associated with LC defects.[53, 94]

3. Disc hemorrhage: One cross-sectional study found that most of the vessel densities and structural measurements were similar (P>0.05) in POAG eyes with and without DH.[95] In contrast, another study found that inferotemporal peripapillary vessel density was significantly lower in POAG eyes with DH compared to POAG eyes without DH. MvD, on the other hand, was found to be significantly associated with DH. Moreover, the prevalence of MvD was higher in POAG eyes with DH compared to POAG eyes without DH.[88, 96]

Subject-related Factors:

1. Demographics: Most studies have reported older age to be associated with lower macular and peripapillary vessel density measurements.[23, 36, 68, 97–100] In studies with a mixture of patients of African and European descent, the vessel density measurements were found to be lower in glaucomatous eyes of patients with European compared to African descent.[99, 101]

2. Diurnal change: Studies have reported that the diurnal changes in OCTA vessel densities were small and clinically insignificant.[102, 103]

3. Exercise: In a small cohort of 13 healthy people before and after exercise, it was found that increased physical activity induced significant reduction in OCTA vessel densities.[104]

4. Systemic conditions: In hypertensive individuals (with no retinopathy), the peripapillary vessel densities were lower, while the macular vessel densities were higher. The vessel densities also were lower in subjects with diabetes (with no retinopathy)[105] and the reduction in vessel density was associated with the duration of diabetes.[100]Another study evaluating the diurnal changes in OCTA measurements found a negative correlation of superficial macular and peripapillary vessel densities with heart rate, and a positive correlation of superficial vessel density with mean arterial pressure.[103]

4. Medication: Effect of medications on OCTA measurements has not been studied well. Topical β-blocker administration has been reported to lead to 3.3% lower superficial macular vessel density compared to prostaglandin analogues, alpha agonists and carbonic anhydrase inhibitors, after adjusting for macular GCC thickness.[36]

Eye-related Factors:

1. Myopia: OCTA measurements in the peripapillary region have been found to be significantly lesser in high myopic eyes compared to emmetropic eyes.[106] Further, in myopia without glaucoma, peripapillary vessel density was lower than in normal eyes, and in myopic glaucoma, it was even more reduced.[107] However, this may be partly related to image magnification in high myopic eyes.[108]

2. Disc area: In a cross-sectional study, optic disc size was not found to affect the OCTA peripapillary measurements.[105]

3. **Signal strength:** Several studies have reported that vessel densities were lesser in OCTA scans with lower signal strength.[23, 56, 102, 105, 109] It is possible that the software does not differentiate between the static structures and blood vessels efficiently at low signal strengths.

4. **Effect of IOP:** The potential relationship between IOP (or IOP reduction/increase) and ocular perfusion has been an important question in glaucoma management. Effect of IOP on OCTA vessel densities are inconclusive. While a few studies showed a significant increase in vessel densities after IOP reduction (either medically or surgically),[110, 111] others found no change in vessel densities after IOP reduction.[112, 113]

(vi) Glaucoma Progression and its Risk Assessment using OCTA

As OCTA is a recently developed technique, there are no long-term studies evaluating its ability to detect progression. However, a few cases reports[98, 99] and case series[23, 114] have shown that OCTA is capable of detecting progressive decrease in superficial vessel densities in glaucomatous eyes even when monitored over short periods of time. It is important to note that vessel density is more variable than RNFL thickness and may reflect IOP changes, status of systemic perfusion, glaucomatous vascular dysregulation, retinal oxygenation, and hypercapnia at the time of measurements.[97, 102, 104, 105, 110] A recent study by Kim et al also showed that increase in MvD area could be detected using serial OCTA scans.[115] Future studies are needed to compare the progression detection ability of OCTA parameters with VF and OCT measurements.

In a longitudinal study assessing the risk of glaucoma progression, it was shown that lower baseline macular and peripapillary vessel densities were associated with a faster rate of RNFL progression in mild to moderate glaucoma over a mean follow-up of 27 months.[116] Importantly, this association was independent of the baseline RNFL thickness, suggesting that OCTA may offer additional information to the evaluation of the risk of glaucoma progression and prediction of rates of disease worsening. Multiple studies have also found that the presence of MvD is associated with a faster rate of RNFL thinning[117, 118] and VF progression.[119] Of interest, a significant association between MvD and faster rate of central VF progression has been reported.[120] Another recent study has reported an association between MvD enlargement and progressive RNFL thinning.[115] All these studies suggest that assessment of OCTA parameters may add significant information to the evaluation of the risk of future glaucoma progression.

OCTA changes in other subtypes of glaucoma

1. Normal tension glaucoma: The vascular theory of glaucoma is considered to be more applicable in eyes developing glaucomatous damage at low IOP. A few studies compared the OCTA measurements in low pressure glaucoma (NTG) and high pressure glaucoma (POAG). However, no difference in OCTA measurements were seen between NTG and severity-matched POAG eyes.[42, 121–123] In contrast, MvD was found to be more common in open-angle glaucoma eyes with lower pre-treatment/baseline IOP in one study.[91]

2. Primary angle-closure glaucoma (PACG): OCTA measurements are found to be reduced in eyes with PACG[81, 124, 125] and after an acute primary angle-closure episode.[126–128] Similar diagnostic abilities of OCTA vessel density measurements in PACG and POAG were found when accounting for the severity of disease, implying that the reduction of vessel density measurements in PACG is probably similar to that in POAG.[81] However, another study reported that POAG and PACG eyes have a different vascular–function relationship when determined by OCTA.[64] Another study found that the prevalence of MvD was lower in PACG compared to severity matched POAG eyes.[91]

3. Pseudoexfoliation glaucoma (PXG): A few studies have reported that the reduction of superficial vessel densities on OCTA was greater in PXG compared to POAG eyes of similar disease severity.[129–132] One of these studies also reported that the prevalence of MvD, unlike superficial vessel densities, was significantly lower in PXG compared to POAG eyes of similar disease severity.[131]

Limitations and recent advances in OCTA

Motion artifacts are common with OCTA imaging due to the prolonged time required to acquire the scans despite methods available to account for the artifacts (Figure 5). Multiple studies have also reported a high number of poor quality images with OCTA.[56, 58, 92, 133] Two significant improvements incorporated recently to overcome the issue of poor quality scans are (i) real time eye tracking technology, for controlling the motion artifacts more effectively[134] and, (ii) high-density (HD) scanning mode, for improving the resolution of the scans. A recent study has reported that the number of poor quality scans significantly decreased with the incorporation of these improvements.[135] Future advances in the technology should aim at reducing the acquisition time to obtain more precise measurements.

Media opacities, especially vitreous opacities, can significantly affect the quality of OCTA scans and the quantification of vessel densities (Figure 6). Pupillary size also affects the quality of OCTA scans and dilation of pupil is necessary for good quality scans.

OCTA technology evaluates well the superficial retinal vessels, but not the deeper retinal and choroidal vasculature. This is because the signals from the superficial retinal vessels project on to the deeper layers causing projection artifacts.[26] Detection of MvD, for example, is affected by the presence of projection artifacts. Newer methods of projection artifact correction have been tried and the newer generations of OCTA (projection resolved OCTA) are likely to evaluate the deeper retinal and choroidal vasculature better.[136]

Segmentation of the angiography slabs differs among commercially available OCTA devices. Campbell et al have recently used projection resolved OCTA to describe a rational segmentation algorithm that respects the normal distribution of vascular networks in the human retina.[136] They demonstrated four unique vascular plexuses in the human retina with distinct vascular patterns, which vary based on depth and location from the optic nerve.[136] Standardization of segmentation methods such as this could help comparability among

different commercially available OCTA devices and improve the clinical applications of OCTA.

Conclusions

OCTA is a novel, noninvasive imaging technology that provides information regarding the severity of impaired perfusion in different depths of the retina and choroid that was not available in the past. Currently, researchers are still understanding the full potential of OCTA in clinical practice and hence, ophthalmologists need to be conservative in the application of this technology in treatment decisions. However, since OCTA is a safe, non-invasive test, it can be performed at the same time as OCT and can provide information that complements VF and OCT examinations for early diagnosis of glaucoma, detection of progression and its risk assessment. Future longitudinal studies should evaluate if OCTA can detect vascular changes earlier than RNFL thinning in glaucoma. If this were shown to be the case, then OCTA can lead to a paradigm shift in the way glaucoma is managed and can also lead to new ways of testing treatment outcomes in glaucoma.

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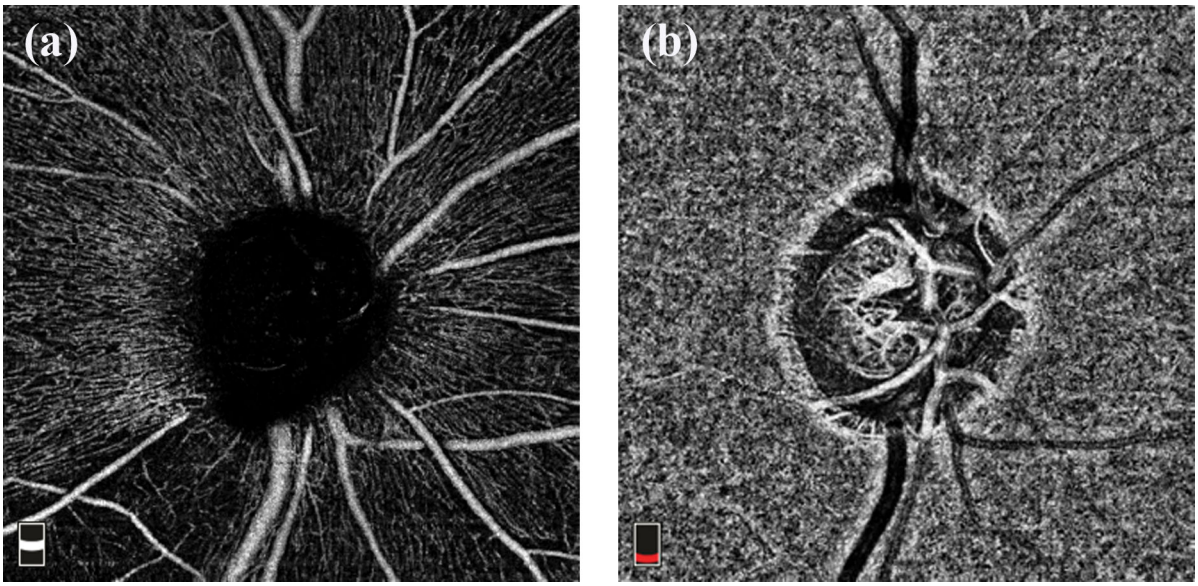

Figure 1.

Angiography slabs of the optic nerve head scan obtained using spectral domain optical coherence tomography showing the radial peripapillary capillary, RPC (a) and choroid (b) slabs.

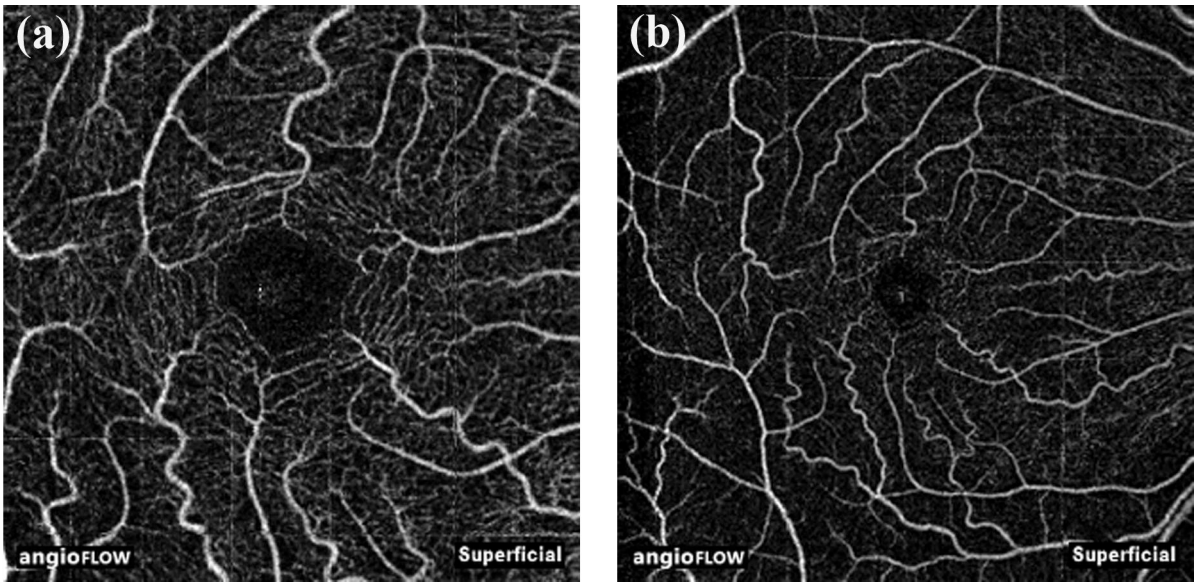

Figure 2.
Superficial angiography slabs of the 3×3 (a) and 6×6 (b) mm macular scan obtained using spectral domain optical coherence tomography.

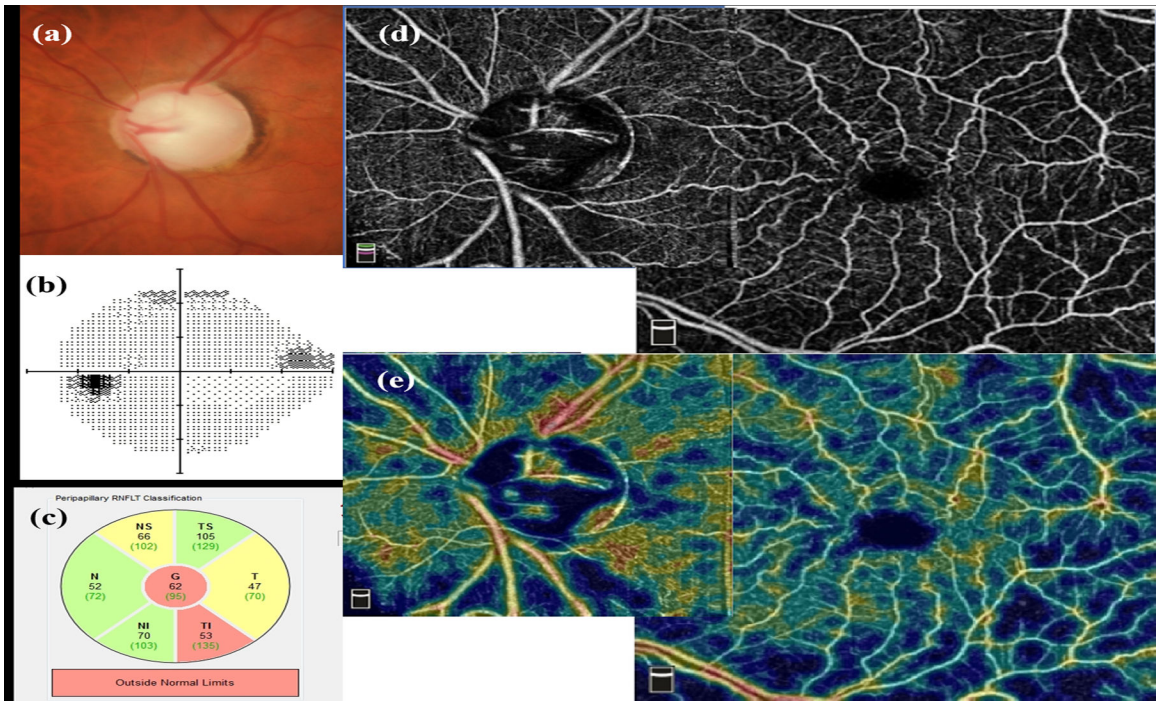

Figure 3.

OCTA features of a glaucomatous eye with mild disease. Optic disc photograph (a) shows inferior neuroretinal rim notch with a correlating superior nasal defect on the visual fields (b) and inferior retinal nerve fiber layer thinning on OCT (c). Composite peripapillary (4.5×4.5 mm scan) and macular (6×6 mm scan) OCTA scan shows reduced vessel density in the inferior region as indicated on the angiography (d) and heat map (e). Vessel density reduction on the macular OCTA scan is less obvious in the inner 3 mm region compared to the outer 3–6 mm region.

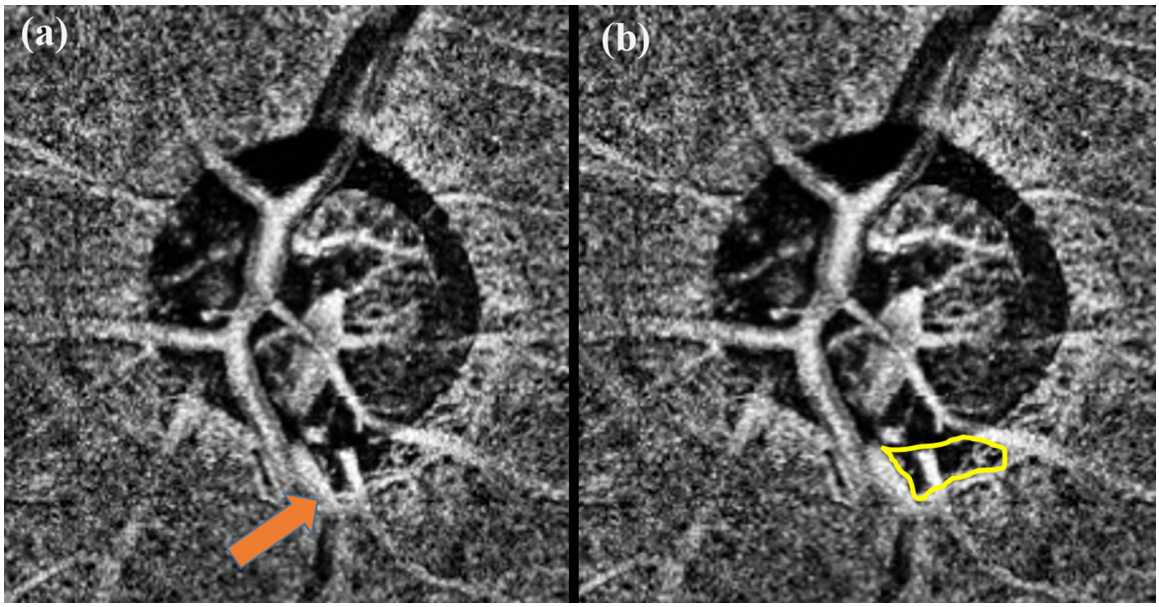

Figure 4.
Choroidal OCTA slab of a glaucomatous eye showing the presence of deep-layer microvasculature dropout (MvD) in the inferior region (a). Arrow points to the MvD. Yellow line marks out the boundary of the MvD (b).

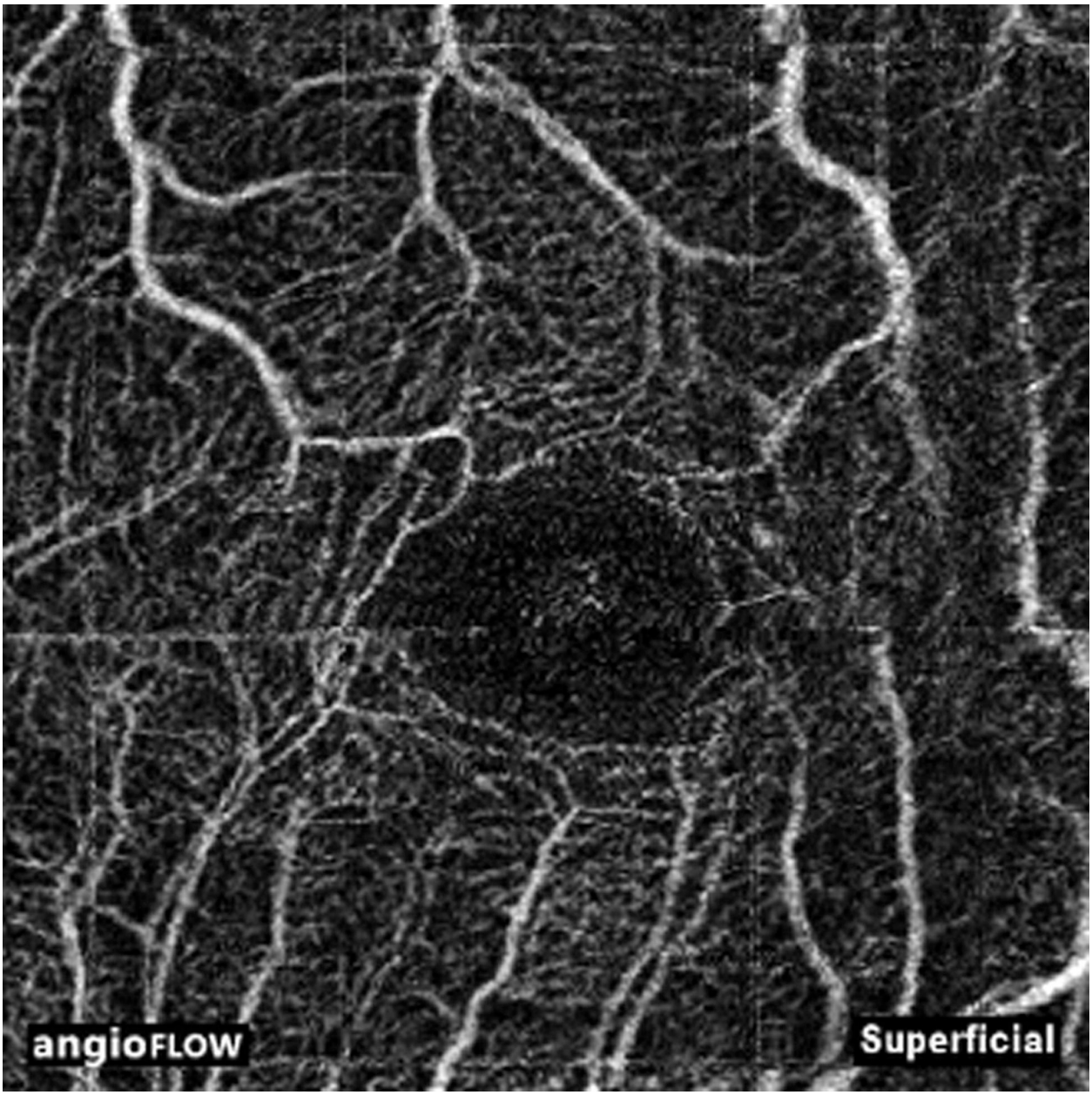

Figure 5.
Macular OCTA scan of a left eye showing two types of artifacts on the angiography map; motion artifacts, recognized as vertical bands temporally and duplication of vessels, recognized inferiorly and nasally.

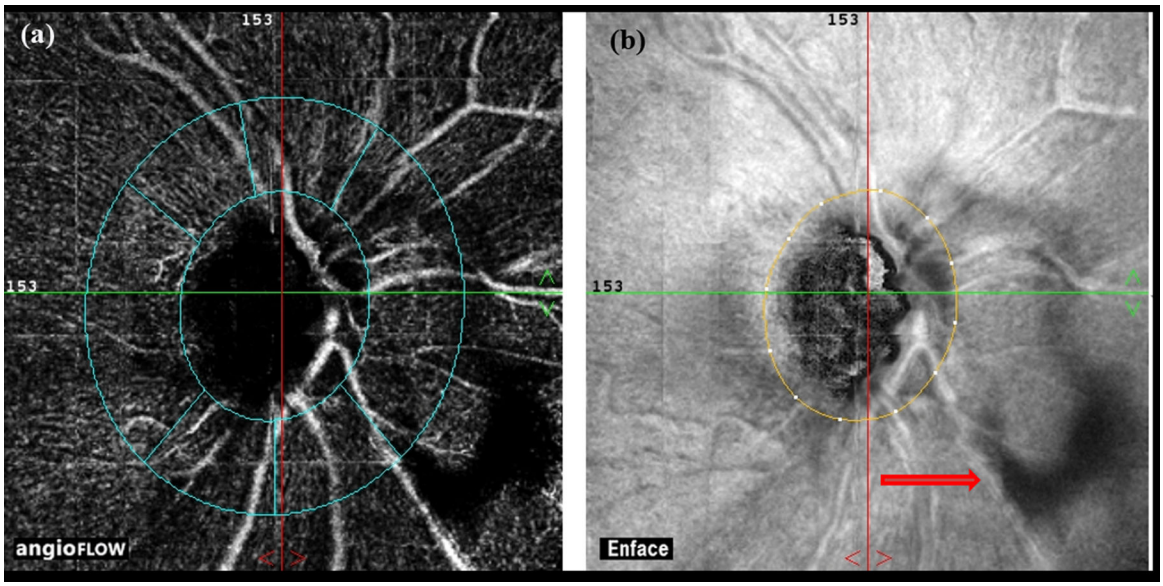

Figure 6.
Vitreous opacity (red arrow on en face map, b) casting a shadow, as seen on the angiography map (a).