Optical Coherence Tomography Angiography and Glaucoma: A Brief Review

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Abstract: Optical coherence tomography angiography (OCTA) is a new modality in ocular imaging which provides non-invasive assessment and measurement of the vascular structures in the retina and optic nerve head. This technique provides useful information in glaucoma, such as quantitative assessment of vessel density. Vessel density measurement can be affected by various subject-related, eye-related, and disease-related factors. Overall, OCTA has good repeatability and reproducibility, and can differentiate glaucoma eyes from normal eyes. It can also help detect early glaucoma, reach a floor effect at a more advanced disease stage than optical coherence tomography (OCT), and adds information about glaucoma patients at risk of progression. Although it has higher variability than OCT, it also promises to be useful for monitoring glaucoma by detecting progression throughout the glaucoma continuum.

Key Words: glaucoma, optical coherence tomography angiography, vessel density

Primary open-angle glaucoma (POAG) is characterized by progressive structural changes of the optic nerve, loss of retinal ganglion cells (RGCs) and their axons, and accompanying damage to the visual field (VF). Elevated intraocular pressure (IOP) is the leading risk factor for glaucoma. However, there are cases which are discrepant with the “mechanical” theory, particularly in patients who have progressive disease despite low IOP levels. For these patients and others, a “vascular” theory has been proposed, i.e., impaired regulation of ocular blood flow results in periods of relative ischemia that damages the optic nerve.

Although numerous technologies — including fluorescein angiography (FA), indocyanine green angiography (ICGA), scanning laser ophthalmoscopy, laser Doppler flowmetry, and laser speckle flowgraphy — 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 the vascular dysregulation in glaucoma. One important reason the study of ocular microcirculation with these technologies has been problematic is related to their inability to directly observe clearly the microvasculature within discrete layers of the retina and optic nerve head (ONH). Moreover, it has not been possible to obtain accurate, reproducible, and quantitative measurements with many of these technologies.

The introduction of optical coherence tomography angiography (OCTA), a technique for non-invasively imaging the blood vessels of the ONH and retina in vivo, addresses these limitations. Further, it offers the potential for enhancing our understanding of the role of ocular blood flow and the retinal microvasculature in glaucoma. Compared with flowmetry, which can only provide insight into blood flow velocity and the amount of avascular zone, OCTA provides a quantitative assessment of “vessel density” (VD). Vessel density is defined as the percentage area occupied by the large vessels and microvasculature in a particular region. For example, in Optovue (RTVue XR Avanti; Optovue, Inc. Fremont, CA, US), the whole en face image VD in ONH is measured in the entire 4.5 × 4.5–mm² image, and circumpapillary VD is calculated in the region defined as a 750-μm–wide elliptical annulus extending from the optic disc boundary. Macular superficial VD measurements are calculated in a slab from the internal limiting membrane to the posterior border of the inner plexiform layer. Macular whole en face image VD measurements are calculated from 3 × 3-mm² or 6 × 6-mm² scans centered on the fovea. Perifoveal VD is measured in an annular region with an inner diameter of 1 mm and outer diameter of 2.5 mm.

Contrary to traditional angiography with fluorescein, OCTA does not require the injection of extrinsic contrast dye. Furthermore, FA and ICGA only provide 2-dimensional images, lacking depth information, whereas OCTA allows for 3-dimensional imaging.

Various OCTA instruments from different manufacturers are currently used in clinical practice. At the time of writing, there are 4 distinct algorithms used for delineating ocular microvasculature: the split-spectrum amplitude-decorrelation angiography (SSADA) used by Optovue; the OCT-based microangiography (OMAG) used by Angioplex (Cirrus HD-5000; Zeiss Meditec, Dublin, CA, US); and the OCTA ratio analysis (OCTARA) used by Topcon DRI OCT Triton (swept-source OCT, Topcon, Japan); and the speckle variance OCTA used by Spectralis OCT2 module (Heidelberg Engineering, Germany).
REPEATABILITY AND REPRODUCIBILITY

Intra-visit repeatability and inter-visit reproducibility of OCTA measurements in the peripapillary retina and the superficial peripapillary layer were investigated by several groups. Overall, OCTA had good repeatability and reproducibility.

Venugopal et al. used SSADA algorithm available in RTVue XR spectral-domain OCT (Optovue Inc, Fremont, CA) and showed that intra-visit coefficient of variation (CV) ranged from 2.4% to 6.6% and coefficient of repeatability ranged from 3.3% to 7.1% for different OCTA parameters, including global and sectoral parameters of the macular and the peripapillary region in healthy and glaucoma eyes. Two other studies with the same algorithm also showed similar results.15,19 This means that any change in peripapillary or parafoveal VD of less than 5% to 7% would fall within the test-retest variability and would be clinically insignificant. Repeatability was found to be similar in healthy and glaucoma eyes.17,19 Repeatability estimates of the peripapillary sectors were worse than those of the global measurement.13 Comparison of intraclass correlation coefficient of OCTA measurements among Spectralis, Optovue, Triton, and Cirrus showed comparable intra-visit repeatability.20 In addition, signal strength index (SSI) values of the scans were positively associated with the intra-visit repeatability of OCTA measurements.17

Inter-visit CV was reported as 3.2% to 9.0% for the global OCTA parameters of macular and peripapillary region,14 and 5.0% to 6.9% for the peripapillary region.18 Same as intra-visit repeatability, inter-visit CV was better for global than sectoral measures.18 However, glaucoma eyes showed worse inter-visit repeatability than healthy eyes.18

Differences in the repeatability, reproducibility, and precision of OCT instruments are known.21 In a recent study, reproducibility of measurements of peripapillary capillaries from 4 OCTA devices (Spectralis, Optovue, Triton, and Cirrus) was investigated.20 The measurements varied significantly among devices, suggesting that the VD measurement cannot be used interchangeably among the different devices.

DIAGNOSTIC ABILITY OF OCTA IN POAG

Within the peripapillary area, most studies have found a good area under the receiver operating characteristic curve (AUC) (above 0.85) for both OCTA22-27 and OCT parameters.23-27,29-30 To date, only 2 studies found a significantly better AUC for the RNFL thickness.28,29 However, both of them involved glaucomatous change in OCT as a criterion of glaucoma diagnosis, which may have biased the diagnostic ability of OCT parameters. In addition to the raw measurements, the inter-eye asymmetry of VD in the peripapillary area also showed comparable discriminatory power with RNFL thickness (Fig. 1).30 However, it is believed that VD measurements may offer advantages in early diagnosis, as supported by a report that VD asymmetry showed significantly higher AUC for differentiating glaucoma suspect from healthy eyes compared with RNFL thickness asymmetry.30

There have been inconsistent reports about the diagnostic performance of macular superficial OCTA parameters. Several studies found a high AUC for the whole-image macular superficial VD (between 0.64 and 0.80).26,29,30,33 Significant differences were not found between ganglion cell complex (GCC) thickness and macular superficial VD to discriminate glaucoma eyes from healthy eyes in some studies.27,31,32 However, a better diagnostic performance of the GCC thickness compared with the macular superficial VD for detection of glaucoma has also been reported in a few studies.29,33,34 One main reason for this difference in AUC is the size of the macular scan. The macular areas that were found to be the most vulnerable to glaucoma are mostly outside the central 3 × 3-mm² area, but inside the 6 × 6-mm² area.35 The studies with a 3 × 3-mm² scan region yielded lower AUCs, whereas the studies with the greater AUC measured a 6 × 6-mm² region. It has been reported that 6 × 6-mm² macular scans had higher diagnostic accuracy compared with 3 × 3-mm² scans for differentiating between healthy and glaucoma eyes.31 The other reason could be that the region for measurements of OCTA parameters did not directly correspond with the region of thickness measurements.33 With the same scan size, GCC thickness showed similar diagnostic ability with macular VD.32 However, the concomitant reduction in scan resolution would decrease the signal-to-noise ratio of the OCTA images and underestimate VD measurement, and measurement of macular superficial VD over the 3 × 3-mm² area was found to have a low test-retest variability.24 To better address this issue, analysis of VD from high-resolution 6 × 6-mm² field macular scans is warranted.32 Similar to the peripapillary OCTA parameters, macular superficial VD also showed better AUC than GCC thickness for differentiating between glaucoma suspect and healthy eyes.33

Most studies found only a moderate AUC for the OCTA parameters of the optic disc (between 0.66 and 0.83),26,28,29,34 with a significantly better AUC for the OCT parameters (RNFL and rim area).28,29 A potential reason for the lower discriminatory power of the OCTA parameters of the optic disc was the considerable heterogeneity in optic disc morphology.37 Another possible explanation is the vascular crowding of large vessels in the optic disc, making it harder to specifically examine the microvasculature in the optic disc region.37

Overall, to differentiate glaucoma eyes from healthy eyes, the discriminatory power of OCTA parameters was comparable to or even better than that of OCT parameters.37 Moreover, the diagnostic abilities increased with increasing severity of glaucoma.26,29,36 However, the results yielded by different instrument systems seem to vary considerably.24,25,34,38,39 Head-to-head comparison study is needed to address this issue. The various data acquisition protocols used by the different versions of software, as well as their accuracy and reproducibility, must be taken into account.40,41 Moreover, the segmentation slab designed to isolate the vascular plexus varies among different devices and this may be a reason for inconsistency in previous studies.42 Interestingly, it has been reported that the combination of OCT and OCTA parameters significantly improved the diagnostic performance comparing with either of them alone.43

FACTORS AFFECTING OCTA MEASUREMENT

Determinants of peripapillary and macular VDs have been shown in previous studies. These factors can be classified into disease-related, subject-related, and eye-related factors. It should be noted that the method of VD calculations varied among

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different studies,\textsuperscript{31,32,44,45} and this might explain some of the discrepancies among the investigations.

**Disease-Related Factors**

Variability in VD has been reported in different subgroups of patients with POAG. It should be noted that POAG eyes are not homogeneous in terms of VD even with similar disease severities and the characteristics of glaucomatous eye might influence the VD measurements.

**Glaucoma Severity**

Increasing severity of glaucoma, in terms of function loss and structural defect,\textsuperscript{46} was spatially associated with more pronounced vascular damage measured by OCTA (Fig. 2).\textsuperscript{22,23,31,47–54} Localized and generalized OCTA parameters are spatially related to the corresponding VF sensitivity or other VF parameters. Peripapillary and macular VD showed a strong positive relationship with VF deterioration both on Humphrey and Octopus perimetry.\textsuperscript{33,55–58} Correlation was also found between the presence of central VF defects and increased size of the foveal avascular zone.\textsuperscript{59} The relationship was particularly strong for superotemporal and inferotemporal peripapillary VD and the spatially corresponding VF sectors.\textsuperscript{55,56} Moreover, multiple studies found a stronger “vasculature-function” association compared with the “thickness-function” association.\textsuperscript{27,47,54–58,60} This finding indicated that OCTA parameters may be more sensitive visual function biomarkers in glaucoma eyes than the OCT parameters. Vascular flow may reduce in eyes with sick or damaged ganglion cells, even before obvious reduction in RNFL thickness.\textsuperscript{58}

The decreases in structural parameters, such as RNFL and GCC thickness, were found directly correlated with the decreases in VD.\textsuperscript{24,30,56,61} It was shown that localized RNFL bundle defects are spatially associated with localized peripapillary VD reductions, even in early and preperimetric open-angle glaucoma.\textsuperscript{50} A few
studies investigated the perimetrically intact hemiretina in glaucoma eyes with VF defects in a single hemifield. One study found significantly lower OCTA parameters with normal RNFL thickness in the perimetrically intact hemiretina. Another study found a significantly lower RNFL thickness with normal VD in the perimetrically intact hemiretina. Both significantly lower VD and RNFL thickness were found in the perimetrically intact hemiretina in the third study.

**Lamina Cribrosa Defect**

A recent study by Suh et al suggested that in eyes with similar severity of VF loss, the reduction in optic nerve VD was greater in those with focal lamina cribrosa defects than those without. They evaluated 82 patients with POAG and found that reduction of VD was spatially correlated with the location of the lamina cribrosa defect.

**Disc Hemorrhage**

There is limited information on the influence of disc hemorrhage (DH) on the peripapillary perfusion. In a cross-sectional study of POAG eyes with or without DH, Rao et al found that most of the VD and structural measurements were similar ($P > 0.05$) in POAG eyes with and without DH. The inferotemporal peripapillary VD had the highest AUC for differentiating between POAG and normal eyes for both eyes with and without DH. In contrast, our recent data have shown that in POAG eyes with DH, inferotemporal peripapillary VD was significantly lower than that in eyes without DH, and they also had higher AUC compared with inferotemporal RNFL. This supports the concept that DH in patients with POAG might be linked to vascular abnormality.

**Subject-Related Factors**

**Demographics**

Yu et al evaluated the effect of age on the macular VD measurements in healthy Chinese subjects and found that the parafoveal VD decreased significantly with increasing age, and the decrease was greater in male subjects as compared with females. The majority of the studies that assess OCTA measurements in POAG and normal eyes have also shown older age to be associated with lower macular and peripapillary VD.

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**FIGURE 2.** Vessel density map of the retinal nerve fiber layer showing progressive decrease in vessel density from healthy eye to mild, moderate, and severe glaucomatous eye. Top row: Optic nerve head vessel density image. Second row: Area vessel density color-coded map. Bottom row: Visual field results showing corresponding visual field defects. Reproduced with permission from Elsevier Science.
measurements. However, Rao et al did not find any association between age and VD measurements in a healthy Indian population. The same authors reported that most of the peripapillary VDs were higher in female subjects, which was not revealed in other studies.

Although previous literature on the effect of race on the peripapillary perfusion is limited, in studies with a mixture of patients with African descent and European descent, the VD measurements were lower in glaucomatous eyes of European desents.

**Diurnal Change**

In a prospective study of 37 subjects with POAG, Mansouri et al found that diurnal changes in OCTA-measured VD in glaucoma patients were small and clinically insignificant. In their study, changes in VD were significantly associated with changes in signal strength but not IOP.

**Exercise and Systemic Disease**

Alnawaiseh et al examined 13 healthy people after exercise and found that increased physical activity induced significant changes in optic nerve and macular perfusion measured by OCTA; they recommended that patients rest before imaging is performed. The same authors noted that blood pressure might affect the VD measurements and that data related to systemic circulation should be included within the evaluation. Another report also showed that diabetic patients and patients with systemic hypertension had lower VDs in peripapillary regions.

**Medication**

No studies evaluated the effect of systemic medications on OCTA measurement. However, Takusagawa et al showed that topical β-blockers could affect VD. In their study, eyes with β-blocker use had 3.3% lower macular VD, after adjusting for macular GCC thickness.

**Eye-Related Factors**

**Myopia**

Wang et al evaluated the effect of myopia on the peripapillary and parafoveal OCTA measurements and found a significant reduction of VD and blood flow index in the peripapillary, but not the parafoveal, region of eyes with high degree of myopia compared with emmetropic eyes. Although high myopic eyes were shown to have lower VD values by OCTA, one explanation might be the effect of image magnification on quantitative characterization of the retinal vasculature.

Sampson et al recommended that ocular biometry should be performed with OCTA to correct image magnification error induced by axial length variation.

In a study by Shin et al in POAG eyes with high myopia, the regional relationship of VF and peripapillary VD was significantly greater than that with the corresponding RNFL thickness. Another study showed that in myopia without glaucoma, peripapillary VD is lower than that in normal eyes, and in myopic glaucoma, it is even more reduced. Similarly to RNFL thickness, parafoveal perfusion is altered in myopia with disc torsion. Therefore, in myopic glaucoma, we cannot expect considerably better diagnostic accuracy from OCTA than from structural OCT parameters.

**Disc Area**

In a cross-sectional study by Rao et al examining 181 normal eyes of 107 subjects, optic disc size was not found to affect the VD measurements.

**Signal Strength**

Although Jia et al in their early work with OCTA reported that the decorrelation values of OCTA were unaffected by signal strength, several studies that used Avanti OCTA for evaluating retina perfusion demonstrated that lower SSI was correlated with lower OCTA measurements. It is possible that the software does not differentiate between the static structures and blood vessels efficiently at low SSI scores, thus clinicians evaluating the OCTA scans quantitatively should consider the SSI value of the scan during interpretation. 

**Effect of IOP**

The potential relationship between IOP or IOP reduction and peripapillary perfusion has been an important question in glaucoma management for decades. Although structural parameters do not change after pressure-lowering treatment, Hölü found in a small number of patients that hypertensive patients, whose untreated IOP was high but decreased by at least 50% to 18 mm Hg or less after treatment, showed significant increase in the initially reduced peripapillary VD. Other investigators used other OCTA systems and IOP-lowering interventions and confirmed these results.

OCTA AND THE GLAUCOMA CONTINUUM

**Glaucoma Suspects and Early Glaucoma**

The majority of studies found a significant difference in OCTA parameters between glaucoma suspects and normal eyes in the peripapillary area. With the SSADA algorithm, the VD decreased significantly when measured in the whole-image peripapillary area. However, when measured in the circumpapillary area, the decrease was often not significant. A possible explanation for this difference is the larger measurement area of the whole image, which may be able to better detect early vessel dropout. With the OMAG algorithm, the blood flow index showed significant results, whereas VD often did not.

Chen et al postulated that the blood flow (blood flow index) decreased at an earlier stage in the glaucoma disease process than the number of measurable capillaries (VD). For macular OCTA parameters, the results of the investigations are less conclusive. While 2 studies found a significantly lower VD in glaucoma suspects in comparison with normal eyes, another one found a significantly greater VD in glaucoma suspects in comparison with control eyes.

So is OCTA helpful in early detection of glaucoma? One of our first OCTA studies showed that VD in a group of glaucoma patients with a single hemifield was reduced in perimetrically intact hemiretinae of these eyes (Fig. 3). The strength of association with VF sensitivity measures was stronger for VD measurements using SSADA compared with RNFL and GCC thicknesses. A similar finding was observed subsequently by Chen et al using OMAG algorithm for VD and flow measurements. Yarmohammadi et al measured the VD in the macular and the peripapillary area in eyes with unilateral glaucoma and
demonstrated that OCTA measurements detect changes in retinal microvasculature before VF damage in unaffected eyes. Hou et al.\textsuperscript{32} studied 68 preperimetric and 162 early glaucoma eyes and compared the percent loss from normal of GCC thickness and macular VD. Both GCC thinning and macular VD dropout were detectable in preperimetric and early POAG eyes. Percent loss of GCC thickness was greater than that of macular VD in early perimetric POAG. However, OCTA and OCT measurements showed similar efficiency to detect early glaucoma. It should be noted that about one-third of the early glaucoma eyes in this study showed greater percent loss of VD than GCC thickness. Given these results, it is clear that there are some eyes in which microvascular attenuation occurs before changes in RNFL thickness or function. Thus, OCTA can help detect early stages of glaucoma in some eyes.

**Advanced Glaucoma**

Detection of glaucomatous change in advanced glaucoma is challenging because of the increased variability of VFs and the existence of “floor effect” observed in RNFL thickness measurements obtained using optical imaging instruments.\textsuperscript{79} Few studies evaluated the role of VD parameters in advanced glaucoma. Rao et al.\textsuperscript{56} demonstrated that VD reached a base level beyond a visual sensitivity loss of −15 dB, whereas the RNFL reached that level at a visual sensitivity loss of −10 to −15 dB. The same authors, in another study, showed that in later stages of glaucoma, the diagnostic ability of VD was better than that of the RNFL.\textsuperscript{38} We have reported a stronger relationship between vasculature and function compared with thickness and function in eyes with advanced glaucoma. Further, OCTA parameters appeared to have less pronounced floor effect compared with

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**FIGURE 3.** A representative glaucoma eye with superior visual field (VF) defect. Macular ganglion cell complex (GCC) thickness map and optic nerve head thickness map shows GCC and retinal nerve fiber layer (RNFL) loss corresponding to the VF defect. Bottom: Vessel density map of the peripapillary RNFL (right) and macular superficial layer (left) illustrating reduced vasculature that spatially correlates with the location of structural loss and VF defect.\textsuperscript{66} Reproduced with permission from Elsevier Science.
thickness parameters and hence better biomarkers in monitoring eyes with advanced glaucoma.\textsuperscript{30}

**SUBTYPES OF GLAUCOMA**

Most of the studies on OCTA focused on POAG. The role of blood flow might differ in other types of glaucoma including pseudoexfoliative glaucoma (PXG) and primary angle-closure glaucoma (PACG).

**Pseudoexfoliative Glaucoma**

Although high baseline IOP and wide IOP fluctuation are associated with more rapid progression and a worse prognosis, PXG with controlled IOP has also been reported to progress more rapidly than POAG, suggesting the possible contribution of non-IOP factors in the progression of PXG.\textsuperscript{31} Optical coherence tomography angiography provides the first quantitative evidence of the microvascular disturbance that accompanies pseudoexfoliation syndrome. In a study by Suwan et al,\textsuperscript{32} VD was lower in PXG compared with POAG eyes and in eyes with pseudoexfoliation syndrome compared with control eyes. In another cross-sectional study, Park et al\textsuperscript{33} included 39 PXG eyes and 39 matched POAG eyes and reported that peripapillary VD was lower in eyes with PXG than in eyes with POAG of similar severity. No difference in RNFL thickness, choroidal thickness, or other optic disc parameters existed between the 2 groups and they proposed that decreased peripapillary VD and the resulting ischemia may render eyes with PXG more vulnerable to glaucomatous damage at the ONH.\textsuperscript{34} However, there are possible limitations in both of these studies. Nuclear cataract is an early feature of pseudoexfoliation syndrome which might affect quality score and lead to lower measured VD values. As POAG and PXG groups were not matched for image quality score and/or lens opacity in these studies, the results may be biased. Moreover, in a more recent study, vascular parameters measured by Angioplex were not statistically different between POAG and PXG eyes. Larger studies controlling for confounders are needed to address the question if the VD is lower in PXG eyes compared with POAG eyes.

**Angle-Closure Glaucoma**

The role of ocular blood flow in the pathophysiology of glaucoma is different between PACG and POAG as the optic nerve damage occurs directly after the increased IOP in PACG eyes. Investigators have found that glaucoma patients with high IOPs had more diffuse axon loss than those with low IOPs, and suggested that the diffuse loss of VF sensitivity from glaucoma is largely pressure dependent and may be secondary to diffuse axonal loss.\textsuperscript{35} A recent study has shown that POAG and PACG eyes have a different vascular-function relationship when determined by OCTA.\textsuperscript{36} Rao et al\textsuperscript{37} showed that microvascular dropout is also detectable in PACG. The AUC of VD in PACG was comparable to those of OCT parameters and to the AUC found in POAG eyes.\textsuperscript{25} The diagnostic ability of VD in PACG eyes was lower than that of OCT parameters in early glaucoma eyes, but better in advanced glaucoma cases; this suggests that the floor effect is less pronounced for OCTA parameters than for OCT parameters, as found in POAG.\textsuperscript{21,38} However, the sensitivity of the peripapillary VD to detect glaucoma appeared to be better in POAG compared with PACG, and it was proposed that the ocular perfusion abnormality in PACG had lower prevalence compared with POAG.\textsuperscript{25}

Acute primary-angle closure, in particular, is an entity in which optic nerve damage occurs after a sudden increase in IOP. Wang et al\textsuperscript{39} detected a significant reduction in ONH VD in eyes with acute primary-angle closure 2 to 120 days after the attack using OCTA, even when the structural measurements were not significantly changed. In their study, a close correlation was found between peripapillary VD and visual functions, but not between RNFL and visual function. The preserved OCT parameters could be caused by retinal edema after the acute attack. In another study of PACG eyes with a history of acute attack, ONH VD decreased significantly compared with the contralateral unaffected eyes.\textsuperscript{47}

**OCTA OF THE PERIPAPILLARY CHOROID**

Peripapillary choroidal circulation is of particular interest in glaucoma as it may be a surrogate marker for the perfusion of the deep ONH structures. Recently, choroidal microvasculature dropout (CMvD), defined as the complete loss of choriocapillaritis in localized regions of parapapillary atrophy, has been observed in POAG eyes using OCTA.\textsuperscript{48} Such dropout has been shown to be a true perfusion defect using ICGA.\textsuperscript{49} Studies have also reported a topographic association between the location of CMvD and structural defects (RNFL thinning and lamina cribrosa defects) as well as VF loss in POAG eyes.\textsuperscript{50,51} In fact, CMvD is a relatively novel finding in glaucoma and its clinical implications are not fully known. It has been proposed that CMvD is likely to precede glucomatous ONH damage.\textsuperscript{50} A recent study reported an association between CMvD and progressive RNFL thinning in POAG eyes with DH.\textsuperscript{52} Longitudinal studies are required to determine the clinical implication of CMvD in glaucoma.

**GLAUCOMA PROGRESSION**

It is important to note that VD 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.\textsuperscript{46,61,67,68,75} As OCTA is a recently developed technique, the literature is limited regarding its ability to detect progression.

In a relatively small number of subjects (9 normal, 20 ocular hypertensive, and 24 glaucoma) with 2-year follow-up, Holló\textsuperscript{62} found a statistically significant negative slope for RNFL thickness in one-third of cases whereas no eye had a significant negative peripapillary VD slope. In his another report, however, Holló\textsuperscript{53} used a software that removed the large retinal vessels–related information and found that capillary VD progression with large vessel removal occurred in 17% of the glaucoma eyes. Half of those progressing cases also showed significant and spatially corresponding RNFL thickness progression. In a longitudinal study with 13 months’ follow-up by Shoji et al,\textsuperscript{54} eyes with POAG had significantly faster loss of macular VD than either glaucoma suspect or healthy eyes. Serial OCTA measurements also detected glucomatous change in macular VD in eyes without evidence of change in GCC thickness (Fig. 4).

In summary, even with a relatively brief follow-up period, OCTA is able to detect a longitudinal reduction of OCTA parameters in glaucoma eyes.\textsuperscript{55} However, additional studies with longer follow-up are needed to explore whether these results can
be replicated across the glaucoma continuum, in areas other than the macula and with other algorithms.

**RISK ASSESSMENT**

Assessing high-risk patients for glaucoma development or progression is critical in the management of glaucoma. Age, IOP, optic DH, and reduced central corneal thickness are established risk factors. In a longitudinal study, Moghimi et al.\(^6\) showed that lower baseline macular and peripapillary VDs were associated with a faster rate of RNFL progression in mild-to-moderate glaucoma over a mean follow-up of 27 months. Importantly, they showed that 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.

Microvascular dropout has also been demonstrated by Park et al.\(^5\) as a biomarker for VF deterioration, especially in eyes with DH. They followed 82 open-angle glaucoma eyes with DH and 68 eyes without DH over 5 years and demonstrated that patients with progressive glaucoma exhibited significantly more microvascular dropout than the stable patients in both DH and no-DH groups. These studies suggest that assessment of peripapillary and macular VD may add significant information to the evaluation of the risk of glaucoma progression and prediction of rates of disease worsening. One reason for these findings might be that reduced optic disc and retina perfusion leads to faster RGC death. Another reason might be that reduced perfusion on OCTA was a biomarker for sick, but not dead, dysfunctional RGCs with lower metabolic demands.

**LIMITATION OF OCTA**

Previously, many captured OCTA images have artifacts which might be due to longer scan time compared with OCT scans. Poor-quality OCTA scans are more common than poor-quality OCT scans and a considerable proportion of OCTA images are suboptimal in quality for interpretation. In studies that evaluated VD in healthy or glaucomatous eye, 17% to 29% of the images were excluded because of suboptimal SSADA-derived.
OCTA image quality.\textsuperscript{38,65} In a study in which both OCTA and OCT measurements were performed by the same commercially available instrument, 29% and 3% of the macular OCTA and OCT scans were considered to have poor quality, respectively.\textsuperscript{38} Similarly, 2% of RNFL scans were graded as poor quality by Moghimi et al.,\textsuperscript{55} which was much lower than OCTA images using the SSADA algorithm (20%).

Additionally, studies that used the lower-resolution scans with smaller field may not be valid for the newer high-resolution ones, which are usually superior.

**CONCLUSION**

Optical coherence tomography angiography is a novel, noninvasive imaging technology that provides an insight into the role of microvascular changes during the glaucomatous process. It gives us additional information to OCT for detecting and monitoring glaucoma patients and offers a clear benefit in early glaucoma and advanced glaucoma cases. Higher-resolution images with wider fields appear to have less artifact particularly with a software that removes large vessels from vascular processing unit. OCT gives us additional information to OCT for detecting dysfunctional RGCs for future neuroprotective therapies.

**REFERENCES**


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