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Optical Coherence Tomography Angiography in Glaucoma: a review on structural-functional relationship

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Abstract

Optical coherence tomography angiography (OCTA) is a non-invasive imaging tool for visualizing the ophthalmic microvasculature. Vessel density (VD) is mainly used as a metric for quantifying the ophthalmic microvasculature. The anatomic area of interest for OCTA in glaucoma are the optic nerve head area including the peripapillary region, and the macular region. Specifically, VD of the superficial peripapillary and superficial macular microvasculature is reduced in glaucoma patients compared to normal subjects. Recently VD has been correlated with functional deficits as measured by visual field (VF). The clinical applicability of OCTA in glaucoma management is limited due to the prevalence of imaging artifacts, and the knowledge of primary or secondary impairment of blood flow and VD in glaucoma. Overall, OCTA can play a complementary role in structural OCT imaging and VF testing to aid in the monitoring of glaucoma.

Keywords: Optical Coherence Tomography Angiography; OCTA; Glaucoma;

Introduction

Glaucoma is the leading cause of irreversible blindness worldwide [1]. The pathogenesis of glaucoma is still not fully understood but elevated intra-ocular pressure (IOP) and impairment of ocular blood flow are known to be two major contributing factors. Since glaucomatous damage is preventable but irreversible, an early diagnosis and close follow-up of glaucoma patients are needed [2]. Optical coherence tomography angiography (OCTA) is a recently developed, reproducible, noninvasive, contrast-free imaging modality that detects blood flow through the motion contrast generated by red blood cells. It is able to provide a quantitative evaluation of the microcirculation of the retina and choroid in different layers. Since glaucoma development and progression are both linked to alterations of retinal vessel density (as either a primary or a secondary effect), this innovative technique could deepen the knowledge about pathophysiology of glaucoma, also bringing new information to improve glaucoma diagnosis and management [3,4]

OCTA has provided insights into the relationship between neuronal and vascular changes in glaucomatous eyes. At the beginning, several papers investigated the peripapillary vessel density in patients with diagnosis of glaucoma, and results of these studies largely demonstrated capillary dropouts in areas corresponding to pRNFL defects. [5,6,7]. However, the diagnostic ability of peripapillary VD has not shown to perform better than pRNFL thickness [8].

OCTA for the study of vasculature in glaucomatous eyes has been largely applied on the radial peripapillary capillaries around the optic nerve head. [9,10,11]. Some authors previously reported a relatively strong relationship between optic nerve head whole image VD and the mean sensitivity of the 24-2 VF [10]. It should be remembered that the peripapillary region is supplied by the superficial vascular plexus (ganglion cell layer and inner plexiform layer) and the radial peripapillary capillary plexus (nourishment of the nerve fiber layer). [12,13]

Other studies focused their attention on the macular region, that has the highest density of retinal ganglion cells (RGCs) and macula damage has been demonstrated in early glaucoma [14]. Studies on microcirculation changes in the macula region in glaucoma have analyzed different regions of interest: whole-image macula scans including parafoveal and perifovea; parafoveal scans that include the inner circle centered on the fovea; perifovea scans that include the annular area from the edge of the parafovea to a larger diameter circle. Macular vessel density in current glaucoma studies involves the inner retina that includes the SCP and the DCP [15].

According to recent data, the macular vessel density was found to be reduced in glaucoma eyes; however, the exact role of macula vessel density measurements in glaucoma diagnosis and progression remains unclear [15].

OCTA pros and cons in brief

Optical coherence tomography angiography (OCTA) is one of the biggest recent advance in ophthalmic imaging.

OCT generates images interferometrically and measures the amplitude and delay of reflected or backscattered light. Since the retina is a stationary object for the most part, if successive B-scans at the same position are acquired, they will be largely similar, except for the motion of blood within the tissue. At the sites of blood flow, the reflectivity changes from one scan to the next. This techniques works by comparing repeated OCT B-scans, through which it is possible to image blood flow by looking for differences among the scans on a pixel-by-pixel basis [16].

Differently from Fluorescein Angiography (FA) and Indocyanine Green Angiography (ICGA), OCTA allows a three-dimensional visualization of the retina and choroidal vessels [17,18,19]. Moreover, this technique is completely non-invasive and does not require dye injection, since red blood cells movement is used as "natural" contrast.

Differently from structural tomography, OCTA analyzes both the intensity of the reflected light and the temporal changes of the OCT signal, through OCT section images (B-Scans) repeated at the same location of the retina. In this way temporal signal changes caused by moving particles (erythrocytes inside vessels) can be detected.

Moreover, with dense volume scans, it is possible to obtain images similar to fluorescein angiography, that still remains the gold standard technique in the study of retinal pathologies.

Another advantage of OCTA of FA is the visualization of structure and blood flow within the vitreous, the retina, and the choroid, separately, while FA provides only two-dimensional images of the fundus. Furthermore, OCTA allows to examine the distinct capillary networks of the retina (with vessel diameters as small as approx. 8 μm) [20]. On the other hand with Fluorescein Angiography and Indocyanine Green Angiography, dynamic phenomena such as dye leakage, pooling, and staining can additionally be observed. This is not possible with OCTA because no motion of blood cells is involved. However, while these characteristics could obscure the structures below in FA and ICGA, OCTA could allow to better define images of the microvasculature under the areas of leakage or hemorrhage [16, 21].

OCTA parameters in Glaucoma

Macular scans are centered on the fovea. The macular "whole image" is defined as the whole surface of the scan, generally 3x3, 4.5x4.5 or 6x6 mm).
The fovea is defined as the central 1-mm circle on the macular scan and parafoveal area is defined as a 1.5- or 2.0-mm-wide circular annulus around the fovea. [4]

Optic disc scans are centered on the optic disc. To define the optic disc area, it is used the neural canal opening, which is the termination of the retinal pigment epithelium/ Bruch membrane complex.
"Peripapillary area" is used to describe both the circumpapillary and the whole image peripapillary area: circumpapillary area is defined as a 0.5-, 0.6-, or 0.75-mm-wide annulus around the optic disc, while the whole image peripapillary area is defined as the whole area of the optic disc scan.
Scans assessing the optic disc, the peripapillary area, and the whole image peripapillary area are generally 4.5x4.5 mm wide.
Vessel density, measured with OCTA, is defined as the ratio of the area occupied by vessels divided by the total measured area.
Parapapillary deep-layer microvascular dropout (MvD), measured with OCTA, is defined as a focal sectoral capillary dropout without any visible microvascular network identified in the deep-layer en face images of the peripapillary area. [4]

Structure-function relationship in glaucoma

In the current clinical practice, two groups of complementary examinations are used for the diagnosis and follow-up of glaucoma patients: structural (mainly represented by OCT) and functional (visual field) optic nerve measurements, both characterized by strengths and limitations [22, 23, 24]. OCT provides objective information on retinal layers' thickness and it is highly repeatable and reproducible [25]. However, there is a floor effect for OCT in advanced glaucoma, when the OCT parameters reach a base level beyond which changes in severity of glaucoma cannot be seen [26]. For these reasons, OCT is not the best method to detect changes in advanced glaucoma.

Regarding functional evaluation, visual field testing is clinically more relevant since it measures visual function and it's still considered the preferred exam in advanced glaucoma due to the absence of the floor effect that exists in OCT [4]. However, it requires greater patient's compliance, resulting less repeatable and reproducible.

Finally, one of most important visual field limitations is the capability to detect damage after it is already recognizable in the structural exams (pre-perimetric glaucoma). It is estimated that automated

visual field test abnormalities can be detected when at least a 25–35% retinal ganglion cells is lost [27].

In recent years, an emerging role in diagnosis and follow-up of glaucoma patients has been attributed to OCT Angiography, that could integrate or overcome the previously mentioned structural and functional examination.

Even if pathogenesis of POAG is still unknown, it has been suggested that retinal blood flow may have a role in the development and progression of the disease [28-30].

Many authors found out the presence of optic nerve blood flow impairment and microcirculatory deficiency in glaucoma patients [28,31,32] but the details of this relationship have not been established precisely [33-35] This is mainly due to the previous available instrumentation and to difficulty in accurately measuring ocular blood flow [36,37]. Numerous imaging modalities have been used to assess the retinal microvasculature and perfusion, including color Doppler echography of retrobulbar circulation, fluorescein angiography and laser speckle flowgraphy.

Laser speckle flowgraphy (LSFG) is a technique that evaluates ocular perfusion through two-dimensional measurements of perfusion at the ONH, the retina and the choroid using the laser speckle phenomenon [38,39]. According to literature, LSFG could be useful in early detection of glaucoma but has several limitation in assessing the severity of the disease in advanced stages [40]

Color Doppler imaging (CDI) has been used to study blood velocity in the ophthalmic artery, the central retinal artery, and the short posterior ciliary arteries; showing statistically significant reductions in the flow velocities and increases in the resistance indices of these vessels in both primary open-angle glaucoma and normal tension glaucoma in comparison with normal control subjects.
[41] CDI technique has several limitations such as technical difficulties and low reproducibility among different operators, for these reasons results are highly variable. [42] On the other hand, fluorescein angiography provides limited visualization of the retinal radial peripapillary capillary vessels and macula capillary networks, requiring exposure to a contrast agent with possibility of adverse reactions. Recently, optical coherence tomography angiography (OCTA) has been used taking advantage of its reprodicibility and noninvasiveness, allowing to visualize vascular circulation without dye injection. Moreover, for glaucoma specialist, OCTA has major advantages that could afford direct and layer-specific imaging of the circulation of blood in the macula and peripapillary region [43].

Several studies used OCTA to evaluate the relationships between decreased vessel density, incidence of glaucoma, and severity of visual field defects [10,44,45]. The aim of these studies was to understand if low vessel density is related to glaucomatous damage or is only an epiphenomenon of retinal thinning.

In literature, some authors evaluated vessel density focusing on the papillary and peripapillary region, while others focused their attention on the macular region.

Papillary and peripapillary region

Yarmohammadi et al. (2016) [10] evaluated the association between vessel density measurements using OCTA (Angiovue, Optovue) and severity of visual field loss in primary open-angle glaucoma. The present study demonstrated a significant relationship between vessel density and severity of visual field damage, both qualitatively, with sparser peripapillary vascular networks on OCTA in severe glaucoma and quantitatively, with lower vessel density parameters associated with more advanced stages of glaucomatous visual field damage. The principal finding of the study was a relatively strong association between vessel density (both whole image and circumpapillary) and visual field loss expressed as MD (R^2=0.54 and 0.51, respectively, P<0.001 for both). This result suggests that reduced OCTA vessel density is associated with more severe glaucoma, in accordance to previous reports that evaluated OCTA vessel density [5, 46, 47]. According to these results, the vascular-functional correlations are stronger compared to the standard structural-function relationships considering RNFL and rim area. Decreased OCTA vascular parameters in glaucoma patients are fundamental evidences that confirm results of previous studies suggesting hemodynamic impairments in optic nerve head, retina, choroid, and retrobulbar circulations in glaucoma eyes.[48,49,50,51,52]

According to Yarmohammadi and colleagues, the independent association of vessel density and visual field MD has several potential explanations: first of all, the existence of dysfunctional (pre-apoptotic) retinal ganglion cells could be responsible for reduced blood flow, decreased vessel density and impaired visual field sensitivity. The reason why a reduction in RNFL thickness and rim area may not yet be detectable is the presence of dysfunctional retinal ganglion cells that have not yet atrophied. Moreover, the functional status of retinal ganglion cells is not totally reflected by RNFL thickness, as shown by previous studies that demonstrated only moderate agreement between RNFL thinning and retinal ganglion cell loss, [53,54]. According to previously explained evidences, there is a stronger correlation between vessel density and visual field damage, this that might suggest that vessel density better reflects retinal ganglion cell functioning than structural alteration.

Another study performed by the same authors (Yarmohammadi et al, 2018) [57] was aimed to characterize OCTA vessel density of primary open angle glaucoma patients with unilateral visual field loss. The authors showed that peripapillary vessel densities were significantly lower in both eyes of POAG patients with unilateral VF loss compared to healthy eyes of similar age ($P<0.05$). Moreover, peripapillary vessel density in the affected eyes was lower than in their fellow unaffected eyes. Evidences of a lower peripapillary vessel density in the affected eyes provide further data to confirm the association between vascular loss in the peripapillary area and functional glaucoma.

However, the differences in cpVD measurements among unaffected and healthy eyes were not significant, differently from previous studies investigating structural-functional relationship in unaffected eyes of glaucoma patients. In contrast to this study, the same authors, in a previous study, [45] showed that cpVD values in the perimetrically intact hemiretinae of glaucoma patients with single-hemifield VF defect was lower than age-matched healthy hemiretinae. These results denoted that the vascular attenuation in the peripapillary region is diffused in glaucoma eyes, and vascular dropout can be seen in both the peripheral and more central regions around the optic disc. In contrast, in glaucoma suspects and perimetrically unaffected eyes, capillary alterations could only be detected in the more peripheral regions of the peripapillary area.

Macula region

Penteado et al (2018) [13] evaluated the association between macula vascular density assessed by OCTA (Avanti Angiovue system, Optovue, Inc. Fremont CA) and central visual field (HFA) threshold sensitivities in healthy, glaucoma suspects and glaucoma patients. Authors found out that superficial macula whole-image and parafoveal vessel densities (OCTA) and GCC thickness (SD-OCT) were lower in patients with moderate to severe glaucoma when compared to healthy subjects, glaucoma suspects or patients with mild glaucoma. Moreover, macula vessel density parameters were significantly associated with 10-2 visual field alterations. In this study the authors evaluated macular vascular information from the superficial capillary plexus that supply the ganglion cell layer, the nerve fiber layer and other inner layers.[56]

The results of this study are confirmed by previous findings by Xu and colleagues that found a positive correlation between wiVD of the superficial and deep retinal layers combined and 10-2 VF. [57]

According to findings of these studies the decline in the microvascular vessel density and possibly the microvascular dropout may precede the loss of retinal nerve fibers in glaucoma, providing an

important role of OCTA in diagnosis of pre-perimetric disease and early glaucoma cases. Conversely, macula wiVD does not seem to perform better than GCC thickness in later phases of the disease.

The previously mentioned study (Yarmohammadi et al, 2018) [55] evaluated not only the peripapillary vessel density but also the macular region. The authors showed that macular vessel densities were significantly lower in both eyes of POAG patients with unilateral VF loss than healthy eyes of similar age ($P<0.05$). They also assessed that the difference in macular vessel density was similar in both eyes of the same patient ($P>0.05$). The authors observed that lower vessel density measurements could be detected even in eyes without detectable VF damage, and wiVD was the parameter with the best diagnostic accuracy in differentiating between perimetrically unaffected eyes of POAG patients from healthy eyes. Therefore, detectable functional loss in unaffected eyes of POAG patients with unilateral VF loss can be anticipated by hemodynamic insufficiencies together with structural damage. The authors concluded that wiVD and pfVD in the unaffected eyes were significantly lower than healthy eyes. According to this study, Rao et al [58] demonstrated that pfVD is less accurate in differentiating between unaffected eyes of glaucoma patients from healthy eyes. According to their results, macula VD has higher diagnostic performance compared to measurements in the peripapillary, even in differentiating glaucoma eyes from healthy eyes. This could be explained by the fact that RGCs in the macular region are concentrated in 4.5 mm foveal center that can remain unaffected in the early stages of the disease [59].

Another recent study by Shin et al (2019) [60] evaluated the relationship between macular vessel density and central visual field sensitivity at different stages of glaucoma and compared this relationship with that between thickness of macular ganglion cell-inner plexiform layer. Global and regional associations between macular vessel density and central VF sensitivity were statistically significant in eyes with moderate-to- advanced glaucoma (all $p<0.05$), but not in early stages (all $p>0.05$). The macular vasculature–function relationship (evaluated through mVD) was stronger than the structure– function relationship in moderate-to-advanced glaucoma eyes. For this reason, the mVD appears to be useful in monitoring central VF sensitivity in advanced glaucoma. The authors explained this finding as follows: although more macular ganglion cell-inner plexiform layer tissue remains (compared with peripapillary RNFL thickness) in advanced glaucoma, mGCIPLT still exhibits a floor effect, below which no more thinning occurs.[60] In contrast to that, vascular parameters may be less subjected to floor effect with more advanced disease, suggesting that macular VD may be a better indicator in advanced glaucoma. According to another possible explanation, vascular dropout in the retina may occur as a secondary change after retinal

ganglion cell damage at early stage glaucoma. However, even after the RGCs and their axons have been severely damaged in eyes with advanced glaucoma, the vasculature may be sustained until functional shutdown, which may explain aforementioned findings.

Jeon et al (2019) [61] in a retrospective case-control study assessed superficial and deep VD of macula by OCTA. The authors used regression analysis and Cox proportional hazards model to identify factors significantly associated with VF progression and they found out that initial IOP and deep VD were related to VF progressive damage in glaucoma. For this reason, deep VD might be used as a surrogate of glaucomatous VF progression related with vascular incompetence. In this study, the superficial VD was not associated with VF progression, in contrast with a previous study of Moghimi *et al*. [62-64]. Jeon et al had concerns about the effects of topical IOP-lowering medication on retinal VD. Topical prostaglandin did not affect VDs significantly, but patients with topical beta blocker (BB) showed lower superficial VD. The difference might be caused by the different initial IOP and MD for topical BB, since PG are often prescribed as a first choice treatment and BBs are added to strengthen the treatment. For these reasons patients with worse glaucoma state or higher IOP might have reduced GCL thickness and this difference could affect superficial VD but not the deep VD located in the INL (not affected by GCL thinning).

OCTA and ocular hypertension

Some authors evaluated OCTA parameters in patients affected by ocular hypertension, without diagnosis of glaucoma. They found out that vessel density and flow index were lower in treated OHT eyes [65, 66], and these changes in vessel density were independent from RNFL thickness and existed in patients with OHT with similar values of IOP when compared to controls [65]. Hollo [67] investigated the relationship between IOP changes and OCTA parameters; according to results of this study vessel density increased significantly in both glaucoma and OHT eyes with large IOP reduction. These results confirmed the existence of reduced OCTA parameters in eyes with OHT and supported the theory of vessel compression caused by a high IOP.

Hollo investigated also the relationship between vessel density and visual field MD in normal, treated OHT, and treated glaucoma eyes. Even if OCTA parameters were similar among healthy and OHT eyes, in glaucoma and OHT eyes there was a strong negative relationship between OCTA parameters and visual function [68].

These results highlighted that the presence of very early glaucomatous alterations in vascular parameters measured with OCTA could suggest dysregulation of the blood flow in these eyes [65]. Since the OHT group used topical eye drops, the lowering-IOP therapy has been considered a possible explanation for reduced OCTA. However, the control and OHT groups did not show different IOP

values after treatment, for this reason compression of retinal vessel caused by a high IOP could no longer explain impaired vascular flow in eyes with OHT after treatment. [4]

Conclusion

In conclusion, OCTA seems to be a useful technique in the early diagnosis and follow-up of glaucoma patients. Indeed, it is highly repeatable and reproducible, showing significantly lower vascular parameters in glaucomatous eyes.

Moreover, it was demonstrated a stronger correlation between the spatial distribution of visual field defects and changes in the OCTA parameters, rather than those of the structural OCT. Another advantage of OCTA is the decrease of the so-called floor effect, that hinder the diagnostic reliability of structural OCT analysis in severe glaucomatous patients. Further studies are needed to shed light on the blood flow changes in patients affected by ocular hypertension.

Declarations

Conflict of Interest

The Author declares that there is no conflict of interest.

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