



# Advances and Current Clinical Applications of Anterior Segment Optical Coherence Tomography Angiography

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Optical coherence tomography angiography (OCTA) is the most relevant evolution based on optical coherence tomography (OCT). OCTA can present ocular vasculature, show detailed morphology for assessment, and quantify vessel parameters without intravenous dye agent. Research on the anterior segment OCTA (AS-OCTA) is only in its initial phase, and its advances in clinical diagnosis and treatment efficacy evaluations require a detailed comparison to traditional imaging methods. In this review of AS-OCTA, we summarize its technical features, imaging advances, current clinical applications in various eye diseases, as well as its limitations and potential future directions. AS-OCTA offers potential advantages in ophthalmic imaging, and with further development it could become a common tool in the near future.

**Keywords:** optical coherence tomography angiography, anterior segment, vascularization, clinical application, clinical diagnosis, efficacy evaluation

## INTRODUCTION

Optical coherence tomography (OCT) provides a non-invasive and rapid way to image the eye *in vivo*. In the early 1990s, OCT was introduced to display retinal structures in cross-sections, such as the macula and optic nerve. Simultaneously, quantitative parameters of retina can also be detected, such as the peripapillary nerve fiber layer thickness, which is specifically identified in the development of open angle glaucoma (1, 2). With continuous development over the last 10 years, a new form of angiography, known as OCT angiography (OCTA), has been created (3). As the most relevant evolution of OCT, OCTA evaluates tissue from morphology to the study of functional components without intravenous injection of dye (4, 5). OCTA was designed for the posterior ocular segment, and has been widely used in age-related macular degeneration, high myopia, retinal vascular diseases, inflammatory diseases, and optic nerve diseases (2, 6, 7). OCTA allows better discrimination of the foveal avascular zone and parafoveal microvasculature than fluorescence angiography (FA), and can detect changes in lesions and early recurrence, even before the exudation detected on OCT (8–12). OCTA has improved identification of capillary non-perfusion, microaneurysms, and retinal ischemia, as well as delineating the foveal avascular zone (11, 13–22).

Most recently, a growing number of studies have been focusing on OCTA for anterior segment diseases. Anterior segment OCTA (AS-OCTA) provides a novel technique for acquiring anterior segment vasculature images (23). Although research on AS-OCTA is only in its initial phase, it has been gaining attention and recognition (7, 24, 25). Therefore, the application of AS-OCTA in clinical diagnosis and treatment needs to be summarized.

AS-OCTA offers several advantages over traditional angiography. Its non-invasive nature and rapid inspection time allow frequent repetition of tests, and avoids the potential risks of dye-based angiography (5). In addition, AS-OCTA provides cross-sectional high-resolution images of the vasculature and allows for analysis according to depth located on a specific axis (7, 26). It is also a more cost-effective method over conventional angiography that is more time-consuming and requires training-certified clinicians (24, 27).

Slit-lamp photography is the most common method for capturing anterior segment vasculature. However, the results of slit-lamp photography are easily influenced by corneal transparency and background iris vessels (24, 28). Dye-based techniques, including FA and indocyanine green angiography, are applied to assess vessels clinically (2, 24). However, dye administration is not suitable for some patients, and has various contraindications (2, 27–29). AS-OCT has advanced as a useful tool in providing rapid, non-contact evaluation of the anterior segment, and it takes a vital role in diagnosing and monitoring the effect of therapy in anterior segment diseases (30–32). However, AS-OCTA has developed the imaging technologies for increasing the speed and image resolution. Moreover, it offers the technology of evaluation of vascular flow (33). Furthermore, with the development of anti-angiogenic therapy, non-invasive techniques are needed for quantitative analysis in anterior segment vasculature (25). Because the OCTA systems are designed for posterior diseases, imaging the anterior segment requires putting on an adaptor lens (24, 29, 34). The quantitative index, including vessel density and blood flow, can monitor the effect of anti-vascular endothelial growth factor (VEGF) treatment, and guide treatment planning and prognostic evaluation (24, 25). Thus, an increasing role for AS-OCTA brings more attention and importance (35).

The aim of this review is to summarize the current applications of the AS-OCTA, including the diagnosis, therapy, and prognosis of detailed anterior diseases. In addition, the study discusses the limitations and potential future directions of AS-OCTA.

## ACQUISITION AND ANALYSIS OF AS-OCTA

Different types of devices have been reported in AS-OCTA scanning (e.g., AngioVue, DRI Triton, and PLEX Elite 9000). The majority of the studies use adaptor lens, and manually adjust the equipment parameters F and Z for anterior segment imaging (F was adjusted to the minimum value and Z was close to the maximum) (36–41). During the whole scanning process, the external lens has been put near the eye, so we need to pay special attention during the inspection process to avoid damage (42). Some studies haven't used adaptor lens, applied the retina scanning procedure and manually adjusted the F value to the maximum value (39, 43). According to the anatomical structure of the eye, the diopter of posterior segment differs by 20D (diopters) from that of anterior segment (42). A self-designed lens holder was made by 3 Dimensions printing technology, which could place a 35D biconvex lens provided by Heidelberg

at a suitable distance about 2 mm in front of the retinal lens to obtain an image (42). For the best image quality, the scanning area should be placed within the B scan range as far as possible. To avoid artifacts from the cornea and iris vessels, the scanning position can be placed flipping the zero-delay line and the image can be obtained “upside down” (39, 44). It is worth noting that the traditional image quality scoring standard and automatic image slicing function are not recommended in the current methods of obtaining AS-OCTA images (42).

## AS-OCTA PRECISE DIAGNOSIS

### Conjunctiva

A chemical burn can lead to rapid and permanent denaturation to ocular surface (44). AS-OCTA was able to identify the normal vasculature in unaffected areas and areas of ischemia, similar in appearance to FA (45). Additionally, it can detect vascular flow through conjunctival edema and hemorrhages (46). In pterygium, AS-OCTA can detect more abundant vascularization in pterygium than in normal conjunctiva. In addition, these vessels are most obvious in the subepithelial connective tissue. The morphology of these vessels is newly formed, with smaller caliber, tortuous and branched shape, and rarely visible lumen (39). In the remaining connective tissue, the blood vessels have a regular diameter and morphology, very similar to normal conjunctiva; their cavities are visible, sometimes dilated, and filled with blood (47). A study of scleral contact lens (ScCL) wearers demonstrates that repeated use of ScCL can cause vascular alterations in conjunctiva detected by AS-OCTA (48). Recent research shows that AS-OCTA works best on superficial and non-pigmented conjunctiva lesions, and malignant lesions always accompanied by deeper and larger perilesional vessels, which could be a significant marker of clinical diagnosis (49, 50).

### Cornea and Limbus

Combining structure and vascular information, OCTA can distinctly diagnose corneal pathologies (24–26). In addition, research suggests that AS-OCTA can show early corneal angiogenesis more clearly than slit-lamp photography (6, 24). OCTA can detect subtle abnormal blood vessels with corneal opacity, vascularization around the cornea or in front of the iris, which may not be detected by slit-lamp photography (6, 24). Both FA and indocyanine green angiography technologies only provide two-dimensional images, and dye leakage may hinder the analysis of deep blood vessels. OCTA allows simultaneous evaluation of the lesion structure and its related vessels in three-dimensions and at any predetermined depth (24). Severe corneal neovascularization (CoNV) always presents thicker, deeper, larger vessels on AS-OCTA (51). It has been noted that the extension and thickness of CoNV is related to the severity of limbal stem cell deficiency (LSCD) and best corrected visual acuity (BCVA) (52). In addition, Varma et al. (53) observed the conjunctivalization of the cornea caused by LSCD. The vascularization concentrated in superficial layer of peripheral cornea is the sign of LSCD, which can be differentiated from deeper vascularization caused by corneal inflammation.

## Ciliary Body and Iris

OCTA provides a non-invasive method for detecting small capillaries or microaneurysm flow, even at an early stage of neovascularization of the iris without leakage of dye, and only need little adjustments to the OCTA device (54, 55). Current assessments for neovascularization of the iris include slit lamp biomicroscopy, gonioscopy, FA, and indocyanine green angiography (56–58). Furthermore, conventional examinations may miss the very fine neovascularization of the iris (59, 60). Moreover, the assessment of neovascularization of the iris always needs a non-dilated pupil using dye-based angiography; thus, it is not possible to perform FA and indocyanine green angiography of the iris and retina at the same time, since most cases are caused by ischemic retinopathy (58).

The inflammation in the anterior uveitis always appears primarily on the iris and the ciliary body (3). During the active stage, the vessel in the iris dilates visibly. However, assessment of that presence is limited to previous examination, like fluorescein angiography (59). The reason is that the capillaries are non-fenestrated in the iris, and the leakage caused by inflammation cannot be shown by fluorescein angiography (59, 61). Since it is dye-free technology, AS-OCTA may provide more than a just promising method for assessing vascular anomalies in active anterior segment inflammation and para-inflammatory conditions. It might also be a safe and more precise method for investigating the pathophysiology of inflammation and the preclinical therapeutic strategies for uveitis (39, 55). Iris cysts appears with no intrinsic vascularity detected by AS-OCTA, and this could become a key imaging feature to distinguish iris cysts from other iris lesions (62).

## AS-OCTA FOR EFFICACY FOLLOW-UP

### Conjunctiva

The evaluation of limbal epithelial stem cells is related to the severity of the conjunctival chemical burn, therefore a reliable and objective assessment of limbal non-perfusion could make prognosis more accurate (63–65). The range of severe limbal ischemia determined by AS-OCTA represented the severity of LSCD (46). The correlation between AS-OCTA prognosis and visual outcome at 3 months supersedes that of FA. AS-OCTA could also be used for longitudinal clinical estimation of recovery and reperfusion (46). En face OCTA can potentially assess the deeper intrascleral vessels, and index the more severe damage that can leads to iris atrophy, cataract, secondary ocular hypertension, or hypotony (46).

Trabeculectomy remains the common surgical procedure for glaucoma when other treatments have failed to control intraocular pressure (66). Fibrosis in the filtering bleb area plays a crucial role in failure of trabeculectomy (67). Hence, an early and objective means of detecting bleb vascularity to minimize fibrosis and lead to better outcomes is important. The Indiana Bleb Appearance Grading Scale and Moorfields Bleb Grading System are clinically used, but these grading systems are quite subjective (68–70). The development in surgical area vascularity and tortuous vessels on bleb are signs of bleb failure (68, 70, 71). AS-OCTA could be applied to address the early

evaluation of bleb, which plays a crucial role in discovering the failure of trabeculectomy (37, 38, 72–74). Bleb vascularity can be examined sensitively; a previous study showed a correlation between the outcome of AS-OCTA and the outcome of previous grading systems (75). AS-OCTA could potentially be used in evaluating vessel parameters pre- and post-trabeculectomy (75). In a recent study, vascularization of the filtering bleb assessed by AS-OCTA at 1-month post-trabeculectomy could predict surgery effects at 6 months post-treatment and provided timely post-surgery intervention for a more successful outcome from the trabeculectomy (37). A study focused on eyedrops finds that the lowering effect of IOP is associated with a lower baseline vessel density detected by AS-OCTA (76).

### Cornea and Limbus

AS-OCTA provides rapid processing and objective assessment of areas for corneal vessel invasion (77). OCTA is also useful for monitoring vascular changes before and after treatment. Furthermore, AS-OCTA allows estimations of the range and the depth of vascularization and fibrosis, such as the penetration of corneal abnormal vessels. This helps in pre-surgery planning, and monitoring of corneal vascularization after surgeries such as keratoplasty, pterygium surgery, and fine-needle diathermy (FND) combined with subconjunctival Ranibizumab (24–26, 78). In patients who received various treatments after graft rejection, AS-OCTA was able to find a significant decrease in the vascularized area after 3 months of treatment, which is consistent with color photographs (79).

### Ciliary Body and Iris

AS-OCTA is not only useful for screening, but also for following-up and assessment of treatments, such as laser or anti-VEGF therapy for neovascularization of the iris. Roberts et al. (55) showed that AS-OCTA provided a new stage for detecting neovascularization of the iris, which is regressed and clinically invisible. Additionally, en face OCTA can non-invasively show the persistent vessels by imaging blood flow after treatment. In the future, longitudinal follow-up will be indispensable for identifying OCTA markers for regression before and after therapy (37).

To better monitor the response to the treatment in clinical trials of anterior uveitis, efforts have been made utilizing multimodal imaging to objectively measure ocular inflammation, for better patient monitoring and response measurement in clinical studies (80, 81). OCTA provides a superior objective measurement for showing the capillaries. Pichi et al. (82) showed that the dilatation and increased blood flow of an iris with acute anterior uveitis in OCTA could be recognized and quantified by AS-OCTA. This means that the iris vascular caliber might be a good index for quantifying the presence of inflammation and monitoring response to treatment. Choi et al. (83) compared the vessels caliber at different time points, whereas in the current study, an objective quantification was employed. A case of chronic retinal necrosis (CRN) finds that AS-OCTA can detect non-perfusion area of iris, and the reperfusion during the proper treatment, which could make an accurate follow-up of the progression (84).

**TABLE 1** | Advantages and applications of AS-OCTA.

	Precise diagnosis	Efficacy evaluation
Conjunctiva	Identification of abnormal vasculature areas and conjunctival lesions Detection of deeper intrascleral vessels Assessment of limbal epithelial stem cell	Longitudinal estimation of reperfusion Early evaluation of blood flow density on filtering bleb after trabeculectomy
Cornea and limbus	Detection of early corneal angiogenesis Detection of subtle abnormal vessels with corneal opacity 3D imaging of cornea layers Scan of predetermined depth of cornea	Preoperative surgical planning by evaluating the depth and area of feeder vessel Repeatable evaluation of treatment effect by vascular progression and regression Better observation of corneal graft rejection
Ciliary body and iris	Early detection of small capillaries and microaneurysms flow Assessment of vascular anomalies in anterior uveitis Identification of iris lesions	Evaluation of regressed neovascularization of the iris during anti-VEGF therapy Exposure of persistent neovascularization

VEGF, vascular endothelial growth factor; 3D, three dimensions.

## CURRENT LIMITATION AND FUTURE DIRECTIONS

Although AS-OCTA has many advantages for clinical applications, its limitations need to be addressed in future AS-OCTA studies. First, the OCTA device and software were designed for the posterior segment; imaging the anterior segment requires putting on an adaptor lens, which may yield lower quality images and inaccurate parameter values. A specific algorithm for anterior imaging with automated adjustment is necessary to improve and standardize the scan quality, such as the automation of focus and scaling (68, 85). Secondly, pupil size might affect vasculature caliber and morphological characteristics (39). Although studies have chosen similar lighting conditions, pupil size changes are unavoidable. The need to control the effect of environmental factors that can influence the vasculature in anterior segment should not be ignored; quantitatively reproducible measurements are needed to solve the problem. Thirdly, the conventional technique of OCTA lacks a sequential image matching function, which makes it hard to fix the same area of interest and reduce motion artifacts caused by severely decreased visual acuity. Thus, an eye-tracking system and sequential image matching system need to be incorporated (24, 85).

Furthermore, the restriction of the scanning field and signal dropout does not support high-quality imaging of both the perimeter part and the central part of region in interest. AS-OCTA evaluates a limited area and depth compared to AS-OCT, which is designed for the external eye. To meet this challenge, AS-OCT with angiography technology needs to be developed to help diagnosis and assessment of anterior segment diseases. Moreover, a wide field swept-source OCTA, which is operated at longer wavelengths, might be able to solve this issue (55, 77). Currently, wide-field swept-source OCTA provides a wider-angle image for

detecting diabetic retinopathy lesions, such as  $12 \times 12$  mm or even  $15 \times 9$  mm using the Montage technique (86). What's more, wide-field swept-source OCTA shows huge prospects for anterior segment imaging due to its sufficient scanning range and high sensitivity in detecting structures.

## CONCLUSION

The imaging methods of AS-OCTA described here provide a rapid and non-invasive tool for specialized imaging. The technique allows detection of vessel diameter, density, and overall appearance, and provides powerful methods for helping clinical prognoses, diagnoses, and treatment outcomes (Table 1). Moreover, the challenges in AS-OCTA that were presented here should encourage the improvement of future techniques.

## AUTHOR CONTRIBUTIONS

ML, YL, and YZ wrote and edited the manuscript. All authors contributed to the article and approved the submitted version.

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