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The OCT Angiography Revolution: Five Emerging Themes

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Introduction

Since its inception in the 1990s, optical coherence tomography (OCT) has transformed the field of ophthalmology.¹ More than any other imaging modality, retina specialists use OCT to facilitate diagnosis, monitor treatment, and to evaluate disease burden. OCT technology has revolutionized patient management in the intravitreal pharmacotherapy era for numerous retinal conditions, such as age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal venous occlusive disease. The high-resolution anatomic detail provides a unique window into surrogates for disease activity and subtle structural alterations in the anatomy of the retina that play critical roles in clinical decision-making on treatment requirements and follow-up intervals. The rapid acquisition time of OCT makes it well-suited for the high-volume nature of the typical retina clinic. In addition, the non-invasive nature of OCT allows for the high frequency of testing required for many patients who are undergoing intravitreal pharmacotherapy.

Prior to the OCT revolution, fluorescein angiography (FA) was the diagnostic staple of the retina clinic. The angiographic images provided not only structural but also functional information related to vascular leakage and nonperfusion. In fact, prior to intravitreal pharmacotherapy, the eligibility for specific therapies were often based on fluorescein angiographic characteristics. However, FA has greater risks, requires a skilled photographer and an individual trained to gain vascular access for fluorescein administration. Testing requires extended time for both patients and staff. Given many of these drawbacks and the emergence of OCT, the utilization of conventional FA has dramatically declined.

With the changes in the use of FA, the real-time clinical information related to the underlying vascular changes in various retinal diseases is not as frequently accessed and evaluated. The emergence of OCT angiography (OCTA) has created renewed interest in the opportunities for vascular imaging in patient management, disease diagnosis, and underlying vascular features in various diseases. Initially described 10–15 years ago as a research modality, multiple algorithms and approaches have been developed that utilize various

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features within the OCT signal to identify the flow signals of the vasculature within the retina and choroid.²⁻⁶

From a conceptual standpoint, OCTA identifies subtle alterations within the OCT signal that can be identified and processed to form a depth-encoded vascular flow map. In OCTA, scans are repeated through the area of interest and then evaluated for change in specific OCT-based feedback signals. Static tissues show minimal to no change in these signals; whereas dynamic processes, such as blood flow, exhibit changes over time that can be identified and analyzed using the various algorithm platforms. OCTA capitalizes on unique features of OCT signals in tissues. For example, varying degrees of speckles occur with OCT based on interference and reflections of light within the tissues of interest. The changes in these speckles are compared in consecutive B-scans at identical pixel locations. The amount of correlation or similarity between these pixels is evaluated. If there is a significant change in the speckle, decorrelation is present. In static tissue, there is minimum change over time in these speckles (i.e., minimal decorrelation). Conversely, in areas with motion, such as with red blood cells, significant changes in speckle occur (i.e., decorrelation). One approach to OCTA is to evaluate the various correlations of these speckles between scans. Numerous techniques in the literature have been utilized to describe the evaluation of these changes including intensity decorrelation and amplitude decorrelation (i.e., the difference in pixel reflection strength). A second approach to generating the OCTA signal is to utilize phase variance. This technique utilizes alterations that occur in the phase of the light waves from scan to scan. Small variations are noted in static tissue, but much larger variations in phase will be noted in areas of active motion. These approaches and others may be complimentary and hybrid methods may offer unique advantages.⁷ Multiple research groups have optimized and developed unique versions of these OCTA algorithms. Although initially these algorithms were only used by research groups, many of these platforms are now employed commercially, including split-spectrum amplitude decorrelation angiography (SSADA), optical microangiography (OMAG), and OCTA ratio analysis (OCTARA).^{2, 4, 5, 7, 8}

Although, OCTA technology has been available for over a decade, the widespread adoption of this technology has taken time because of its requirement for rapid scan speeds and overall enhancements in algorithm efficiency. Since the FDA-clearance of the first commercial system in 2015, OCTA utilization, research, and clinical experience have exploded. It is not unusual to see imaging sections at ophthalmic meetings specifically devoted to OCTA. In fact, meetings have now been established to focus on clinical and translational research in the OCTA space. The first FDA-cleared spectral domain OCT systems that were enabled for clinical OCTA were the Cirrus HD-OCT 5000 with AngioPlex (Zeiss, Oberkochen, Germany) and the Avanti with AngioVue/AngioVueHD (Optovue, Fremont, California). In addition, the first FDA-cleared swept source OCT system, the Plex Elite 9000 (Zeiss) was recently released is available for research use as part of the Advanced Retina Imaging Network, a collaborative research group established to evaluate the role of swept source OCT in various retinal disease.

With the explosion of knowledge in the OCTA arena, several key issues and topics have emerged as focal points for clinicians and researchers. Five of these themes related to the technology are outlined below.

Theme 1: The Complexities of Image Review Strategies

Perhaps more than any other conventional modality used for retinal imaging, the review strategies involved for interpreting OCTA images are widely-varied and complex. In the midst of high-volume retina clinics, optimizing image review protocols for accuracy and efficiency is critical. OCTA assessment generates multiple windows of information that contribute to accurate interpretation. These windows of information may include any or all of the following: the structural B-scan, decorrelation overlay, *en face* OCT, segmentation overlay, and the *en face* vascular flow maps. In addition, newer software reports include perfusion density mapping and measures for lesion size. These reports may be automatically generated by the software platform and pushed to a review system for the clinician. Conversely, the scans may be reviewed directly on the system to optimize segmentation location and to customize specific viewing windows. Subsequently, the OCTA scan can be reviewed on a “fly-through” basis by manually altering the segmentation slab through the various retinal depths and utilizing user-controlled manipulation of the slab location.

With all of this information, how does a clinician optimize their review strategy? Key approaches to these strategies may vary significantly based on the region of interest or suspected pathology. For example, superficial retinal vascular abnormalities with minimal architectural alterations may lend themselves to rapid review with the automated report. Whereas, complex choroidal neovascularization with significant architectural distortion may benefit more from an individualized review strategy through the system review software or at the device. More research is needed into the benefits and drawbacks of various review strategies to help better guide clinicians on how to integrate OCTA into a busy clinic workflow.

Theme 2: Clinical Applications for Disease Diagnosis and Management

As with many new technologies, the product of that technology appears amazing, but the place for that technology in our day-to-day patient management is an evolving affair. When OCT was first introduced, the widespread value of the technology was questioned. As image quality improved, the technology found a clear role in the diagnosis of vitreoretinal interface disorders. However, it was the advent of the pharmacotherapy era that exponentially changed the place of OCT in our clinical toolbox, from an occasional adjunct to a critical component.

In a similar way, OCTA is in that early stage of finding its footing within the diagnostics toolbox. However, the widespread availability of the technology, the ease of obtaining the testing, and the clinician’s comfort with OCT technology is catapulting our knowledge of OCTA in retinal disease forward. New categories of disease severity are emerging, such as “nonexudative neovascular AMD” and “silent” diabetic retinopathy (i.e., retinal vascular alterations without clinical retinopathy).⁹ The evaluation of retinal vascular dynamics in the natural history and response to treatment in conditions such as diabetic retinopathy and retinal venous occlusive disease is underway and reports are already surfacing. As an easy non-invasive test, the role for OCTA in the diagnosis of indeterminate choroidal neovascularization appears to be clear. However, the impact of OCTA data on treatment decision-making in AMD and CNV-related diseases is less obvious. Will various lesion

characteristics on OCTA be identified as key biomarkers for disease activity or prognosis? While, conventional OCT fluid markers still drive most treatment decision-making for treat-and-extend or *pro re nata* regimens, OCTA has the potential to provide additive or even superior information regarding the need for additional treatment.

For other conditions, OCTA is being explored as a primary diagnostic modality and as an exploratory imaging system for understanding disease pathophysiology. Preliminary reports have suggested that alterations in choriocapillaris perfusion may occur in nonneovascular AMD and potentially be a precursor to geographic atrophy.¹⁰ Other conditions, such as macular telangiectasia type 2 (MacTel2) and paracentral acute middle maculopathy (PAMM) have very characteristic findings on OCTA suggesting its role as a mainstay in diagnosis of these conditions.^{11, 12} In both of these conditions, the value of the depth-resolved nature of OCTA is particularly apparent. For PAMM, previous studies had strongly suggested the underlying pathophysiology was an infarct of the inner nuclear layer, but the depth-resolved vascular flow information provided through OCTA provides clear evidence of this hypothesis through hypoperfusion of the deep capillary retinal plexus.¹² For MacTel2, some of the earliest changes are subtle alterations in the temporal parafoveal deep capillary plexus.¹¹ OCTA easily visualizes these alterations and also functions as an excellent surveillance tool for underlying CNV.

Theme 3: A Newfound Appreciation for the Impact of Artifacts

All imaging modalities are subject to various artifacts that can add, remove, or alter visual information within the image. Software processing and quantitative metrics may also pose an additional area where artifacts may emerge. As an example, media opacities may create artefactual alterations in fundus photographs. Automated segmentation is frequently used by OCT software to identify specific regions within the OCT, such identification of the retinal pigment epithelium or internal limiting membrane. Segmentation errors (i.e., misidentification of retinal layers or anatomic locations) in OCT analysis software may create false impressions of atrophy or retinal thickening that can lead to misinterpretation.

With the complexities involved with OCTA image acquisition and image processing, OCTA images have unique artifact challenges.¹³ Several key artifact categories have been described and should be considered when reviewing OCTA images, including projection artifacts, motion artifacts, and others.¹³ Projection artifacts are recognized as the appearance of retinal vascular structures in layers deeper to where they actually reside. This artifact occurs due to the transmission and reflection of the OCT signal through the vasculature to the tissues below that results in a decorrelation signal that is interpreted (incorrectly) as vascular flow. These artifacts can be easily recognized through successive review of *en face* images.¹³ In addition, recent significant advances in software techniques have the potential to dramatically reduce projection artifacts, such as projection-resolved OCTA and other algorithm solutions.^{14, 15}

OCTA is also uniquely susceptible to motion artifacts. Even subtle changes and small movements can result in false positives and incorrect representation of the decorrelation signals. Software adjustments for motion correction have significantly improved the impact of artifacts on the final dataset. However, even software correction can result in new image

artifacts/alterations, including image quilting, stretch artifacts, and vessel doubling.¹³ Segmentation features and errors may also lead to image artifacts, such as artefactual flow signals when the segmentation boundaries intersects a hyperreflective boundary (e.g., retinal pigment epithelium over drusen).¹⁶

Theme 4: Questions Around Revenue and Workflow

The current climate of healthcare economics requires consideration of cost and value in any discussion regarding new technologies. There are multiple sides to this coin that can be discussed and considered when evaluating the impact of OCTA on the economics of the practice of medicine as it relates to retinal disease. As it currently stands, there is no separate code for OCTA. A practice can simply be reimbursed for conventional OCT. From the practice standpoint, this creates a revenue gap when considering the investment in a new system. In addition, the increased utilization of OCTA may result in a corresponding reduction of fluorescein angiography further reducing practice revenue. From a volume-based reimbursement system this creates administrative challenges for justification. However, in the ever-changing world of payer environments, in a shared savings/shared risk system this reduction in cost could provide the clinician with increased information and added value to patient care without adding additional cost to the system. From the broader healthcare system standpoint, the combined nature of OCT/OCTA billing increases the overall value of OCT technology through increasing the yield of information from a single diagnostic while maintaining cost. As previously mentioned, this technology has the potential continue to drive a reduction in utilization of macular fluorescein angiography and subsequently reducing cost within the system. However, it is critical for payers to recognize the overall costs/investments involved that practices must shoulder to obtain the latest technology that maximizes patient care quality and adds inherent value to the care that retina specialists provide.

Theme 5: Opportunities for Disruptive Changes for the Future

Since the FDA-clearance of the first OCTA system, it feels like the floodgates have opened for related advancements for the technology. Software advancements for artifact corrections, such as projection removal and motion correction, have already had significant impacts on image quality and OCTA consistency.^{14, 15, 17} Future improvements in tracking and artifact removal will continue to enhance OCTA quality.

Quantitative metrics is also an area of great interest. The high contrast images provide an amenable substrate for automated analysis, including perfusion density assessment. Future opportunities in quantitative assessment include automated CNV evaluation and automated detection/assessment of pathologic features, such as nonperfusion.^{18–20}

Emerging system technology, including faster scan speeds, extended range systems, and widefield capabilities have the potential to dramatically impact the overall functionality of OCTA in retinal disease management and evaluation.²¹ Already today, the increased speed of many swept source systems significantly increases the potential scanning area for OCTA while maintaining overall image quality. Functional metrics are also of great interest for the future. One recently described technique utilized variable interscan time analysis (VISTA) to

provide information related to relative blood flow speeds within different vascular anomalies (e.g., microaneurysms, CNV). These technology advances and others have the potential to continue the revolution of OCTA and expand the capabilities of this powerful diagnostic tool within the retina clinic.

Conclusion

Overall, enthusiasm for OCTA has spread like wildfire since its widespread availability from FDA-clearance. Hardware and software advancements continue to push the envelope for the capabilities of OCTA systems. Additional research is needed to expand our knowledge base for its specific role in various disease management strategies and to enable retina specialists to harness the power of OCTA to enhance patient care.

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