

Optical coherence tomography angiography in wet age-related macular degeneration (AMD)

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Submitted Feb 01, 2016. Accepted for publication Feb 20, 2016.

doi: 10.3978/j.issn.1000-4432.2016.02.02

View this article at: <http://dx.doi.org/10.3978/j.issn.1000-4432.2016.02.02>

Over the last decades, substantial developments in retinal imaging offered a paradigmatic change in the understanding of the pathophysiology of wet age-related macular degeneration (AMD). We have reached a point of sophistication that seemed unattainable a few years ago. A myriad of imaging devices is now available at our discretion, representing a unique opportunity to offer our patients better clinical care. In order to reduce the risk of progressive and enduring visual loss associated with wet AMD, early identification and prompt initiation of treatment is warranted. Since its introduction in 1961 by Novotny and Alvis (1), fluorescein angiography (FA) became the gold standard for the diagnosis and classification of choroidal neovascularization (CNV). However, a major limitation of traditional angiography resides in its inability to image the entire retinal capillary system or to directly visualize new vessels, resorting on indirect clues such as fluid accumulation or leakage to recognize neovascularization (2). Wide-field image acquisition, confocal scanning laser ophthalmoscopy, adaptive optics and indocyanine green angiography (ICGA) have broadened the use of classic angiography. With complementary ICGA, better visualization of the deep vessels can be obtained due to peak excitation (805 nm) and emission (835 nm) in the near-infrared region. Nevertheless, ICGA is neither available nor routinely performed in many institutions throughout the world. Also, despite the ability to detect dynamic patterns of dye transit and leakage, angiography systems (FA and ICGA) remain expensive, time-consuming and invasive procedures. Although generally safe, side effects like nausea; vomiting or even severe allergic reactions may develop in a

minority of patients, thus limiting its repeated use (3).

The advent of optical coherence tomography (OCT) revolutionized retinal imaging by providing a fast, simple, and noninvasive method to assess retinal structure at a microscopic level. Since its debut more than two decades ago, profound improvements in the scanning speed, resolution and image depth led to an explosive growth of OCT in clinical practice, with a significant effect in clinical decision making (4). Even though technical sophistication improved the OCT diagnostic yield for wet AMD, there are no agreed-on standards for diagnosing CNV based strictly on cross-sectional OCT (5). Structural OCT cannot detect blood flow, nor can it reliably distinguish vasculature from fibrous and other surrounding tissue (6). Therefore, structural OCT must ultimately be used in combination with angiography systems to diagnose CNV accurately.

By conveying noninvasive, three-dimensional scans of both the superficial and deep retinal capillary plexuses and the choriocapillaris, OCT angiography (OCTA) brought a new insight into the vascular abnormalities that accompany neovascularization. OCTA detects endoluminal flow by mapping erythrocyte movement over time and comparing sequential OCT B-scans at a given cross-section, thus allowing simultaneous visualization of structure and blood flow (5). In addition to providing enhanced anatomic detail, OCTA allows quantitative metrics of the CNV area and generates data on vascular flow (2). Several studies have demonstrated that OCTA can accurately identify type 1 and type 2 neovascularization (5-10), offering an unrivaled morphological characterization of the CNV net (e.g., tree-like, glomerular, fragmented) that far exceeds FA, ICGA

and OCT. In addition, the presence of a fibrovascular capsule, afferent feeder trunk and peripheral anastomosis within the CNV can be clearly assessed (10). Preliminary findings from a recent study by de Carlo *et al.* (5) where 30 eyes with OCTA and same-day FA were evaluated, reported a sensitivity of 50% (4/8) and a specificity of 91% (20/22) for CNV detection with OCTA. In the future, we may be able to correlate the morphological patterns of CNV with disease course, prognosis, and response to treatment. Furthermore, the non-invasive nature of the technique allows comprehensive lesion monitoring after treatment with anti-VEGF compounds. Quantitative measurements of the CNV flow area and flow index reported by Huang *et al.* (11) showed a rapid shutdown of flow over the initial 2 weeks after treatment with anti-VEGF, followed by reappearance of the CNV channel by the fourth week and fluid reaccumulation at 6 weeks. As demonstrated by Lumbroso *et al.* (12) and Marques *et al.* (10), sequential examinations can shadow morphological changes in the neovascular network, closely tracking the timings of vascular network remodeling in patients undergoing treatment. Ultimately, this may allow the advent of tailored and customized treatment regimens for wet AMD patients, built upon the CNV net morphology at baseline and its response to treatment.

OCTA may also be useful in the screening of eyes at risk for CNV. Unilateral CNV is an established risk factor for the development of neovascularization in the fellow eye. Screening this population for early detection of CNV may have both therapeutic and prognostic implications. A pilot study by Palejwala *et al.* (13), showed that OCTA was able to identify focus of CNV that were not identifiable on FA and structural OCT. OCTA detects CNV by the presence of an abnormal pattern of vascular flow above the Bruch membrane, therefore being able to identify neovascular lesions that do not leak on FA. Whether nonexudative CNV is a predecessor of wet AMD or a distinct clinical entity is yet to be determined, as well as if we should or should not start anti-VEGF treatment in these cases.

In conclusion, this revolutionary imaging modality is redefining our understanding of wet AMD by conveying detailed, depth-resolved information on the retinal and choroidal vascular networks, both at a structural and functional level. The ability to accurately image CNV noninvasively and to qualitatively and quantitatively appraise its changes longitudinally, turn OCTA into an attractive alternative to more invasive imaging modalities such as FA and ICGA. However, attention should be drawn to first

validate its accuracy and assess the reproducibility of its data in high-powered studies. Also, further study is needed to determine the clinical significance of nonexudative CNV, including how often these lesions convert to wet CNV and at what point, if any, anti-VEGF treatment is warranted. We embark on this new era of retinal imaging with great expectations in mind, hoping that OCTA can point out new clinical coordinates to improve the everyday management of exudative AMD. As new functionalities and technical enhancements continue to ripen, only further improvement is to be expected.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Marques JP, Silva R. Optical coherence tomography angiography in wet age-related macular degeneration (AMD). *Eye Sci* 2016;31(1):1-3. doi: 10.3978/j.issn.1000-4432.2016.02.02