Optical Coherence Tomography Angiography of Dry Age-Related Macular Degeneration

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Abstract

Optical coherence tomography angiography (OCTA) can be used to visualize alterations in the choriocapillaris of patients with dry age-related macular degeneration (AMD). These changes seem to be present during all stages of the disease. Earlier stages are associated with patchy thinning of the choriocapillaris, while geographic atrophy is associated with loss of choriocapillaris lying under the area of geographic atrophy and asymmetric alteration of choriocapillaris at the margins of the geographic atrophy. The use of high-speed, long-wavelength swept-source OCT for angiography, with its better penetration into the choroid and high acquisition speeds, enable OCTA with scaled slowest detectable flow and fastest distinguishable flow. This will enable us to better investigate choriocapillaris changes in patients with dry AMD. The ability to image the choriocapillaris structure and flow impairments may be useful in the future for detecting and monitoring the progression of dry AMD and for monitoring treatment responses in clinical trials to therapies that target disease progression in dry AMD.

Nonneovascular or dry age-related macular degeneration (AMD) is one of the leading causes of vision loss in people over 60 years of age in the developed world. Dry AMD accounts for 85–90\% of all cases of AMD \cite{1, 2}. In its early stages, it is characterized by the presence of drusen and pigmentary abnormalities resulting from alterations in the retinal pigment epithelium (RPE). In later stages, it can progress to geographic atrophy (GA) or outer retinal atrophy \cite{3–6}. Late atrophic AMD is an important cause of irreversible vision loss, even in patients with neovascular AMD, because the use of vascular endothelial growth factor inhibitors successfully suppresses neovascularization and results in the progression of these lesions to atrophy \cite{7}.

Until recently, most research investigating AMD has been focused on the neovascular, or wet, form of AMD and the conversion from dry to wet AMD. While the pathological events leading from early-stage dry AMD to late-stage wet or atrophic AMD remain poorly...
understood, both histological and optical coherence tomography (OCT)-based studies have shown that the earliest detectable changes that characterize the progression of the disease occur at the interface of the retina and choroid, where the outer segments of the photoreceptors, RPE, Bruchs membrane, and choriocapillaris are located [8–12].

Early changes in AMD include the deposition of material within Bruchs membrane and between Bruchs membrane and the RPE. These deposits present clinically as a thickened sub-RPE layer, which includes drusen, and pigmentary abnormalities, which correspond to disruption of the RPE layer [13–16]. These changes are associated with progression down one of the following two late AMD pathways: the development of neovascularization or the development of atrophy, characterized by the loss of photoreceptors, the RPE, and the choriocapillaris.

A healthy RPE is essential for normal photoreceptor cell metabolism and the visual cycle. In dry AMD, RPE degeneration is accompanied by concomitant photoreceptor degeneration, giving rise to areas of GA [17]. However, the nature of the insults that initiate the pathway of RPE and subsequent photoreceptor cell loss have yet to be ascertained. Genetic factors, ischemia, inflammation and oxidative stress, RPE dysfunction, and the complement pathway all may play roles in the development of AMD [18–21]. However, there is considerable debate as to whether the initial changes take place in the choroid, in the RPE, or in the photoreceptors. There is evidence of early changes in the choroid, RPE, and photoreceptors in patients with dry AMD [22, 23].

OCT has been used extensively to study dry AMD. With the advent of high-resolution spectral-domain (SD) OCT, we have been able to observe and quantify the structural changes that occur in the retina and RPE and to some extent, the choroid, in patients with dry AMD. Drusen are evident as deposits in Bruchs membrane that elevate and distort the RPE, which appears to cause outer retinal disruption and eventual breakdown of the RPE and photoreceptors. GA often follows the disappearance of drusen and is characterized by the well-delineated loss of the RPE, photoreceptors, and choriocapillaris [24]. Moreover, it has been demonstrated that there may be asymmetric changes in the outer retina at the margins of GA and that the locations of these changes in the photoreceptor outer segments surrounding the GA may predict the direction of GA progression [4]. Software enhancements in OCT have enabled the quantification of drusen volume and GA size [25].

Traditional intensity-based and ultra-high-resolution SD-OCT techniques provide images of anatomical details of the photoreceptors and RPE and show that structural changes precede the development of GA, but they do not provide detailed anatomic images of the choriocapillaris, which may be crucial for understanding the sequence of events that are responsible for disease progression. For example, a fundamental debate in AMD is whether it is a primary disease of the photoreceptors, the RPE, or the choriocapillaris or whether it results from the choreographed dysfunction among all three layers, with specific layers playing more dominant roles in different patients depending on their genetics, environment, and overall health. The incomplete picture of disease progression in AMD results in part from the need to extrapolate longitudinal changes derived from histopathological findings in autopsy eyes with AMD, which are obtained at fixed time points and leave unanswered
questions about the progressive changes that result in end-stage disease. For example, we do not know whether photoreceptor loss is primarily due to an abnormality of the photoreceptors or whether RPE dysfunction leads to photoreceptor loss. If RPE dysfunction is the primary defect, then we need to determine whether RPE dysfunction is due to a primary RPE abnormality or whether it results from loss of the choriocapillaris. Up until now, we have been unable to untangle the web of interdependence between these three layers because we can only measure anatomic and functional changes in the photoreceptors in vivo and anatomic changes in the RPE in vivo, but we have been unable to visualize the microvasculature of the choriocapillaris in vivo. To help unravel the mystery of disease progression, we need to understand the temporal sequence of anatomic and functional changes in the macula. Optical coherence tomography angiography (OCTA) may bring clarity to the role of the choriocapillaris in disease progression. With the advent of OCTA, it is now also possible to visualize the vascular changes that occur in dry AMD [26–28].

OCTA provides three-dimensional, depth-resolved images of the vasculature in the retina and choroid. This enables us to independently evaluate the vasculature of the inner and outer retina and the choriocapillaris. Because the vascular images of OCTA are intrinsically co-registered with structural OCT data, it is possible to correlate the vascular changes with structural changes noted on OCT scans. Another advancement is the application of swept-source (SS) OCT technology to OCTA [29, 30]. SS-OCT technology has a lower sensitivity roll-off with depth and a longer wavelength, which enables better image penetration below the RPE and therefore better visualization of the choroid [31–33]. SS-OCT also can support faster A-scan acquisition rates compared with SD-OCT and provide greater retinal coverage. The faster acquisition speeds in SS-OCT are especially important because OCTA relies on decorrelation between sequentially acquired OCT B-scans of the eye [34, 35]; therefore, acquisition speed forces trade-offs among imaging time, retinal coverage and pixel density in OCTA data sets. Higher acquisition speeds also support OCTA protocols with multiple repeated B-scans and the use of techniques that can detect flow impairment, such as variable interscan time analysis (VISTA), which will be explained in greater detail below [36].

**Early Age-Related Macular Degeneration**

Early and intermediate AMD are characterized by drusen and pigmentary abnormalities, but it is unknown whether changes in the choriocapillaris occur at these stages. Drusen and RPE changes can be visualized on structural OCT images [17]. Software enhancements in SD-OCT instruments enable quantification of drusen volume and their progression over time [25]. With the advent of OCTA, it is now possible to visualize the microvasculature of the retina and choriocapillaris in vivo and to correlate microvascular alterations to structural changes in the retina and RPE [26, 27, 37].

As expected, no significant changes are present in the retinal vasculature in early AMD. However, OCTA of the choriocapillaris shows changes that may not be related to aging alone. OCTA imaging of the choriocapillaris in normal eyes shows a dense homogenous network, with a fine pattern in the macula that is near the transverse resolution limit of OCT imaging. More peripheral OCTA images of the choriocapillaris exhibit a lobular architecture, consistent with the known morphology reported by vascular casting studies.
These patterns are observed using SD-OCT, centered at a wavelength of 840 nm, as well as using SS-OCT, centered at a longer wavelength of 1,050 nm. With age, the density of the choriocapillaris is likely to be reduced; however, a homogenous and regular pattern of vasculature is still present.

OCTA images of early non-neovascular AMD eyes suggest that there is a general reduction in choriocapillaris density compared to age-matched normal controls, with some focal areas of choriocapillaris loss or flow impairment. The dark patches at the level of the choriocapillaris that correspond to choriocapillaris loss may sometimes be accompanied by displacement of the larger choroidal vessels into the space previously occupied by the choriocapillaris. These changes become more marked in more severe cases. These findings are in agreement with histopathological studies, which have noted that drusen form over areas devoid of capillary lumens and extend into the intercapillary pillars [38, 39]. Increased drusen density in histopathologic studies has been shown to correspond to a decreased vascular density of the choriocapillaris [40]. Analysis of en face structural OCT-B images of early AMD has also shown a reduction in visible choriocapillaris compared with normal eyes, but with a reduction in the OCT signal intensity underlying the drusen, it can be challenging to distinguish between loss of signal and loss of the choriocapillaris [22].

Although these changes in choriocapillaris density are visible in both SD-OCT and SS-OCT images, SS-OCT systems have better penetration into the choroid and therefore enable more reliable visualization of the choriocapillaris. In SD-OCT systems, drusen and RPE changes are more likely to cause signal attenuation shadowing. Strong structural OCT signals are required to obtain OCTA images, and shadowing causes dark areas on en face OCTA at the level of the choriocapillaris that are caused by poor signal rather than lack of blood flow. These areas of shadowing (as opposed to decreased perfusion) can be identified by concurrently looking at an en face OCT intensity image at the level of the choriocapillaris and an OCTA image and by examining a cross-sectional OCT image of the area of suspected choriocapillaris pathology. Areas of shadowing will appear dark on both the OCT intensity image and the angiographic image, whereas areas of decreased blood flow will appear normal on the intensity image but will appear dark on the en face OCTA image. Areas of shadowing are much more prevalent in SD-OCT images than in SS-OCT images because longer wavelengths have increased image penetration; thus, it is much easier to assess loss of choriocapillaris flow on SS-OCTA images than on SD-OCT images. Figure 1 shows a composite image of same-day SS-OCTA and the corresponding en face OCT intensity images at the level of the choriocapillaris (fig. 1b, c), an SD-OCTA image with the corresponding en face OCT intensity image at the level of the choriocapillaris (fig. 1e, f) and the corresponding B-scan (fig. 1d) and a same-day color fundus image. The green arrows show an area of shadowing under the drusen, visible as a dark area on both the intensity and angiographic images. Note that the SS-OCTA image at the 840 nm wavelength (fig. 1b) has less pronounced shadowing in the area underneath the drusen than the SD-OCTA image (fig. 1e) at 1,050 nm due to the lower attenuation experienced by longer wavelengths.
Late Dry Age-Related Macular Degeneration

In patients with GA, OCTA shows loss of choriocapillaris flow under the regions of GA. In these areas of choriocapillaris alteration, larger choroidal vessels may be displaced into the area ordinarily occupied by the choriocapillaris and may be seen on the en face OCTA image at the depth level where the choriocapillaris is ordinarily seen. Figure 2 shows SS-OCTA images from a patient with GA, with corresponding red-free (fig. 2a) and fundus autofluorescence images (fig. 2b). In this patient, there were no changes in the retinal vasculature, as visible on OCTA segmented at the level of the retinal vasculature in figure 2c. In many cases, the areas of choriocapillaris alterations extend beyond the margins of GA in an asymmetric pattern (fig. 2d, e). These alterations outside of the margins of GA may be quite extensive or may be very limited and subtle. In a smaller number of cases, the choriocapillaris alterations may be limited to the area of GA and may not extend beyond that area. The changes underlying the area of GA are usually well visualized on both SD- and SS-OCTA since the RPE in these areas is missing and therefore does not attenuate the SD-OCT signal. However, especially at the margins of GA where the RPE is still intact, it may be more difficult to visualize changes in the choriocapillaris with SD-OCT.

One of the debates regarding visualization of choriocapillaris alterations in patients with GA is whether they truly represent the absence of flow or merely reduced flow. OCTA creates flow images by comparing differences between consecutive OCT B-scan images. Micro-saccadic eye motion is always present, and changes due to erythrocyte flow must be separated from overall retinal motion. If the velocity of flow in the vessels is very slow, then OCTA may not be able to detect this slow flow versus the parasitic retinal motion. In addition, if flow is fast, then the OCTA image saturates (fast flow appears white), and variations in flow cannot be differentiated.

Thus, OCTA machines have a slowest detectable flow, or sensitivity threshold, below which they cannot detect flow at slow speeds, as well as a fastest distinguishable flow, or saturation limit, above which different flow speeds appear the same. The slowest detectable flow depends on the time between repeated B-scans, with longer interscan times producing a lower slowest detectable flow rate because erythrocytes have more time to move between B-scans. In addition, a longer interscan time also reduces the fastest distinguishable flow rate. The interscan time of current SD-OCT machines is 5 ms, while that of the SS-OCTA prototype instrument reported here is 1.5 ms. SD-OCT and SS-OCT instruments have acquisition speeds of 70,000 and 400,000 A-scans per second, respectively. The faster scanning speed allows SS-OCT to acquire larger numbers of repeated B-scans for the OCTA scanning protocol in the same amount of time as SD-OCT. This allows OCTA data to be generated between B-scans with longer versus shorter interscan times. Viewing the same areas on consecutive B-scans (fig. 2d) versus every second B-scan (fig. 2e) using OCTA helps to identify areas of flow impairment that may not be distinguishable using instruments with slower acquisition speeds or OCTA with long interscan times. Using SS-OCTA with VISTA to vary the slowest detectable flow and fastest discernable flow rates, we can show that choriocapillaris alterations within the borders of GA tend to have slow flow rates and may be primarily atrophic, while choriocapillaris alterations beyond the borders of GA have flow impairment. Figure 2f and g show magnified images that correspond to a region within
the borders of GA analyzed using OCTA with varying interscan times. In figure 2g, we are better able to visualize slow flow in some vessels in this region of atrophy. However, compared to the surrounding choriocapillaris, it is clear that there are considerable areas of absent flow or reduced flow underlying this area of GA. The images shown in figure 2h and i correspond to a region at the margin of GA analyzed using varying interscan times. Figure 2h shows an OCTA image obtained with a 1.5-ms interscan time, while figure 2i depicts an image acquired with a 3.0-ms interscan time. With increased interscan times, we are able to better visualize that most of the areas of choriocapillaris alteration in this region have slow flow rather than the complete loss of flow. Conversely, if OCT A was performed using only a longer interscan time (which would be typical for SD-OCT instruments), then it would not be possible to distinguish areas of flow impairment.

It is still unclear why these choriocapillaris flow changes take place in patients with GA. However, these changes clearly seem to precede the obvious detectable atrophic structural changes in the RPEs and retinas of these patients observed using conventional structural OCT. These results suggest that microstructural changes detectable on OCTA are present before they become detectable on conventional intensity-based OCT. Additional longitudinal studies are needed to better characterize the progression of these choriocapillaris alterations. In response to the debate about whether the primary site of pathogenesis of GA is the choriocapillaris or the RPE, these OCTA findings that choriocapillaris alterations appear to be at least the size of GA, and often greater, appear to support the hypothesis that choriocapillaris loss may precede RPE changes. However, additional studies using high-resolution SD-OCT may be needed to confirm these findings.

In summary, OCTA can be used to visualize alterations in the choriocapillaris of patients with dry AMD. These changes seem to be present during all stages of the disease. The use of high-speed, long-wavelength SS-OCT for angiography, with its better penetration into the choroid and high acquisition speeds, enable OCTA with VISTA to be performed. Scaling the slowest detectable flow and fastest distinguishable flow will enable us to better investigate choriocapillaris changes in patients with dry AMD. The ability to image the choriocapillaris structure and flow impairments may be useful in the future for detecting and monitoring the progression of dry AMD and for monitoring treatment responses in clinical trials to therapies that target disease progression in dry AMD.

References

1. Velez-Montoya R, Oliver SC, Olson JL, Fine SL, Quiroz-Mercado H, Mandava N. Current knowledge and trends in age-related macular degeneration: genetics, epidemiology, and prevention. Retina. 2014; 34:423–441. [PubMed: 24285245]
2. Friedman DS, OColmain BJ, Munoz B, Tomany SC, McCarty C, de Jong PT, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol. 2004; 122:564–572. [PubMed: 15078675]
3. Fleckenstein M, Schmitz-Valckenberg S, Adrion C, Kramer I, Eter N, Helb HM, et al. Tracking progression with spectral-domain optical coherence tomography in geographic atrophy caused by age-related macular degeneration. Invest Ophthalmol Vis Sci. 2010; 51:3846–3852. [PubMed: 20357194]
4. Nunes RP, Gregori G, Yehoshua Z, Stetson PF, Feuer W, Moshfeghi AA, et al. Predicting the progression of geographic atrophy in age-related macular degeneration with SD-OCT en face
imaging of the outer retina. Ophthalmic Surg Lasers Imaging Retina. 2013; 44:344–359. [PubMed: 23883530]

5. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology. 1992; 99:933–943. [PubMed: 1630784]

6. Ferris FL 3rd, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, et al. Clinical classification of age-related macular degeneration. Ophthalmology. 2013; 120:844–851. [PubMed: 23332590]

7. Velez-Montoya R, Oliver SC, Olson JL, Fine SL, Mandava N, Quiroz-Mercado H. Current knowledge and trends in age-related macular degeneration: todays and future treatments. Retina. 2013; 33:1487–1502. [PubMed: 23222393]

8. Complications of Age-related Macular Degeneration Prevention Trial Research Group. Risk factors for choroidal neovascularization and geographic atrophy in the complications of age-related macular degeneration prevention trial. Ophthalmology. 2008; 115:1474–1479. [e1–e6]. [PubMed: 18502512]

9. Joachim N, Mitchell P, Rochnitta E, Tan AG, Wang JJ. Incidence and progression of reticular drusen in age-related macular degeneration: findings from an older Australian cohort. Ophthalmology. 2014; 121:917–925. [PubMed: 24332537]

10. Joachim ND, Mitchell P, Kifley A, Wang JJ. Incidence, progression, and associated risk factors of medium drusen in age-related macular degeneration: findings from the 15-Year follow-up of an Australian Cohort. JAMA Ophthalmol. 2015; 133:698–705. [PubMed: 25838066]

11. Schuman SG, Koreishi AF, Farsiu S, Jung SH, Izatt JA, Toth CA. Photoreceptor layer thinning over drusen in eyes with age-related macular degeneration imaged in vivo with spectral-domain optical coherence tomography. Ophthalmology. 2009; 116:488–496.e2. [PubMed: 19167082]

12. Moussa K, Lee JY, Stinnett SS, Jaffe GJ. Spectral domain optical coherence tomography–determined morphologic predictors of age-related macular degeneration–associated geographic atrophy progression. Retina. 2013; 33:1590–1599. [PubMed: 23538573]

13. Lutty G, Grunwald J, Majji AB, Uyama M, Yoneya S. Changes in choriocapillaris and retinal pigment epithelium in age-related macular degeneration. Mol Vis. 1999; 5:35. [PubMed: 10562659]

14. Curcio CA, Millican CL. Basal linear deposit and large drusen are specific for early age-related maculopathy. Arch Ophthalmal. 1999; 117:329–339. [PubMed: 10088810]

15. Curcio CA, Messinger JD, Sloan KR, McGwin G, Medeiros NE, Spaide RF. Subretinal drusenoid deposits in non-neovascular age-related macular degeneration: morphology, prevalence, topography, and biogenesis model. Retina. 2013; 33:265–276. [PubMed: 23266879]

16. Zhang Y, Wang X, Rivero EB, Clark ME, Witherspoon CD, Spaide RF, et al. Photoreceptor perturbation around subretinal drusenoid deposits as revealed by adaptive optics scanning laser ophthalmoscopy. Am J Ophthalmol. 2014; 158:584–596.e1. [PubMed: 24907433]

17. Bhutto I, Lutty G. Understanding Age-related Macular Degeneration (AMD): relationships between the photoreceptor/retinal pigment epithelium/Bruchs membrane/choriocapillaris complex. Mol Aspects Med. 2012; 33:295–317. [PubMed: 22542780]

18. Curcio CA, Johnson M, Huang JD, Rudolf M. Aging, age-related macular degeneration, and the response-to-retention of apolipoprotein B-containing lipoproteins. Prog Retin Eye Res. 2009; 28:393–422. [PubMed: 19698799]

19. Seddon JM, Reynolds R, Yu Y, Daly MJ, Rosner B. Risk models for progression to advanced age-related macular degeneration using demographic, environmental, genetic, and ocular factors. Ophthalmology. 2011; 118:2203–2211.

20. Age-Related Eye Disease Study Research Group. Risk factors for the incidence of advanced age-related macular degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report no. 19. Ophthalmology. 2005; 112:533–539. [PubMed: 15808240]

21. Seddon JM, Francis PJ, George S, Schultz DW, Rosner B, Klein ML. Association of CFH Y402H and LOC387715 A69S with progression of age-related macular degeneration. JAMA. 2007; 297:1793–1800. [PubMed: 17456821]
22. Sohrab M, Wu K, Fawzi AA. A pilot study of morphometric analysis of choroidal vasculature in vivo, using en face optical coherence tomography. PLoS One. 2012; 7:e48631. [PubMed: 23189132]

23. McLeod DS, Grebe R, Bhutto I, Merges C, Baba T, Lutty GA. Relationship between RPE and choriocapillaris in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2009; 50:4982–4991. [PubMed: 19357355]

24. Wu Z, Luu CD, Ayton LN, Goh JK, Lucci LM, Hubbard WC, et al. Optical coherence tomography-defined changes preceding the development of drusen-associated atrophy in age-related macular degeneration. Ophthalmology. 2014; 121:2415–2422. [PubMed: 25109931]

25. Freeman SR, Kozak I, Cheng L, Bartsch DU, Mojana F, Nigam N, et al. Optical coherence tomography-raster scanning and manual segmentation in determining drusen volume in age-related macular degeneration. Retina. 2010; 30:431–435. [PubMed: 19952989]

26. de Carlo TE, Romano A, Waheed N, Duker JS. A review of Optical Coherence Tomography Angiography (OCTA). International Journal of Retina and Vitreous. 2015; 1:5. [PubMed: 27847598]

27. Matsunaga D, Yi J, Puliafito CA, Kashani AH. OCT angiography in healthy human subjects. Ophthalmic Surg Lasers Imaging Retina. 2014; 45:510–515. [PubMed: 25423629]

28. Jia Y, Bailey ST, Hwang TS, McClintic SM, Gao SS, Pennesi ME, et al. Quantitative optical coherence tomography angiography of vascular abnormalities in the living human eye. Proc Natl Acad Sci U S A. 2015; 112:E2395–E2402. [PubMed: 25897021]

29. Moul E, Choi W, Waheed NK, Adhi M, Lee B, Lu CD, et al. Ultrahigh-speed swept-source OCT angiography in exudative AMD. Ophthalmic Surg Lasers Imaging Retina. 2014; 45:496–505. [PubMed: 25423628]

30. Choi W, Mohler KJ, Potsaid B, Lu CD, Liu JJ, Jayaraman V, et al. Choriocapillaris and choroidal microvasculature imaging with ultrahigh speed OCT angiography. PLoS ONE. 2013; 8:e81499. [PubMed: 24349078]

31. Unterhuber A, Povazay B, Hermann B, Sattmann H, Chavez-Pirson A, Drexler W. In vivo retinal optical coherence tomography at 1,040 nm - enhanced penetration into the choroid. Opt Express. 2005; 13:3252–3258. [PubMed: 19495226]

32. Povazay B, Hermann B, Unterhuber A, Hofer B, Sattmann H, Zeiler F, et al. Three-dimensional optical coherence tomography at 1,050 versus 800 nm in retinal pathologies: enhanced performance and choroidal penetration in cataract patients. J Biomed Opt. 2007; 12:041211. [PubMed: 17867800]

33. Adhi M, Liu JJ, Qavi AH, Grulkowski I, Lu CD, Mohler KJ, et al. Choroidal analysis in healthy eyes using swept-source optical coherence tomography compared to spectral domain optical coherence tomography. Am J Ophthalmol. 2014; 157:1272–1281.e1. [PubMed: 24561169]

34. Jia Y, Tan O, Tokayer J, Potsaid B, Wang Y, Liu JJ, et al. Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. Opt Express. 2012; 20:4710–4725. [PubMed: 22418228]

35. Tokayer J, Jia Y, Dhalla AH, Huang D. Blood flow velocity quantification using split-spectrum amplitude-decorrelation angiography with optical coherence tomography. Biomed Opt Express. 2013; 4:1909–1924. [PubMed: 24156053]

36. Kraus MF, Potsaid B, Mayer MA, Bock R, Baumann B, Liu JJ, et al. Motion correction in optical coherence tomography volumes on a per A-scan basis using orthogonal scan patterns. Biomed Opt Express. 2012; 3:1182–1199. [PubMed: 22741067]

37. Nagiel A, Sadda SR, Sarraf D. A promising future for optical coherence tomography angiography. JAMA Ophthalmol. 2015; 133:629–630. [PubMed: 25856444]

38. Lengyel I, Tufail A, Hosaini HA, Luthert P, Bird AC, Jeffery G. Association of drusen deposition with choroidal inter-capillary pillars in the aging human eye. Invest Ophthalmol Vis Sci. 2004; 45:2886–2892. [PubMed: 15326099]

39. Sarks SH, Arnold JJ, Killingsworth MC, Sarks JP. Early drusen formation in the normal and aging eye and their relation to age related maculopathy: a clinicopathological study. Br J Ophthalmol. 1999; 83:358–368. [PubMed: 10365048]
40. Mullins RF, Johnson MN, Faidley EA, Skeie JM, Huang J. Choriocapillaris vascular dropout related to density of drusen in human eyes with early age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011; 52:1606–1612. [PubMed: 21398287]
Fig. 1.
A composite image of a color photo (a) and a same-day swept-source optical coherence tomography (OCT) angiography (OCTA) image and the corresponding en face OCT intensity image at the level of the choriocapillaris (CC) (b, c) and a spectral-domain OCTA image with the corresponding en face OCT intensity image at the level of the CC (e, f) and the corresponding B-scan (d). The green arrows show an area of shadowing under drusen, visible as a dark area on both the intensity and angiographic images. Note that the swept-source OCTA (b) image has less pronounced shadowing in the area underneath the drusen than the spectral-domain OCTA image (e), likely due to improved choroidal penetration at longer wavelengths. The corresponding OCTA image (b) shows a relatively normal CC with little, if any, dropout of the CC.
Fig. 2.
Fundus autofluorescence, OCT and OCTA in a 75-year-old patient with nonexudative age-related macular degeneration with geographic atrophy (GA). The fundus autofluorescence (a) and mean en face projection of the entire OCT volume (b) clearly show the region of GA, outlined by the yellow dashed contour (b). The GA region appears lighter due to increased light penetration into the choroid caused by retinal pigment epithelium atrophy. c The mean en face projection of the OCTA volume through the depths spanned by the retinal vasculature; the vasculature appears normal. (d) A 4.4-μm-thick en face OCTA slab at the
CC level obtained using a 1.5-ms interscan time. The yellow dashed contour from (b) is superimposed, and a severe CC alteration appears within it. The severe CC alteration is also evident outside of the GA margin. (e) The same 4.4-μm-thick en face OCTA CC slab as (d), obtained using a 5.0-ms interscan time. Note how some areas with a low decorrelation signal (d) have increased decorrelation (e), suggesting flow impairment rather than complete atrophy. Enlarged views of the solid orange and green boxes (d, e) are shown (f, g), respectively. Note that some choroidal vessels that are not visible (f) become visible (g). Enlarged views of the dashed orange and green boxes (d, e) are shown (h, i), respectively. Note that some of the regions with low decorrelation signals (h) have higher decorrelation signals (i), suggesting flow impairment along the GA margin. OCT (top) and OCTA (bottom) B-scans through the red, blue, and purple horizontal dashed lines (d) are shown (j–l), respectively. All scale bars are 1 mm.
Variable interscan time analysis. OCTA images are generated using 5 repeated B-scans at the same location, with a time interval of 1.5 ms between each scan. Comparisons between B-scans are used to generate the decorrelation signal. Decorrelation signals can be generated by comparing adjacent B-scans, with an interscan time of 1.5 ms (a), or between every second B-scan, increasing the interscan time to 3 ms (d). Figures (b, e) show schematic representations of how the decorrelation signal varies with the erythrocyte flow speed. Areas with no flow generate a decorrelation signal that appears black, while areas with high flow appear as white on OCTA. The dynamic range of OCTA for each interscan time is marked with brackets, indicating the slowest detectable flow and the fastest distinguishable flow. The asterisk, square, and circle indicate three hypothetical flow speeds. The slow flow,
marked with the asterisk, does not fall within the OCTA *dynamic range* with the 1.5-ms interscan time, and it cannot be seen on the corresponding OCTA (c). However, when the interscan time is increased to 3 ms, this slow flow can be visualized. When the interscan time is increased to 3 ms, many vessels are visible that are either partially visible or absent on OCTA with an interscan time of 1.5 ms (d). Conversely, comparing OCTA with a 3.0-ms interscan time to OCTA with a 1.5-ms interscan time identifies area of flow impairment that are not distinguishable on the image obtained with a 3.0-ms interscan time alone. The scale bars are 250 μm, and the images are enlarged views from a 6 × 6 mm field of view.