Relationship Between Choriocapillaris Flow and Scotopic Microperimetry in Early and Intermediate Age-related Macular Degeneration

MARCO NASSISI, TUDOR TEPELUS, GIULIA CORRADETTI, AND SRINIVAS R. SADDA

• PURPOSE: To evaluate the correlation between choriocapillaris (CC) flow alterations and scotopic macular sensitivity (sMS) in patients with early and intermediate age-related macular degeneration (AMD).
• DESIGN: Prospective cross-sectional study.
• METHODS: We acquired 2 3 × 3 mm and 2 6 × 6 mm swept-source optical coherence tomography angiography (OCTA) images of 1 eye of consecutive early or intermediate AMD patients at the Doheny UCLA Eye Centers. After 30 minutes of dark adaptation, the same eye underwent scotopic microperimetry with an 18-degree-wide grid (52 stimuli) centered on the fovea. The 2 en face CC angiograms obtained from each scan pattern were compensated for signal loss and averaged. The main outcome measures were correlation between percentages of flow deficits (FD_{3mm} and FD_{6mm}) and sMS in the central 10° (MS_{10}) and the overall pattern (MS_{18}).
• RESULTS: Thirty eyes of 30 patients were enrolled, with 14 (46.7%) having subretinal drusenoid deposits (SDD). In the averaged OCTA scans, the FD_{3mm} was 12.56% ± 2.41% while the FD_{6mm} was 9.33% ± 1.84%. The mean MS_{10} and MS_{18} were 13.84 ± 5.89 dB and 14.64 ± 5.21 dB, respectively. For the MS_{10}, the multivariate regression analysis showed a significant association only with FD_{3mm} (β: −0.628, $P < .001$) while the MS_{18} was significantly correlated with both SDD (β: −0.32, $P = .047$) and FD_{6mm} (β: −0.473, $P = .005$).
• CONCLUSIONS: Our study reports a significant correlation between the CC flow impairment and the sMS in eyes with early or intermediate AMD. If replicated in future longitudinal studies, the choriocapillaris FD may prove to be a useful parameter for evaluating the functional status and prognosis of these eyes. (Am J Ophthalmol 2021;222:302–309. © 2020 Elsevier Inc. All rights reserved.)

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INTRODUCTION

AGE-RELATED MACULAR DEGENERATION (AMD) IS A progressive disease characterized by the accumulation of drusen at the level of the macula. In its late stages, AMD leads to an irreversible central vision loss; it is often associated with the conservation of a good visual function in its early and intermediate stages.[1] Several studies investigating the pathogenesis of AMD have shown that alterations to the photoreceptors, retinal pigment epithelium (RPE), Bruch membrane, and choriocapillaris (CC) complex are relevant to the progression of the disease.[2–4] Whether the RPE or CC are the first site of degeneration is still a topic of debate, but recent studies have suggested that CC alterations may play a primary role in disease pathophysiology.[5–8] Optical coherence tomography angiography (OCTA) has created an opportunity to study the choriocapillaris in vivo at high resolution and without the need for dye injection.[9,10] In particular swept-source OCTA (SS-OCTA) with its deep light penetration (wavelength: 1,050 nm) provides high-quality images of the CC meshwork, which may resemble histologic images in healthy eyes.[11–13] Furthermore, the quality of the images may be significantly improved with postacquisition processing methods such as the averaging of multiple images from multiple acquisitions.[14–16] Although several studies have investigated the structural characteristics of the CC in various stages of AMD and correlated the status of the CC with disease progression,[17–20] few studies have correlated CC alterations with photoreceptor impairment reflected by visual function.[21–23] Scotopic microperimetry is a promising diagnostic method that can evaluate the function of the rods.[24] Abnormalities of the sensitivity of the rods may precede the impairment of the cones in several retinal diseases, such as rod-cone dystrophy, pigmentary retinopathy, retinal telangiectasia, and congenital stationary night blindness.[25–27] Recent histologic evidence shows that rods can be damaged earlier than cones in the early stages of age macular degeneration, particularly in parafoveal regions where they are found in greater numbers.[28–30] In line with this morphologic data, there is evidence that patients with AMD may demonstrate impairment in scotopic function and dark adaptation.[24,31–34] In this study, we investigated the relation between CC flow deficits and scotopic

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function (as assessed by microperimetry) in patients with early and intermediate AMD.

METHODS

IN THIS PROSPECTIVE STUDY, SS-OCTA IMAGES WERE ACquired in consecutive patients with early or intermediate AMD[35] who were evaluated at the Doheny UCLA Eye Centers by 1 physician (S.R.S.) between January and August 2018. Eligible patients had early or intermediate AMD according to the Beckman classification.[35] Eyes with non–visually significant vitreoretinal interface disease, such as a subtle epiretinal membrane only visible by OCT, were not excluded. Patients affected by any other ocular diseases, including vascular and/or inflammatory diseases; patients who had previous retinal surgery; those with a refractive error greater than 6 diopters; and/or those with the presence of significant media opacities that could impact the quality of the OCT images were excluded from the study. The study was performed in accordance with the Health Insurance Portability and Accountability Act and adhered to the principles of the Declaration of Helsinki. All subjects provided written informed consent to participate in this observational study. The informed consent form and research was approved by the institutional review board of the University of California–Los Angeles (UCLA). All patients underwent a complete ophthalmic examination, including best-corrected visual acuity (BCVA) with test of refraction, using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts, slit-lamp biomicroscopy, tonometry, and SS-OCTA.

• **IMAGING:** Patients underwent SS-OCTA imaging with the PLEX Elite 9000 device (Carl Zeiss Meditec, Dublin, California, USA), which uses a swept laser source with a central wavelength of 1,050 nm (1,000-1,100 nm full bandwidth) and operates at 100,000 A-scans per second. This instrument employs a full-width at half-maximum axial resolution of approximately 5 μm in tissue and a lateral resolution at the retinal surface estimated at approximately 14 μm. OCTA imaging of the macula was performed using a scan pattern with a 3 × 3 mm area (300 A-scans × 300 B-scans) and a 6 × 6 mm area (500 A-scans × 500 B-scans) both centered on the fovea. Each eye was repeatedly imaged with pupil dilation to obtain 2 OCTA volume scan sets per pattern with sufficient image quality (signal strength index >7) that fulfilled the acceptance criteria of the Doheny Image Reading Center, as previously reported.[16] A fully automated retinal layer segmentation algorithm was applied to the 3-dimensional structural OCT data in order to segment the CC slab as defined previously (10 μm thick starting 31 μm below the RPE fit).[16,36] Scans were evaluated for any segmentation errors, which were manually corrected. This segmentation was then applied to OCTA flow intensity data to obtain vascular images. The maximum flow projection method was used to generate the en face images of the CC plexus (1,024 × 1,024 pixels). Before exporting all angiograms, projection artifact removal was performed using the automated algorithm of the instrument software.[37,38] Postacquisition image processing to compensate for CC signal attenuation resulting from the RPE and pathologic alterations at the RPE/BM complex level (eg, basal laminar deposits) was performed using a previously described method.[14] For each eye, the resulting compensated CC en face images generated from 2 different OCTA cube scan sets were stacked to create a 2-frame video and were registered before multiple image averaging.[16] A central square area of 819 × 819 pixels was cropped for registration and averaging. Registration was first performed on the 2-frame video based on the superficial capillary plexus en face images, as previously reported. This same transformation was then applied to the CC layer, as described in detail in a previous publication.[16] After registration, the 2 frames of the CC were compounded into a single image by projecting the average intensity (Figure 1).

The resultant averaged CC en face image was exported and analyzed using ImageJ software V.1.50 (National Institutes of Health, Bethesda, Maryland, USA; available at http://rsb.info.nih.gov/ij/index.html)[39] and binarized for quantitative image analysis of the signal voids. Flow deficits were defined as a percentage of the area of the region with flow below a fixed threshold and the area of the entire scanned region. The threshold for flow deficits was determined by 1 standard deviation (SD) from a normal database (20 subjects at 20-39 years old) as previously described.[14] Finally small flow deficits (diameter < ~24 μm) were removed from the obtained map, as they have been suggested to be within normal intercapillary spacing and within normal oxygen diffusion capability.[15] The resultant images were then processed with the Analyze Particles command in order to count the flow deficits as a percentage of the area analyzed (FD_{3mm} and FD_{6mm}). Structural OCT images were also used to assess the mean central retinal thickness (CRT, central millimeter), central choroidal thickness (CCT), drusen volume, and presence of subretinal drusenoid deposits (SDDs). CCT was measured manually at the foveal center from Bruch membrane to the choroid-sclera border. To ensure the repeatability of the method, the measurements were repeated twice by 2 independent reading center graders. Then, the average of the 2 measurements was taken for the analysis. Drusen volumes in the central circular 3 × 3 and 5 × 5 mm (DV_{3mm} and DV_{5mm}) were generated using automated instrument Advanced RPE Analysis software (version 0.4, Carl Zeiss Meditec, Dublin, California, USA). SDD (corresponding to reticular pseudodrusen on infrared reflectance) was qualitatively assessed and deemed to be present when at least 3 SDD were evident on a single B-scan.

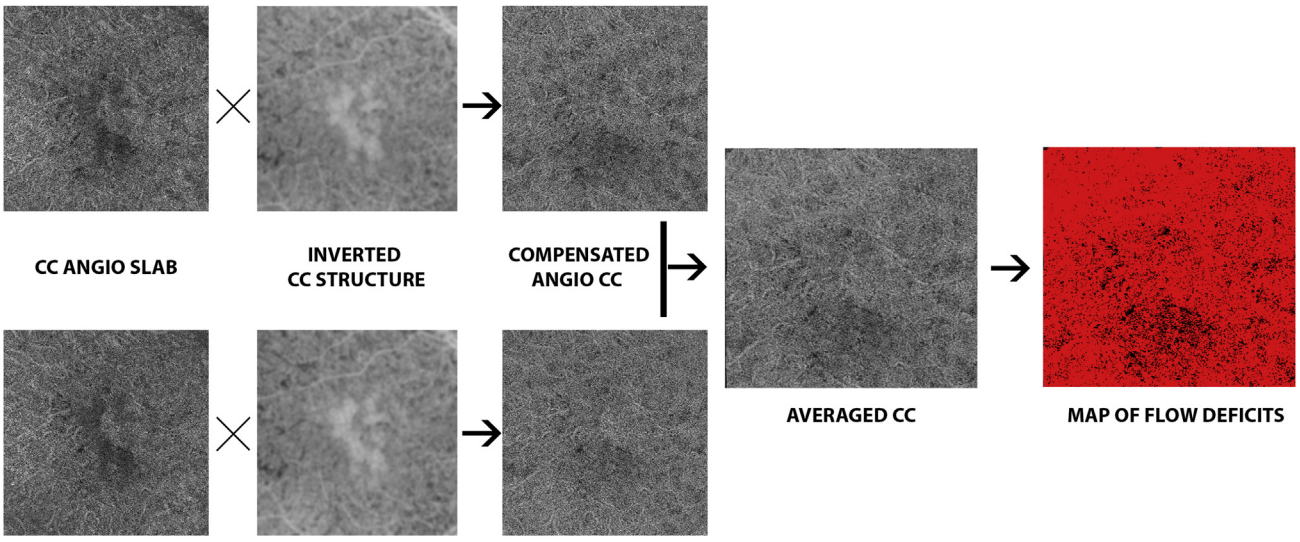

FIGURE 1. Two different acquisitions underwent an identical postacquisition quality enhancement strategy by signal compensation and averaging, in order to obtain the final high-quality image of the choriocapillaris flow. The resultant angiogram was then thresholded to allow the analysis of the flow deficits. CC = choriocapillaris.

• **MICROPERIMETRY:** All subjects underwent scotopic examinations of the central retina in the study eye following pupil dilatation and dark adaptation for 30 minutes, using the modified Macular Integrity Assessment device (S-MAIA, CenterVue Spa, Padova, Italy).[40] Prior to testing, instructions regarding the testing procedure were given, and the correct operation of the subject response trigger was practiced. Testing parameters included a Goldmann size III stimulus, 200 ms presentation time; 4-2 strategy threshold, and 52 stimulus points distributed within a circular area approximately 18° in diameter, centered on the fovea (Figure 2).

A high fixation loss rate (>30%) was prespecified as a criterion for exclusion. The mean sensitivity calculated in the central 10° × 10° (MS_{10}, 37 stimuli) was correlated with the 3 × 3 mm OCTA while the mean sensitivity of the overall pattern (MS_{18}) was correlated with the 6 × 6 mm OCTA.

• **STATISTICS:** Statistical analyses were performed using SPSS Statistics V.20 (IBM Corp., Armonk, New York, USA). The normal distribution of the data was verified using the Shapiro-Wilk test. Inter-operator repeatability for CCT measurement was assessed by calculating the intraclass correlation coefficient (ICC). This was also calculated to evaluate the difference in the percentage of flow deficits between the 2 repeated acquisitions and then their respective compensated images. A univariate linear regression was used to correlate the MS_{10} and the MS_{20} with age, type of AMD, drusen volume, presence of SDD, CCT, CRT, and CC flow deficits. When 2 or more variables showed significant correlations, a multivariate linear regression was performed. All data are presented as mean ± SD; $P < .05$ was considered significant.

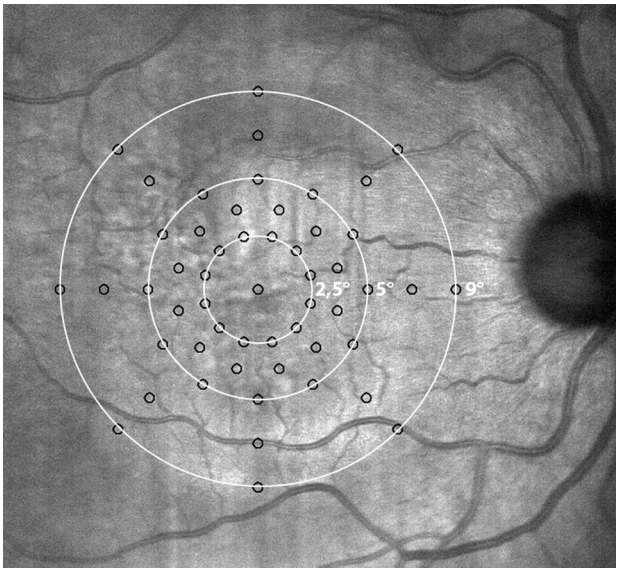

FIGURE 2. Test pattern for the scotopic assessment (52 stimulus points centered on the fovea) within the central 18°.

RESULTS

THIRTY EYES OF 30 CONSECUTIVE PATIENTS (16 FEMALE, mean age: 77.69 ± 8.17, range: 65-95) with early (23 patients) or intermediate (7 patients) AMD were recruited. When both eyes were eligible for the study, the right eye was chosen for the examination. Mean BCVA was 0.19 ± 0.18 LogMAR (20/32 Snellen equivalent, median: 20/32, range: 20/200-20/20). Fourteen out of the 30 eyes (46.7%) had evidence of SDD. Mean CRT was 273.13 ±

TABLE. Results of the Linear Regression Analysis Assessing the Association Between Scotopic Mean Sensitivity and Age, Type of AMD (Early or Intermediate), SSDs, CRT, CCT, DV_{3mm}, DV_{5mm}, FD_{3mm}, and FD_{5mm}

	Mean Sensitivity 10°				Mean Sensitivity 20°			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	β Coefficient	*P* Value	β Coefficient	*P* Value	β Coefficient	*P* Value	β Coefficient	*P* Value
Age	−0.105	.589	—	—	−0.124	.522	—	—
Type of AMD	−0.234	.213	—	—	−0.213	.259	—	—
SSD	−0.386	.035	−0.129	.404	−0.409	.025	−0.32	.047
CRT	−0.146	.441	—	—	−0.158	.404	—	—
CCT	0.043	.822	—	—	0.05	.795	—	—
DV_{3mm}	−0.243	.196	—	—	—	—	—	—
DV_{5mm}	—	—	—	—	−0.169	.373	—	—
FD_{3mm}	−0.681	<.001	−0.628	<.001	—	—	—	—
FD_{6mm}	—	—	—	—	−0.533	.002	−0.473	.005

AMD = age-related macular degeneration; CCT = central choroidal thickness; CRT = central retinal thickness; DV_{3mm} = Drusen volume within a circular area of 3 mm; DV_{5mm} = Drusen volume within a circular area of 3 mm; FD_{3mm} = percentage of flow deficits in the 3 × 3 mm optical coherence tomography angiography scan; FD_{6mm} = percentage of flow deficits in the 6 × 6 mm optical coherence tomography angiography scan; SSD = subretinal drusenoid deposits (SSDs).

32.48 μm. CCT was 242.22 ± 92 μm. Mean DV_{3mm} and DV_{5mm} were 0.03 ± 0.05 and 0.04 ± 0.07 mm^3, respectively. In the averaged scans, the FD_{3mm} was 12.56% ± 2.41% while the FD_{6mm} was 9.33% ± 1.84%. All subjects were able to perform the scotopic microperimetry successfully, yielding a mean scotopic MS_{10} of 13.84 ± 5.89 dB and a mean scotopic MS_{18} of 14.64 ± 5.21 dB.

• **CHORIOCAPILLARIS VS SCOTOPIC FUNCTION CORRELATION:** The results of the regression analysis are shown in the Table.

For the $MS_{10,}$ the univariate linear regression analysis showed a significant association with the presence of SDD (standardized coefficient β: −0.386, $P = .035$) and an even stronger association with the FD_{3mm} (β: −0.681, $P < .001$). In the multivariate analysis, only the association with FD_{3mm} remained significant (β: −0.628, $P < .001$). For the $MS_{18,}$ the univariate linear regression analysis showed a significant association with the presence of SDD (standardized coefficient β: −0.409, $P = .025$) and the FD_{6mm} (β: −0.533, $P = .002$). In the multivariate analysis, the association remained significant for both SDD (β: −0.32, $P = .047$) and FD_{6mm} (β: −0.473, $P = .005$) with an overall correlation coefficient of the model R = 0.635.

• **REPEATABILITY ANALYSIS:** The CCT had an ICC of 0.987 (95% confidence interval [CI]: 0.972-0.994). The FD_{3mm} had an ICC of 0.899 (0.787-0.952) and of 0.908 (0.806-0.956) for the noncompensated and the compensated acquisitions, respectively. The FD_{6mm} had an ICC of 0.893 (0.774-0.949) and 0.895 (0.780-0.950) for the noncompensated and compensated acquisitions, respectively.

DISCUSSION

THIS STUDY EVALUATED THE CORRELATION BETWEEN THE impairment of the CC flow as assessed by OCTA and the scotopic sensitivity in patients with early or intermediate AMD (Figure 3).

A physiologic decline of the number of rods with age has been documented and a disorganization of the outer segments with an irregular loss of the nuclei of the photoreceptors has been shown to gradually occur.[24,41,42] Histologic studies demonstrated that rod density can decrease by 30%, with a topographic decline that culminates in a ring of greatest loss at 0.5 to 3 mm eccentricity in older individuals.[28,29] This loss of rods appears to exceed that of loss of cones, and this has been confirmed by functional studies that show that the loss of scotopic sensitivity is greater (about double) than the loss of photopic sensitivity.[43,44] This is particularly evident in patients affected by AMD. For example, Feigl and associates. demonstrated a significant delay in the average response of rods in the multifocal electroretinogram of patients with early AMD compared to the control group, while the average cone-mediated responses were within the normal range.[45] Owsley and associates' findings also support this concept as they observed that rod function (assessed by scotopic sensitivity) showed a greater impairment in AMD patients than age-matched control subjects.[42] Thus, in many patients, tests of rod function may permit detection of AMD at earlier stages than other standard tests of cone function such as visual acuity.[46]

The RPE, Bruch membrane, and the choroid are vitally important for the well-being of the photoreceptors. Dysfunction of the RPE or an impairment to the CC blood flow could cause a slowdown in photopigment formation with resultant dysfunction and loss of photoreceptor cells,

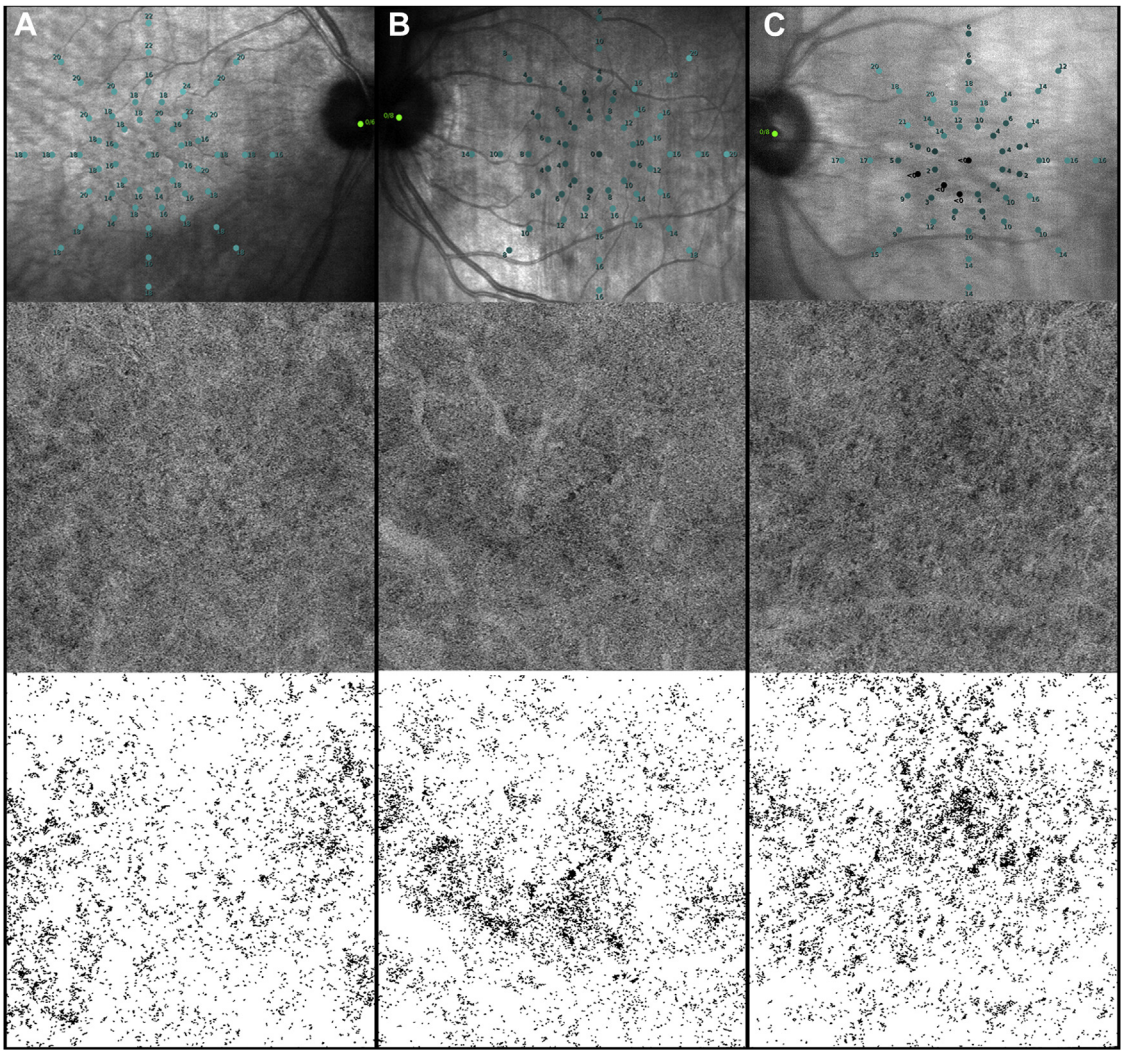

FIGURE 3. One eye of 3 patients with intermediate AMD (A,B,C) included in the study. Patient A shows an overall mean scotopic sensitivity (MS_{18}) of 18.03 dB (top) while Patient B has an MS_{18} of 10.03 dB. As seen in the 6 × 6 mm choriocapillaris optical coherence tomography angiography slabs (middle) and in the relative thresholded version (bottom), Patient A shows less extensive flow deficits (FD) than Patient B (6.5% and 9.3%, respectively). Both Patient A and Patient B do not show subretinal drusenoid deposits (SDD). SDD are present in Patient C, who showed a lower MS_{18} (9.83 db) as well as a higher percentage of FD (11.21), compared with both patients without SDD.

especially in the parafoveal area, which has a greater density of rods.[43]

Recently, several studies have suggested that the status of the CC on OCTA may prove to be useful as an early biomarker of the status of the overlying RPE in both early and intermediate AMD, as well as in the fellow eyes of neovascular AMD patients.[5,47,48] Furthermore, CC alterations can predict the incidence and enlargement of drusen as well as the incidence and the progression of RPE atrophy.[17–19]

The perfusion of the CC has been correlated with multifocal electroretinography, and in particular it was related to the N1 implicit times, suggesting an association with photoreceptor function.[21] In our study, we demonstrated that the CC perfusion was significantly associated with the scotopic sensitivity in patients with early and intermediate AMD. We also found an association between the presence of SDD and scotopic sensitivity.

This association was significant in both univariate and multivariate regression analysis only for the 6 × 6 mm acquisition. Considering that the distribution of the SDD is often in the more peripheral sectors of the macula, it might not be surprising that the correlation becomes stronger with the inclusion of more peripheral stimuli in the scotopic microperimetric test pattern.

This is in line with recent studies that demonstrated rod function is more severely affected than cone function in retinal areas with SDD.[23] As SDD are proven risk factors

for progression to late AMD (either exudative or geographic atrophy),[49,50] our study further confirms the functional relevance of SDD in patients with AMD. Unfortunately, we were not able to perform a precise automated quantification of SDD nor the analysis of their exact localization to see whether the correlation with scotopic microperimetry would improve. This step is mostly limited by the available technology, which still does not allow reliable measurements. Further investigations will be required to better clarify this point. Our study is not without limitations, including the small sample size, its cross-sectional nature, and the lack of age-matched control for the scotopic microperimetry. In addition, although there is now an extensive literature on CC quantification using the methods and strategies described in this report, validation against histology or adaptive optics–based visualization of the CC is still lacking. Furthermore, although we used projection artifact removal and signal compensation to remove artifacts, the impact of these techniques also requires validation. Recently, Camino and associates. used a machine learning approach, which, in contrast to our method, does not rely on reflectance to detect significant shadowing in the angiograms. This technique would allow the removal of shadowing even under large drusen whose height and density might block the backscattered light without retrievable OCTA signal. However, in our cohort of early and intermediate AMD patients, we did not encounter large drusen with such a severe degree of shadowing, and thus we were able to achieve a reliable compensation of the signal based on OCT reflectance.[51] Finally, the best processing strategies (optimal slab selection, thresholding approach) for visualization and quantification of the CC are still evolving. Given all of these concerns, it may be premature at this time to claim that we are visualizing the true CC using our approach. On the other hand, we have shown that our approach is repeatable, and the CC flow deficits quantified in this way do appear to correlate with other markers of interest. Thus, these CC flow deficits have potential value as biomarkers in AMD. Future prospective, longitudinal studies assessing the progression of the CC and scotopic impairment over time, and their relevance to overall AMD disease progression over time, will be important to best define how these biomarkers may be used. In summary, we observed that CC flow deficits appeared to correlate with scotopic sensitivity by microperimetry in eyes with early and intermediate AMD. These findings further highlight the relevance of the CC pathophysiology of AMD.

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