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Correlation Between Choriocapillaris Density and Retinal Sensitivity in Age-Related Macular Degeneration

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Purpose: The purpose of this study was to investigate the relationship between perfusion of the choriocapillaris (CC) and retinal sensitivity in eyes with intermediate age-related macular degeneration (iAMD).

Methods: This prospective study included patients with iAMD and healthy controls. All enrolled subjects underwent optical coherence tomography angiography (OCT-A) in order to compute the percent perfused choriocapillaris area (PPCA). In patients with iAMD, microperimetry (MP) testing was performed in order to quantify: mean retinal sensitivity (MRS), over an area of 10 degrees; mean macular sensitivity (MMS), over the macular area scanned with OCT-A; and retinal sensitivity (RS) in each macular point.

Results: Eighteen eyes of 13 patients were included in the analysis. In addition, 18 eyes of 12 healthy subjects were enrolled as controls. No statistically significant difference (P value > 0.2) was observed in age between patients (73.9 ± 2.0 years) and controls (70.1 ± 2.8 years). We observed significantly lower values of PPCA between patients with iAMD and healthy controls ($42.0\% \pm 3.8\%$ vs. $66.4\% \pm 3.0\%$; $-\beta = 23.8\%$; P value < 0.001). Among iAMD eyes, higher values of PPCA were significantly associated with higher values of MRS (P value $= 0.002$) and MMS (P value $= 0.013$). Finally, higher values of RS in each macular point analyzed with MP were significantly (P value < 0.001) associated with higher values of PPCA computed in circular regions of interest (ROIs) centered in each analyzed MP point with radii of 0.5 degrees and 1.0 degree.

Conclusions: Using OCT-A, we demonstrated a significant association between CC impairment and macular dysfunction, quantified by MP, in iAMD eyes.

Translational Relevance: OCT-A could be a useful tool for detecting CC alterations and to monitor disease progression.

Introduction

Age-related macular degeneration (AMD) is a multifactorial disease and is the leading cause of vision loss among the elderly in developed countries. Two types of AMD, the "dry" (or atrophic) and "wet" (or neovascular) forms of the disease, have been extensively described. However, the current clinical classification of AMD defines three stages according to the severity of fundus lesions (drusen size and pigmentary abnormalities) assessed within 2-disc diameters of the fovea in persons aged > 55 years.[1] This basic clinical classification scale defining early, intermediate, and late AMD, including geographic atrophy (GA) and neovascularization, also is of value in predicting risk estimates of progressing to advanced AMD stages. Early AMD is characterized by the presence of drusen in diameter $>$ 63 µm and < 125 µm without pigmentary abnormalities. Intermediate AMD (iAMD) is clinically characterized by the accumulation of drusen > 125 µm in diameter with or without pigmentary abnormalities and can progress to the late form of AMD. The late form of AMD is characterized by choroidal or retinal neovascularization or GA. A recent meta-analysis,[2] including 14 studies conducted in European Countries, showed

a prevalence of early AMD increasing with age from 3.5% at 55 to 59 years to 17.6% in persons aged ≥ 85. Similarly, the prevalence of late AMD rose from virtually zero in the youngest age group to 9.8% for those in the highest age group.

Despite the high prevalence of the disease, the etiology of AMD remains largely unknown. Although several factors are thought to be implicated in the pathogenesis of this disorder, a strong body of evidence suggests that AMD may be ultimately characterized by alterations of the photoreceptors, retinal pigment epithelium (RPE), Bruch's membrane, and choriocapillaris (CC) complex.[3,4] The CC is a highly specialized capillary layer (approximately 10 µm thick) located at the inner aspect of the choroid and one of its functions is to supply oxygen and metabolites to the RPE and photoreceptors.[5] Because the CC may play a relevant role in the etiopathogenesis of the disease, CC loss in relationship with AMD has been investigated in several studies.[6–9]

Recent imaging advancements using optical coherence tomography angiography (OCT-A) enabled to detect blood flow and to visualize blood vessels at various depth-resolved levels of the retina and choroid without the need for dye injection.[10–12] Therefore, some previous studies adopted OCT-A to evaluate the blood flow of CC and investigated on the relationship between the alteration of CC flow and the loss of macular function in AMD.[6,13,14] These studies evaluated macular function through visual acuity[6,13] and only one study[14] adopted multifocal electroretinography, that is a relatively invasive and uncommon test in AMD. More recently, Nassisi et al.[15] showed in eyes with early and iAMD that CC flow deficits appeared to correlate with scotopic sensitivity by using scotopic microperimetry, a promising diagnostic method, which can evaluate the function of the rods. On the contrary, mesopic microperimetry (MP) is a simple test to evaluate macular sensitivity, particularly, related to macular cone function, also adopted in patients with AMD.[16] However, whereas previous studies investigated the correlation between macular sensitivity assessed by MP and CC flow loss in patients with Stargardt disease[17] and diabetic retinopathy,[18] to the best of the authors' knowledge, the correlation between macular sensitivity quantified by mesopic MP and CC flow loss was not evaluated in patients with AMD.

The aim of this study was to characterize the CC flow and retinal sensitivity in patients affected by iAMD, using an OCT-A device and MP, and to compare these examinations in order to find correlations between anatomic and functional data that could be of use for clinical practice.

Methods

In this prospective, observational, cross-sectional study, patients older than 55 years of age with iAMD in at least one eye were enrolled at the eye clinic of the University of Campania Luigi Vanvitelli, Italy. Healthy control subjects, negative to AMD screening, older than 55 years of age were also enrolled.

The study was approved by the institutional review board and adhered to the tenets of the Declaration of Helsinki. Informed consent approved by the institutional review board was obtained from all patients.

We followed the Ferris classification[1] for the diagnosis of iAMD eyes (i.e. presence of drusen > 125 µm in diameter) with or without pigmentary abnormalities as assessed by clinical examination and confirmed by dense volume OCT. Exclusion criteria for iAMD eyes were: poor quality images (i.e. an automated signal quality lower than 30 out of 40 evaluated by the equipment), significant artifact, pseudodrusen on the OCT scan; history of antivascular endothelial growth factor therapy; any maculopathy secondary to causes other than AMD (including the presence of an epiretinal membrane or vitreomacular traction syndrome); the presence of significant media opacities; myopia greater than 6.00 diopters; and any optic neuropathy, including glaucoma.

The healthy controls were excluded in case of significant media opacities in both eyes, myopia greater than 6.00 diopters, and any ocular pathology (e.g. glaucoma, diabetic retinopathy, and macular hole). Exclusion criteria for healthy controls' eyes were poor quality images (i.e. an automated signal quality lower than 30 out of 40 evaluated by the equipment), significant artifact; and the presence of significant media opacities.

All patients underwent a complete ophthalmic examination, including evaluation of best-corrected visual acuity (BCVA), measurement of intraocular pressure, slit-lamp biomicroscopy of anterior segment and fundus examination, MP, OCT, and OCT-A.

The healthy controls, enrolled after a screening visit for AMD, underwent only OCT and OCT-A.

BCVA was performed with 2 meters early treatment diabetic retinopathy study (ETDRS) charts. For the evaluation of intraocular pressure we used a Goldmann tonometer.

MP was performed by an automatic fundus-related perimeter (MP1 Microperimeter, Nidek Technologies, Padova, Italy). The following parameters were used: a fixation target of 2 degrees in diameter consisting

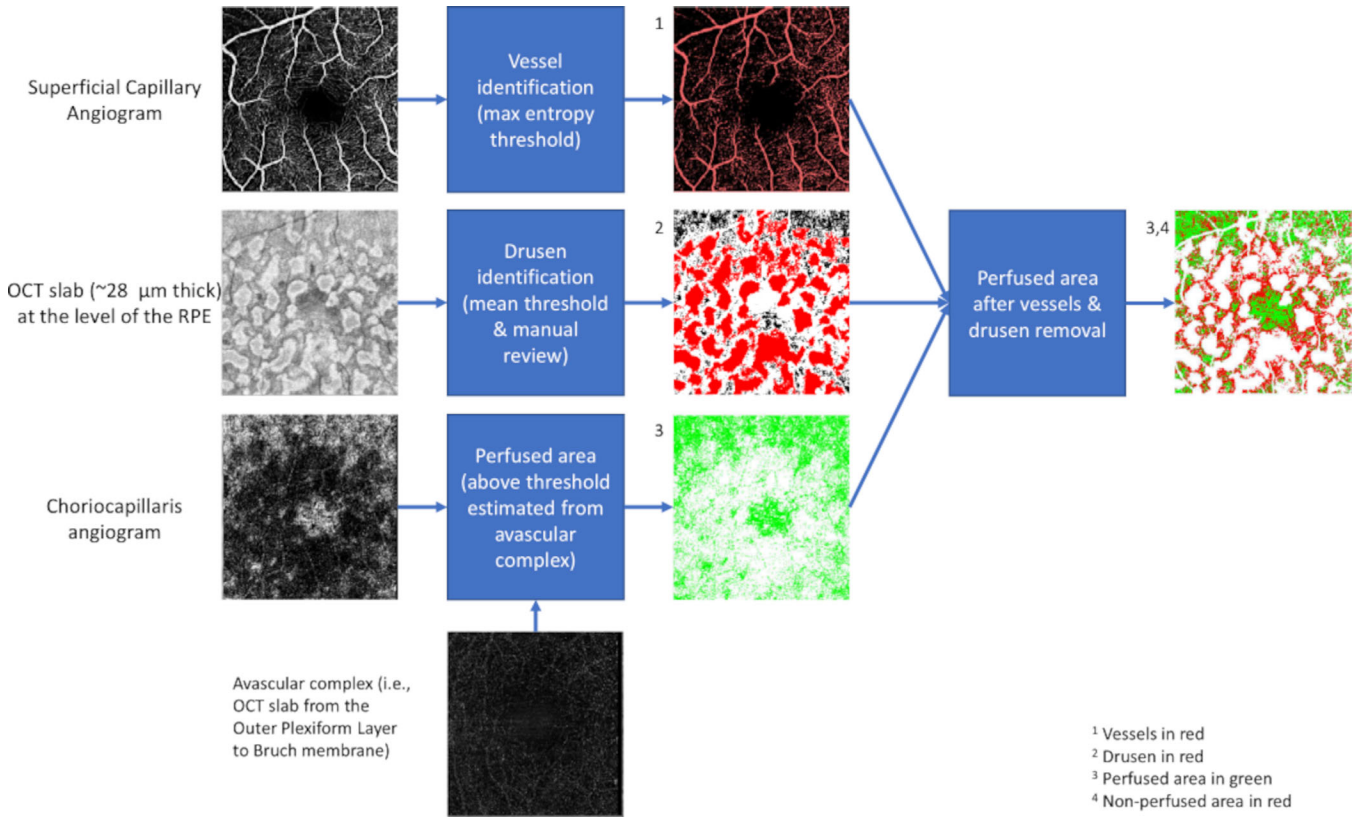

Figure 1. Workflow of image processing to measure area of perfusion of choriocapillaris.

of a red ring; a white, monochromatic background with a luminance of 1.27 cd/m^2; a Goldman III–size stimulus with a projection time of 200 ms; and predefined automatic macular test pattern covering 10 degrees centered onto the gravitational center of all the fixation points with 68 stimuli (Humphrey 10-2). The following MP parameters were computed: mean retinal sensitivity (MRS; i.e. average among the 68 analyzed points); mean macular sensitivity (MMS; i.e. average among the 16 analyzed macular points corresponding to the OCT-A scan area); retinal sensitivity (RS) in each analyzed point; the percentage of fixation points within 2 degrees (fixation stability [FS] 2 degrees) and within 4 degrees of the diameter circle (FS 4 degrees) centered at the gravitational center of all the fixation points. The percentage values were used to define three grades of fixation stability: (I) "stable," when more than 75% of fixations fall within the 2 degree circle; (II) "relatively stable," when more than 75% of fixations fall within the 4 degree circle; and (III) "unstable," when less than 75% of fixations fall within the 4 degree circle. RS measurements are expressed in dB with 0 dB and 20 dB corresponding to the ability to perceive a stimulus with the maximum luminance (i.e. 400 asb) and the minimum luminance (i.e. 4 asb), respectively. In other words, 0 dB and 20 dB correspond to the worst and best measurable RS, respectively.

OCT and OCT-A were performed with Spectralis OCT Plus (Heidelberg Engineering, Heidelberg, Germany). Imaging protocol for SD-OCT was a high-resolution volume centered in the fovea with 19 lines, 20 × 15 degrees, 9 frames automatic real time (ART). Two operators (authors L.D.P. and C.G.) evaluated the integrity of ellipsoid zone band (EZ). Imaging protocol for the OCT-A was a high-resolution volume centered in the fovea 10 × 10 degrees, 4 frames ART. The main outcome measurement was the percent perfused choriocapillaris area (PPCA), which represents a measurement of the total area of CC perfusion density.

To evaluate the PPCA we analyzed the images as already described[13,14] and Figure 1 summarizes the workflow of the image processing. In brief, the PPCA was computed as the percentage of pixels in the CC en face image (slab 30-µm thick starting 31 µm posterior to the RPE reference) above a "non-perfusion" (or noise) threshold, which was calculated as the mean of all pixel values in the outer avascular retina (slab autosegmented by the instrument from the Outer Plexiform Layer to Bruch membrane [BM]). The PPCA

was thus calculated as the number of pixels falling above the threshold divided by the total number of pixels in the analyzed area of CC. PPCA computation relied on image thresholding performed exclusively by automated algorithms, with the exception of manual revision of the drusen identification, as described in more detail below.

Notably, the CC directly beneath drusen, as well as under superficial retinal vessels, was excluded from the analysis to avoid shadowing or projection artifacts that could confound the analysis, as already shown.[13] In order to identify shadow artifacts generated by drusen, we created a map of the drusen using an en face structural OCT slab (approximately 28 microns thick) at the level of the RPE. We used this slab because it highlighted drusen elevating the RPE as hyporeflective lesions. The drusen were identified using mean threshold algorithm implemented with ImageJ and the segmentation was manually reviewed. The manual revision was performed independently by two authors (L.D.P. and C.G.) and in case of disagreement was adjudicated by a third author (S.R.). In order to identify shadows from retinal blood vessels, the superficial capillary angiogram was also segmented with ImageJ using Max entropy threshold algorithm. The segmentation was independently checked by two authors (L.D.P. and C.G.), who confirmed that no manual revision was required.

To perform the PPCA calculation, the drusen image, superficial capillary plexus angiogram, and the CC angiogram were imported into a custom MATLAB software (MathWorks, Inc., Natick, MA).

To correlate OCT-A and MP, we performed a rigid registration of the two selected images, using "automated feature matching" (implemented by Matlab) and then we considered circular areas (ROIs) of the same size centered on the zones analyzed with MP. We considered two different area sizes on OCT-A, with a radius of 0.5 degrees and of 1 degree. Each considered area was then analyzed and correlated to the sensitivity found in the same zone with MP. A total of 16 points, according to the numbers of points tested by MP in the OCT-A scan area were considered for each included eye.

Continuous variables are reported as mean ± standard error of the mean (SEM) and categorical variables are reported as counts (frequency). Regression models, estimated by a generalized estimating equation (GEE), were fitted to compare the PPCA between patients with iAMD and healthy controls, also with age adjustment, and to explore the correlation between PPCA and the other selected parameters (e.g. BCVA, MRS, MMS, …). Furthermore, we investigated the correlation between retinal sensitivity in each of 16 analyzed macular points and the PPCA measured in circular ROIs centered in each point with a radius of 0.5 degrees and of 1.0 degrees. GEEs were applied because this method could accommodate measurements in the same subjects (e.g. between the 2 eyes of the same subject; and measurements in different retinal areas of the same eye).[19]

Results

Of the 15 enrolled patients, only 18 eyes of 13 patients (5 men and 8 women) were included in the analysis, because 2 patients were excluded because of poor scan quality and for 8 patients only one eye is included, because the contralateral eye showed a different disease stage (e.g. early or late-stage AMD). In addition, 18 eyes of 12 healthy subjects (4 men and 8 women) were enrolled as controls. Actually, in six healthy subjects one eye was excluded because of poor scan quality (due to significant cataract). No statistically significant difference (P value > 0.2) was observed in age between patients (73.9 ± 2.0 years) and controls (70.1 ± 2.8 years). Mean BCVA in iAMD eyes was 0.27 ± 0.04 logMAR. MP showed a lower retinal sensitivity in iAMD eyes (MRS = 13.0 ±1.1 dB and MMS = 13.2 ± 1.0 dB) compared to normal subjects. Fixation was stable in all study eyes but one, which showed a relatively stable fixation: FS2 degrees and FS4 degrees, on average, were 93.7 ± 1.8% and 98.4 ± 0.6%, respectively. At SD-OCT the EZ band was preserved in all patients with iAMD, being only rarefied in correspondence to the drusen. Figure 2 shows the comparison of the CC slab and foveal SD-OCT in an eye with iAMD and a healthy subject, showing the reduction of CC flow in addition to the alterations of the EZ band in the iAMD eye.

At the OCT-A, we observed significantly lower values of PPCA between patients with iAMD and healthy controls (42.0% ± 3.8% vs. 66.4% ± 3.0%, -β = 23.8%, standard error [SE] = 5.3%, 95% confidence interval [CI] = −34.2% to −13.5%, P value < 0.001). Whereas the regression models failed to show a significant progression of PPCA with age ($\beta = -0.7$%/year, SE = 0.5; 95% CI = −1.6% to 0.2%, P value = 0.113), age-adjusted models confirmed the decreased PPCA in patients with iAMD compared to healthy controls (β = −22.2%, SE = 5.36%, 95% CI = −33.2% to −11.2%, P value < 0.001).

Among patients with iAMD, we observed a significantly decreased PPCA in the 150-µm-wide peri-drusen ring regions compared to the drusen-free regions (41.7% ± 3.2% vs. 54.4 ± 5.1%, mean difference = 12.7% ± 4.1%, P value = 0.010). We also investigated

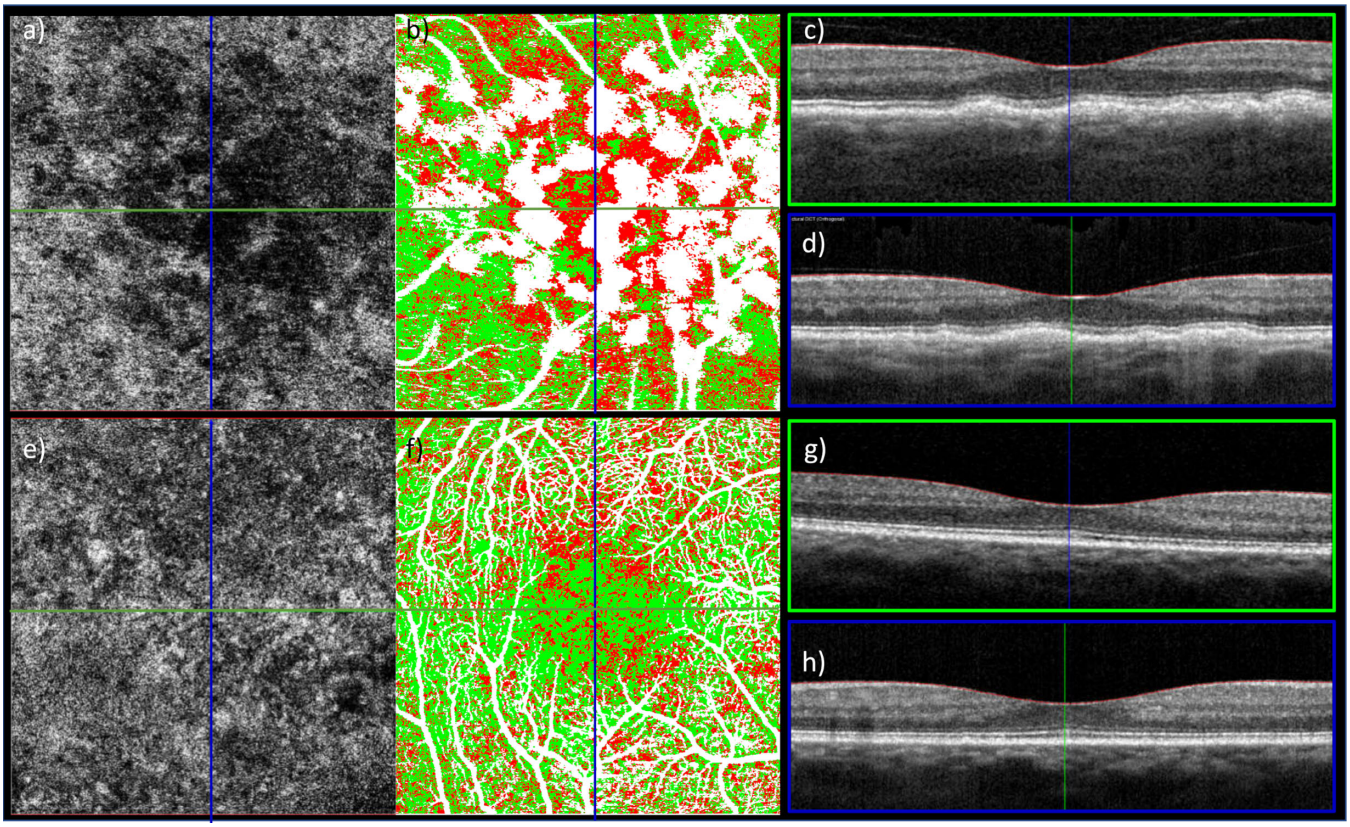

Figure 2. Comparison of the CC angiogram and foveal SD-OCT in an eye with iAMD and a healthy subject. The evaluation of CC angiogram in an iAMD eye (i.e. raw) (**a**) and processed CC slab (**b**) showed a reduction of CC perfusion compared to a healthy subject (i.e. raw) (**e**) and processed CC slab (**f**); in addition, horizontal (**c**) and vertical (**d**) OCT scans in the iAMD eye showed that EZ band is preserved, being only rarefied in correspondence to the drusen, compared horizontal (**g**) and vertical OCT scans (**h**) of a healthy subject.

the relationship between PPCA and the other selected parameters, showing no significant relationship (P value > 0.05) with BCVA and fixation parameters, whereas, as shown in Figure 3, lower values of PPCA were significantly associated with lower values of MRS ($\beta = 1.4\%$, SE $= 0.4\%$, 95% CI $= 0.5\%$ to 2.2%, P value $= 0.002$) and MMS ($\beta = 1.5\%$, SE $= 0.6\%$, 95% CI $= 0.3\%$ to 2.7%, P value $= 0.013$). Finally, lower values of RS in each macular point analyzed with MP were associated with lower values of PPCA computed in circular ROIs centered in each analyzed MP point with a radius of 0.5 degrees ($\beta = 0.4\%$, SE $= 0.9\%$, 95% CI $= 0.2\%$ to 0.5%, P value < 0.001) and 1.0 degree ($\beta = 0.8\%$, SE $= 0.1\%$, 95% CI $= 0.5\%$ to 1.0%, P value < 0.001), as shown in Figure 4.

Discussion

The current study investigated the correlation between alteration in CC perfusion, evaluated using OCT-A, and retinal dysfunction, quantified using MP in patients with iAMD. Overall, we found a reduced PPCA in areas not affected by drusen of iAMD eyes compared to control group. Moreover, among iAMD eyes, more reduced PPCA was associated with worse retinal sensitivity. To date, many studies have been carried out with OCT-A to investigate the role of CC perfusion in the pathogenesis of AMD, which are supported by numerous histopathological hypotheses that explain the reduced CC perfusion and includes: reduced CC flow velocity, reduced number of CC vessels per unit area or decreased CC vessel caliber.[13] All of these possibilities could result in hypoxia of RPE and photoreceptors, with consequent retinal dysfunction. To this regard, several histopathologic studies identified CC disfunction as a relevant factor for the development of AMD.[20–22] In particular, Biesemeier et al.[21] using optical and electron microscopy demonstrated a thickening of the Bruch membrane with the presence of multiple deposits between the RPE and its basement membrane and inside the Bruch membrane itself in eyes with AMD compared to controls. These alterations were associated with increased loss of photoreceptors, RPE cells, and CC.

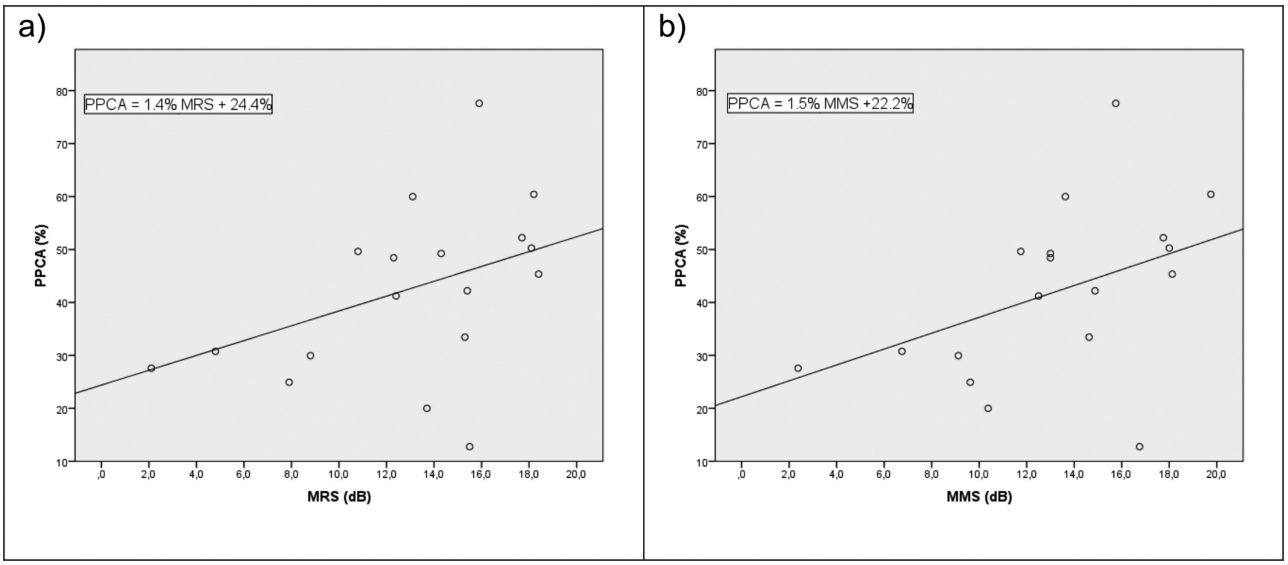

Figure 3. Plot of PPCA as function of MRS (**a**) and of MMS (**b**). Significant linear relationships were observed between PPCA and MRS (**a**) and between PPCA and MMS (**b**).

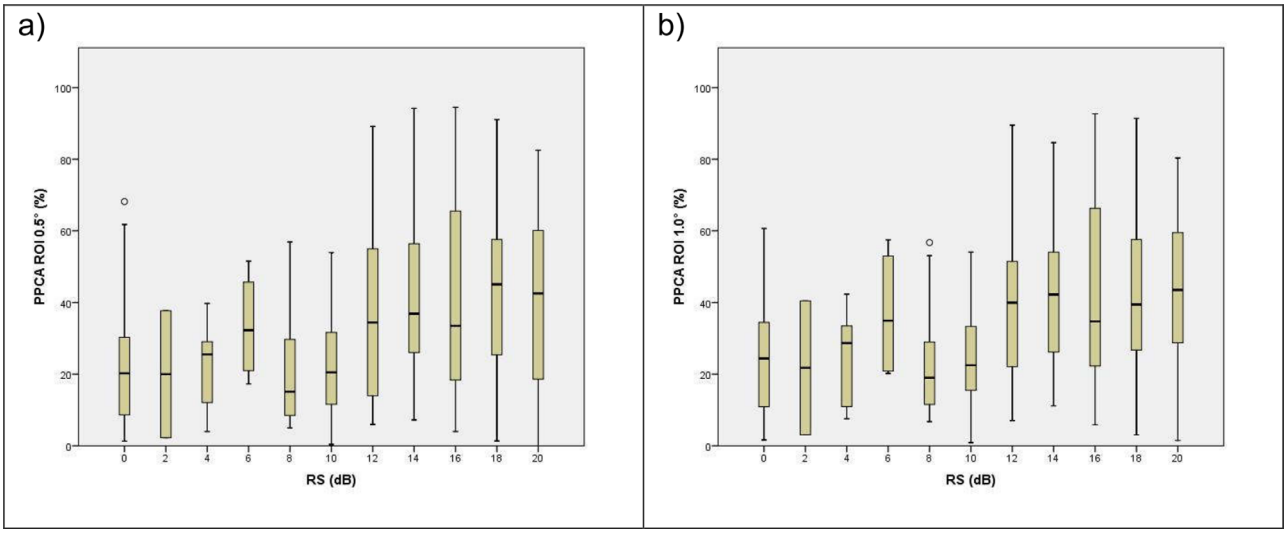

Figure 4. Boxplot of PPCA computed in ROIs of 0.5 degrees (**a**) and 1.0 degree of radius (**b**) in function RS. Significant linear relationships were observed between PPCA computed in circular ROI of 0.5 degrees of diameter and RS (**a**) and between PPCA computed in circular ROI of 1 degree of diameter and RS (**b**).

The authors concluded that CC loss is an aging phenomenon that precedes RPE atrophy and photoreceptor loss in AMD.[21] Similarly Seddon et al., in post mortem histopathology studies, demonstrated that CC loss occurs without RPE atrophy in early and iAMD.[23] Furthermore, supporting this hypothesis, by analyzing the EZ band at SD-OCT, which is an anatomic parameter known to be strongly associated with BCVA and visual function, we observed that it was preserved in all patients with iAMD, independently from the number of drusen and from the estimated CC flow. In fact, the EZ band was only rarefied in correspondence to the drusen but always detectable, as evident in the example reported in Figure 2, which shows a case of AMD in comparison to a healthy subject. Therefore, in addition to evaluation of structural findings by SD-OCT, in particular the EZ band, the measurement of CC perfusion could be sensitive and useful for the early detection of any vascular alterations and for monitoring patients with AMD.

Our findings were in agreement with recent studies that showed OCT-A is useful in studying

AMD eyes and in particular that iAMD eyes are characterized by reduced CC perfusion density.[6,24] Only a few studies,[6,13,14] investigated the relationship of CC perfusion and macular function. In particular, two studies[6,13] adopted visual acuity as a functional parameter and failed to find a significative correlation, probably because the function information provided by VA is limited in AMD that is a disorder affecting the regions beyond the foveola. The results in our cohort confirmed these previous findings. A recent study[14] assessed macular function by using multifocal electroretinogram (mfERG), showing that decreased PPCA was associated with changes in mfERG implicit time, but not response amplitude, and the authors speculated that the CC changes may affect the postphotoreceptor function. More recently, Nassisi et al.[15] investigated the correlation between CC flow alterations and scotopic macular sensitivity in patients with early and iAMD and showed that CC flow deficits appeared to correlate with scotopic sensitivity.

In our study, we decided to assess macular function by quantifying retinal sensitivity by mesopic MP, which evaluates macular cone function, because decreased retinal sensitivity has been shown to be related to photoreceptorial damage in advanced stages of AMD.[16] Among our iAMD cohort, we observed that a more decreased CC perfusion was associated with lower values of retinal sensitivity, averaged both over a retinal area of 10 degrees of radius and over a macular area of 5 degrees of radius corresponding to the OCT-A scan area. According to a topographical method, we also performed a subanalysis by correlating retinal sensitivity in each point analyzed by MP and PPCA estimated in circular ROIs centered in each point. We showed a strong correlation between the two parameters, confirming the relationship between CC flow alteration and macular dysfunction in AMD. Furthermore, we observed in patients with iAMD a significant decreased PPCA in the 150-µm-wide peri-drusen ring regions compared to the drusen-free regions, as already described by Borrelli et al.,[6] and also a reduced PPCA in areas nonaffected by drusen compared to control group suggesting CC perfusion to be a greater sensitivity parameter for early detection of disease.

The current study has some limits. First, the cross-sectional design of the current study did not enable to evaluate any temporal or causal association between the RPE and CC alterations. For that reason, longitudinal observations are needed to provide further information in the debate about the mutualistic relationship between RPE and CC in AMD. Another limit of the current study is the adoption of spectral domain OCT-A, which, when imaging the CC underlying drusen, is more prone to producing thresholding artifacts than longer-wavelength swept source OCT-A.[25] To this regard, a compensation strategy to detect CC flow loss under the drusen with swept source OCT-A has been recently validated[26] and, in future studies, may provide further information about the relationship between CC perfusion loss and the progression of AMD. Finally, 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. For instance, we adopted a common approach based on the global threshold technique where all the pixels with values higher than the threshold are identified as perfused area, otherwise as nonperfused area. However, other approaches have been proposed, for instance, based on local thresholding and, the investigation of the best processing strategies, including optimal slab selection and thresholding approach, for visualization and quantification of the CC are still evolving.[27]

In conclusion, using OCT-A, we demonstrated a significant association between CC impairment and macular dysfunction, quantified by mesopic MP, in iAMD eyes. In this context, OCT-A could be a useful tool for detecting CC alterations and to monitor the disease progression. Nevertheless, further studies are warranted to better understand the mutualistic relationship between loss of macular function and CC alteration in non-neovascular AMD.

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* LDP and PM contributed equally to this paper.

References

1. Ferris FL, III, Wilkinson C, Bird A, et al. Clinical classification of age-related macular degeneration. *Ophthalmology*. 2013;120:844–851.
2. Colijn JM, Buitendijk GHS, Prokofyeva E, et al. Prevalence of age-related macular degeneration in Europe: the past and the future. *Ophthalmology*. 2017;124:1753–1763.

3. Klein R, Myers CE, Cruickshanks KJ, et al. Markers of inflammation, oxidative stress, and endothelial dysfunction and the 20-year cumulative incidence of early age-related macular degeneration: the Beaver Dam Eye Study. *JAMA Ophthalmol*. 2014;132:446–455.
4. Saksens NT, Geerlings MJ, Bakker B, et al. Rare genetic variants associated with development of age-related macular degeneration. *JAMA Ophthalmol*. 2016;134:287–293.
5. Wangsa-Wirawan ND, Linsenmeier RA. Retinal oxygen: fundamental and clinical aspects. *Arch Ophthalmol*. 2003;121:547–557.
6. Borrelli E, Uji A, Sarraf D, Sadda SR. Alterations in the choriocapillaris in intermediate age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2017;58:4792–4798.
7. 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.
8. Ramrattan RS, van der Schaft TL, Mooy CM, de Bruijn WC, Mulder PG, de Jong PT. Morphometric analysis of Bruch's membrane, the choriocapillaris, and the choroid in aging. *Invest Ophthalmol Vis Sci*. 1994;35:2857–2864.
9. Waheed NK, Moult EM, Fujimoto JG, Rosenfeld PJ. Optical coherence tomography angiography of dry age-related macular degeneration. *Dev Ophthalmol*. 2016;56:91–100.
10. Kuehlewein L, Bansal M, Lenis TL, et al. Optical coherence tomography angiography of type 1 neovascularization in age-related macular degeneration. *Am J Ophthalmol*. 2015;160:739–748.e732.
11. Kuehlewein L, Sadda SR, Sarraf D. OCT angiography and sequential quantitative analysis of type 2 neovascularization after ranibizumab therapy. *Eye (Lond)*. 2015;29:932–935.
12. Moult E, Choi W, Waheed NK, et al. Ultrahigh-speed swept-source OCT angiography in exudative AMD. *Ophthalmic Surg Lasers Imaging Retina*. 2014;45:496–505.
13. Nesper PL, Soetikno BT, Fawzi AA. Choriocapillaris nonperfusion is associated with poor visual acuity in eyes with reticular pseudodrusen. *Am J Ophthalmol*. 2017;174:42–55.
14. Borrelli E, Mastropasqua R, Senatore A, et al. Impact of choriocapillaris flow on multifocal electroretinography in intermediate age-related macular degeneration eyes. *Invest Ophthalmol Vis Sci*. 2018;59:AMD25–AMD30.
15. Nassisi M, Tepelus T, Corradetti G, Sadda SR. Relationship between choriocapillaris flow and scotopic microperimetry in early and intermediate age related macular degeneration. *Am J Ophthalmol*. 2021;222:302–309.
16. Takahashi A, Ooto S, Yamashiro K, et al. Photoreceptor damage and reduction of retinal sensitivity surrounding geographic atrophy in age-related macular degeneration. *Am J Ophthalmol*. 2016;168:260–268.
17. Mastropasqua R, Senatore A, Di Antonio L, et al. Correlation between choriocapillaris density and retinal sensitivity in Stargardt disease. *J Clin Med*. 2019;8(9):1432.
18. Ro-Mase T, Ishiko S, Omae T, Ishibazawa A, Shimouchi A, Yoshida A. Association between alterations of the choriocapillaris microcirculation and visual function and cone photoreceptors in patients with diabetes. *Invest Ophthalmol Vis Sci*. 2020;61:1.
19. Glynn RJ, Rosner B. Regression methods when the eye is the unit of analysis. *Ophthalmic Epidemiol*. 2012;19:159–165.
20. Biesemeier A, Taubitz T, Julien S, Yoeruek E, Schraermeyer U. Choriocapillaris breakdown precedes retinal degeneration in age-related macular degeneration. *Neurobiol Aging*. 2014;35:2562–2573.
21. Moult EM, Waheed NK, Novais EA, et al. Swept-source optical coherence tomography angiography reveals choriocapillaris alterations in eyes with nascent geographic atrophy and drusen-associated geographic atrophy. *Retina*. 2016;36(Suppl 1):S2–S11.
22. Sacconi R, Corbelli E, Carnevali A, Querques L, Bandello F, Querques G. Optical coherence tomography angiography in geographic atrophy. *Retina*. 2018;38:2350–2355.
23. Seddon JM, McLeod DS, Bhutto IA, et al. Histopathological insights into choroidal vascular loss in clinically documented cases of age-related macular degeneration. *JAMA Ophthalmol*. 2016;134:1272–1280.
24. Toto L, Borrelli E, Mastropasqua R, et al. Association between outer retinal alterations and microvascular changes in intermediate stage age-related macular degeneration: an optical coherence tomography angiography study. *Br. J. Ophthalmol*. 2017;101:774–779.
25. Lane M, Moult EM, Novais EA, et al. Visualizing the choriocapillaris under drusen: comparing 1050-nm swept-source versus 840-nm spectral-domain optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2016;57:OCT585–OCT590.

26. Zhang Q, Zheng F, Motulsky EH, et al. A novel strategy for quantifying choriocapillaris flow voids using swept-source OCT angiography. *Invest Ophthalmol Vis Sci*. 2018;59:203–211.

27. Chu Z, Cheng Y, Zhang Q, et al. Quantification of choriocapillaris with phansalkar local thresholding: pitfalls to avoid. *Am J Ophthalmol*. 2020;213:161–176.