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Impact of Reticular Pseudodrusen on Choriocapillaris Flow Deficits and Choroidal Structure on Optical Coherence Tomography Angiography

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Purpose. To examine the impact of reticular pseudodrusen (RPD) on choriocapillaris blood flow and choroidal structure in individuals with intermediate age-related macular degeneration (AMD).

Methods. Individuals with bilateral large drusen underwent optical coherence tomography (OCT), color fundus photography, near-infrared reflectance, and fundus autofluorescence imaging to determine the presence of RPD. These participants also underwent swept-source OCT angiography (SS-OCTA) imaging to determine (1) choriocapillaris flow deficit (FD) parameters, including the percentage, mean size, and number of FDs present; and (2) choroidal structural parameters, including mean choroidal thickness and choroidal vascularity index. Differences in these parameters between eyes with and without coexistent RPD were examined with and without adjustment for potential key confounders such as drusen volume from the SS-OCTA scans and age.

Results. This study included 102 eyes from 51 individuals with bilateral large drusen, and the analyses showed that there were no significant differences in the choriocapillaris FD parameters ($P \geq 0.062$ for all) and choroidal structural parameters ($P \geq 0.059$ for all), with or without adjustment for potential confounders in this cohort. However, the percentage of FDs and the mean FD size were both significantly greater with increasing drusen volume ($P \leq 0.038$ for both).

Conclusions. The coexistence of RPD in eyes of individuals with intermediate AMD was not associated with significant impairments in choriocapillaris blood flow and choroidal vascular structural changes, with or without adjustment for key confounders. These findings suggest that macular changes in these vascular parameters may not be associated with the presence of RPD.

Keywords: reticular pseudodrusen, subretinal drusenoid deposits, optical coherence tomography angiography, choriocapillaris

Reticular pseudodrusen (RPD), or subretinal drusenoid deposits, have become an increasingly recognized feature in individuals with age-related macular degeneration (AMD) since their first description over three decades ago.[1] These distinct accumulations, localized above the retinal pigment epithelium (RPE),[2] can be effectively distinguished from conventional drusen using optical coherence tomography (OCT) imaging.[3] Several studies have reported that their presence in the non-late, fellow AMD eyes of individuals with unilateral neovascular AMD is associated with an increased risk of developing late AMD.[4–10] Their presence in individuals with intermediate AMD[11] has also been reported to be associated with an increased risk of developing late AMD, although this has not been observed in other studies.[12–14] The potential prognostic significance of RPD being present in AMD highlights the need to understand the mechanisms behind their formation and how they may drive vision loss in AMD.[15]

Previous histopathological evaluations have observed choroidal vessel loss and stromal fibrosis[16] or patchy choriocapillaris (CC) loss with choroid thinning[17] in eyes with RPD. These findings are supported by a previous clinical study reporting that RPD colocalized with CC filling defects on fluorescein angiography (FA) and indocyanine green angiography, which suggests an association between CC flow impairment and the presence of RPD.[18] Other clinical studies reported that eyes with RPD more often showed choroidal filling abnormalities on FA, supporting the histopathological findings.[19,20]

Recent studies have also used optical coherence tomography angiography (OCTA), a method that allows noninvasive, high-resolution, and depth-resolved assessment of

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microvascular information in the retina and choroid,[21] to examine CC changes in eyes with RPD. One study reported that eyes with RPD, with or without drusen, had a significantly larger percentage of CC flow deficits (defined as pixels falling below a global "nonperfusion" threshold in this study) than eyes with drusen only, where a 2 × 2-mm scanned region of interest on OCTA imaging was used for analysis.[22] However, another study did not observe a significant difference in the total area of CC flow deficits (FDs) between eyes with RPD compared to eyes with only drusen, although it was unclear in this study if the eyes with RPD also had coexistent drusen.[23]

Many previous studies have also reported that the choroid thickness on OCT imaging is less in eyes with RPD (with or without non-late AMD) when compared to those without RPD,[24–30] although there have also been several studies that did not observe this finding or only observed them in specific subgroup comparisons.[31–36] The choroidal vascularity index (CVI), a measure of the proportion of the total choroidal volume occupied by choroidal vessels, has been recently proposed as a more robust measure of choroidal vasculature changes than choroidal thickness measurements, as it is less affected by physiological or anatomical variability.[37] One study recently observed a significant difference in CVI between eyes with and without RPD,[36] but another study did not observe any significant differences.[38]

The conflicting findings to date about whether significant macular CC flow impairments and macular choroidal vasculature changes are associated with the presence of RPD in the setting of AMD warrants further investigation to better understand what, if any, are the associations between measures of choroidal and CC vascular parameters and the presence of RPD in eyes with AMD. This study aims to examine these changes in a well-defined cohort, where all individuals have the same stage of AMD—namely, intermediate AMD.

Methods

Participants in this study were enrolled in an ongoing observational study at the Centre for Eye Research Australia. This study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the tenets of the Declaration of Helsinki. All participants provided written informed consent after being provided with a comprehensive explanation of the study procedures.

Participants

Participants were included in this study if they were at least 50 years of age and had bilateral large drusen secondary to AMD, and they were required to have at least one druse > 125 µm in diameter and within 1500 µm of the fovea as determined on color fundus photography in both eyes (meeting the criteria for intermediate AMD as per the Beckman classification).[39] Any participants with late AMD (defined as having exudative neovascular AMD), geographic atrophy, or OCT-defined atrophy (from nascent geographic atrophy[40,41] or worse) in either eye or any other ocular or systemic conditions that could affect the assessment of AMD or the retina were excluded. This study did not specifically assess for the presence of non-exudative macular neovascularization; thus, there may be cases with non-exudative macular neovascularization in this cohort.

Study Procedures

All participants underwent visual acuity testing, pupillary dilation, and then imaging of the macular region, which included (1) non-stereoscopic digital color fundus photography; (2) near-infrared reflectance covering a 30° × 30° region; (3) short-wavelength (or blue-light) fundus autofluorescence, with an excitation wavelength of 488 nm and capture of the emitted fluorescence signals between 500 and 700 nm, also covering a 30° × 30° region; (4) an OCT volume scan covering a 20° × 20° region (49 horizontal B-scans, 25 frames averaged per scan) using the SPECTRALIS HRA+OCT (Heidelberg Engineering, Heidelberg, Germany); and (5) an OCTA scan covering a 6 × 6-mm region (500 A-scans per horizontal B-scan; 500 B-scans acquired and each repeated twice at the same location) using the PLEX Elite 9000 (Carl Zeiss Meditec, Dublin, CA, USA). The PLEX Elite 9000 is a swept-source OCT angiography (SS-OCTA) device with a scanning rate of 100,000 A-scans per second, a central wavelength of 1050 nm, a bandwidth of 100 nm, an axial resolution of approximately 6 µm, and a lateral resolution of approximately 20 µm estimated in retinal tissue. FastTrac (Carl Zeiss Meditec) motion tracking was used during all scans to minimize possible motion artifacts. The complex optical microangiography (OMAG^{C}) algorithm[42] was used to generate OCTA volumes. Only scans that were free from significant motion or blink artifacts and only scans with a signal strength score ≥ 7 were included in this study.

Multimodal Imaging Determination of RPD

Color fundus photography, near-infrared reflectance, and fundus autofluorescence (three en face imaging modalities) and the OCT volume scan consisting of 49 B-scans were used to determine the presence of RPD, and a senior medical retina clinician (RHG) performed all assessments. The presence of RPD could only be determined if the OCT volume scan and two or more en face modalities were gradable, with RPD otherwise being considered ungradable. RPD were deemed to be definitely present if (1) five or more definite RPD were present on more than one OCT B-scan, and RPD were definitely present or questionable on at least one or more en face modality; or (2) RPD were definitely present on two or more en face modalities. RPD were deemed absent if they were absent on OCT B-scans (i.e., there were not five or more definite RPD present on more than one OCT B-scan), and if either (1) absent on all en face modalities or (2) questionable on only one en face modality and absent on the remaining en face modalities. The presence of RPD was deemed questionable if RPD were not considered either definitely present or absent.

OCTA Image Processing

The OCTA scans were processed to compute the following CC and choroidal vascular parameters: (1) measures of CC FDs, a term chosen over "flow voids" to describe areas of low signal, which may reflect areas of flow below the detection sensitivity of the SS-OCTA system or areas without flow[43]; (2) choroidal thickness; and (3) CVI. To compute these parameters, an automated algorithm was used to obtain accurate segmentation of Bruch's membrane (BM), and all segmentation was reviewed and manually corrected, when necessary, by one grader masked to the RPD grading data. For the CC FDs measures, en face CC slab (defined as the

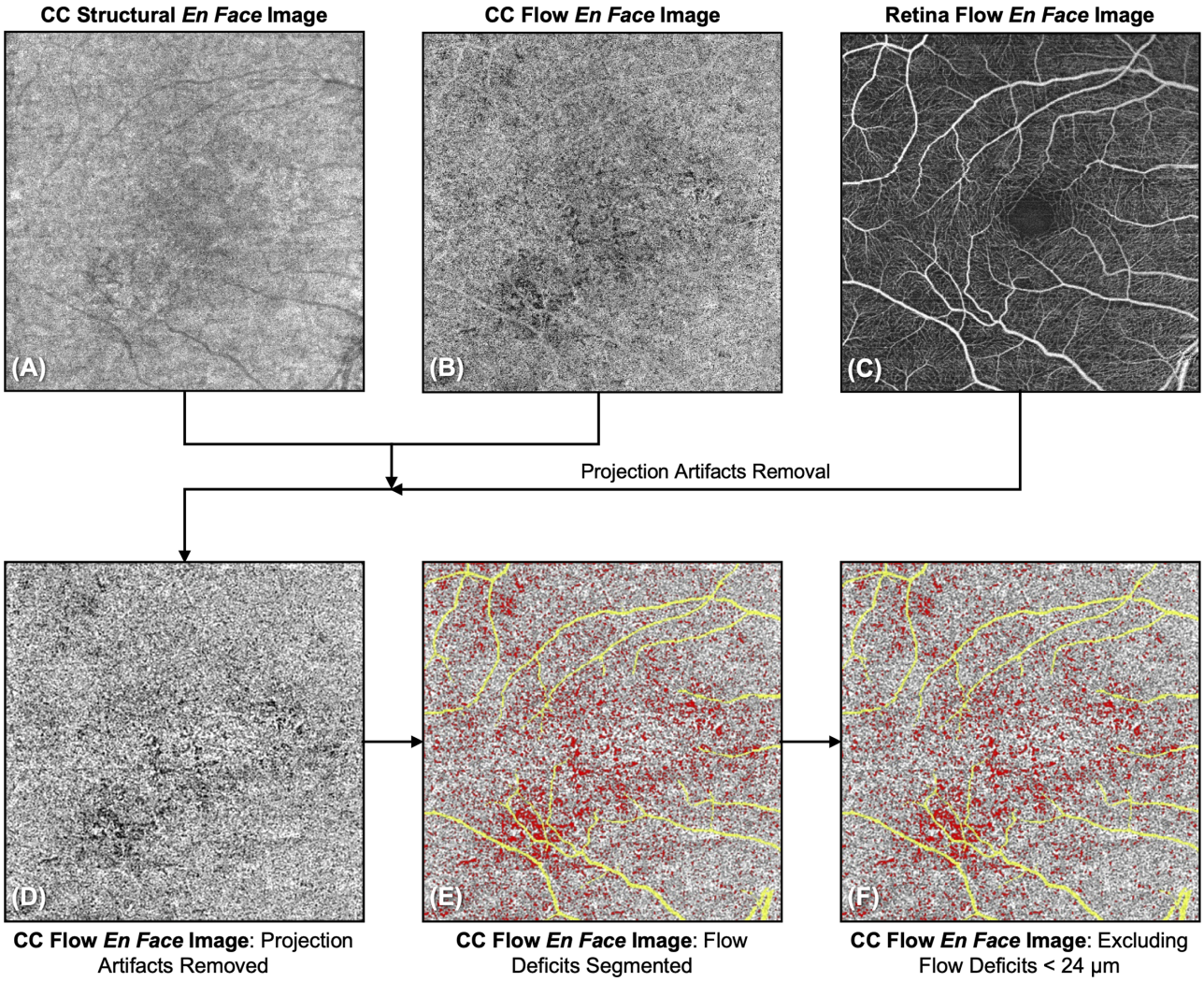


Figure. CC quantitative analysis using SS-OCTA. The CC slab was defined extending from 4 to 20 µm below the Bruch's membrane. (**A**) SS-OCTA CC en face structural image generated by maximum projection. (**B**) SS-OCTA CC en face flow image generated by maximum projection. (**C**) SS-OCTA retina en face flow image generated by mean projection. (**D**) SS-OCTA CC en face flow image after signal compensation and projection artifacts removal. (**E**) Segmented FDs (*red*) overlaid with the SS-OCTA CC en face flow image (*gray*) and the regions corresponding to the relatively large retinal vessels (>~30 µm) were excluded from analyses (*yellow*). (**F**) The same as in **E** except where FDs with an equivalent diameter smaller than 24 µm (the normal intercapillary distance) were removed.

region from 4 to 20 µm below the BM) images were generated using a maximum projection method.[44] A compensation strategy was applied to adjust for the signal attenuation due to drusen as previously described.[45,46] Regions in structural CC slab images with low signal (weaker than 3 dB above noise floor) were excluded. Retinal projection artifacts were also subsequently removed using a previously published method,[47] excluding regions that were likely shadowed by relatively large retina vessels (>~30 µm). Retinal projection artifacts were subsequently removed,[47] and the regions likely shadowed by relatively large retina vessels (>~30 µm) were excluded in further analysis. The fuzzy C-means method was used to segment FDs in this study. This method automatically assigns all pixels in the entire image into different clusters based on histogram distribution.[48] The cluster with the lowest intensity is then segmented as the FDs. After thresholding, any FDs with an equivalent diameter smaller than the average normal intercapillary distance (24 µm) were removed.[43] These steps for processing the OCTA scans to calculate CC FDs are illustrated in the Figure, and the following parameters within the entire scan were derived and examined in this study: (1) FD density (FD%, a percentage of the total scan area with FDs), (2) mean size of FDs, and (3) number of FDs per mm^2 of the CC analyzed (which differed between eyes based on the extent of regions of low signal and retinal projection artifacts excluded).

Measurements of the choroidal structures were also derived from the SS-OCTA scans following segmentation of the choroidal layer (from BM to the choroidal–scleral interface) with an automated algorithm as described previously.[49] This algorithm corrected for SS-OCT signal attenuation to enhance the visibility of the choroidal–scleral interface prior to segmentation of this boundary, which is then used to calculate the mean choroidal thickness in the entire SS-OCTA scan. Choroidal vessels were then segmented using Otsu's global threshold method,[49] and the CVI was calculated as a ratio of the volume choroidal vessels to the total choroidal volume in the entire OCTA scan. Drusen volume measurements from the OCTA scans were also derived using

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Table 1. Comparison of Differences in Choriocapillaris FD Parameters in Eyes With (n = 47) and Without (n = 55) Definite Coexisting RPD With or Without Adjusting for Potential Confounders

Potential Factors Associated With Outcome	Mean (95% Confidence Interval)* FD Outcome Parameter Evaluated		
	Density (%)	Mean Size (μm²)	Number Per mm²
Univariable model			
RPD (yes vs. no)	0.0 (−0.6 to 0.5)	69 (−5 to 143)	−3.9 (−7.9 to 0.2)
Multivariable model†			
RPD (yes vs. no)	0.1 (−0.5 to 0.7)	44 (−32 to 120)	−1.9 (−6.1 to 2.3)
Drusen volume (per mm)‡	1.9 (0.1 to 3.7)§	289 (94 to 485)§	−3.1 (−15.1 to 8.9)
Age (per decade)	0.0 (−0.4 to 0.4)	60 (7 to 113)§	−2.4 (−5.3 to 0.5)

* All data are presented as mean (95% confidence interval) for the association between the potential factors evaluated (independent variables) and the choriocapillaris flow deficit parameters (dependent variable).
† Adjusted also for sex and smoking status.
‡ Cube-root transformed.
§ $P < 0.05$.

version 0.8 of the Advanced RPE Analysis algorithm (Carl Zeiss Meditec) over the entire scan based on the automated retinal layer segmentation of the RPE and BM.

Statistical Analysis

CC flow and choroidal structural parameters were compared between eyes with and without coexistent RPD using linear mixed models to account for the correlations between two eyes of the same participant. These analyses were performed using a univariable model including only RPD, referred to as the *unadjusted model*, and then following adjustments for potential confounders including cube-root drusen volume, age, sex, and smoking status (past or current vs. never), referred to as the *adjusted model*.

Results

A total of 102 eyes from 51 participants were included in this study, and these participants were on average 73 ± 8 years old (range, 55–86) and predominantly female (80%). A total of 47 eyes (46%) from 24 participants (47%) had definite RPD, and all eyes had ≥5 definite RPD present on more than one B-scan within the central 20° × 20° region on OCT imaging. Among the participants with definite RPD in either eye, 23 participants (96%) had bilateral definite RPD. Individuals with definite RPD in either eye were significantly older (average, 77 ± 5 years old) than individuals without definite RPD in either eye (average, 69 ± 7 years old; $P <$ 0.001).

The median drusen volume of all eyes was 0.08 mm³ (interquartile range [IQR], 0.04–0.15). For the CC FD parameters, the median FD% (percentage of total scan area with FDs), mean FD size, and number of FDs per mm² were 9.6% (IQR, 8.6–10.7), 1462 μm² (IQR, 1359–1567), and 67.1 (IQR, 58.4–72.3), respectively.

Impact of RPD on CC FDs

When comparing eyes with and without definite coexistent RPD, we found no statistically significant difference in the FD% (unadjusted $P = 0.931$, adjusted $P = 0.678$), mean FD size (unadjusted $P = 0.068$, adjusted $P = 0.258$), or number of FDs per mm² (unadjusted $P = 0.062$, adjusted $P = 0.381$). In the multivariable models, both the FD% and mean FD size were significantly associated with drusen volume (adjusted $P \leq 0.038$ for both), but not the number of FDs per mm² ($P = 0.618$); these findings are summarized in Table 1.

Impact of RPD on Choroidal Structure

There were no significant differences between eyes with and without coexistent RPD for mean choroidal thickness (unadjusted $P = 0.059$, adjusted $P = 0.867$) or for the CVI (unadjusted $P = 0.450$, adjusted $P = 0.798$). Note that there was a significant association between choroidal thickness and age ($P < 0.001$), but not between CVI and age ($P = 0.279$). There was also no significant association between either choroidal thickness or CVI with drusen volume ($P \geq 0.571$); these findings are summarized in Table 2.

Table 2. Comparison of Differences in Choroidal Structural Parameters in Eyes With (n = 47) and Without (n = 55) Coexisting RPD With or Without Adjusting for Potential Confounders

Potential Factors Associated With Outcome	Mean (95% Confidence Interval)* Choroidal Outcome Parameter Evaluated	
	Mean Thickness (μm)	Vascularity Index (%)
Univariable model		
RPD (yes vs. no)	−16 (−33 to 1)	0 (−2 to 1)
Multivariable model†		
RPD (yes vs. no)	1 (−15 to 18)	0 (−1 to 1)
Drusen volume (per mm)‡	3 (−38 to 44)	−1 (−4 to 2)
Age (per decade)	−28 (−40 to −16)§	−1 (−1 to 0)

* All data are presented as mean (95% confidence interval) for the association between the potential factors evaluated (independent variables) and the choroidal structural parameters (dependent variable).
† Adjusted also for sex and smoking status.
‡ Cube-root transformed.
§ $P < 0.001$.

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Discussion

This study found that the coexistence of RPD in eyes of individuals with bilateral large drusen was not significantly associated with any differences in CC FDs either the percentage of FDs present, average size of individual FDs, or the number of FDs present. It also revealed no significant differences in the choroidal thickness and vascularity between eyes with and without coexistent RPD. These findings highlight an important absence of evidence to support the potential contribution of macular CC and choroidal vascular changes in the pathogenesis of RPD in intermediate AMD.

Our findings suggest that the coexistence of RPD in eyes of individuals with intermediate AMD were not significantly associated with a significant difference in the percentage of macular CC FDs present. Our observations are supported by a recent study by Nam et al.,[23] who also did not observe a significant difference in this parameter when comparing eyes with RPD to eyes with large drusen only (note that the coexistence of drusen in the eyes with RPD was not stated in this study). In contrast, one previous study by Nesper et al.[22] reported that eyes with RPD, with or without drusen, had a larger extent of CC FDs (which they termed "non-perfusion") compared to eyes with drusen only. The differences in these observations could potentially be due to the OCT devices used, as our current study and the previous study by Nam et al.[23] used swept-source OCT devices with a laser that had a central wavelength of 1050 nm, but the other study by Nesper et al.[22] used a spectral-domain OCT device with a laser that had a central wavelength of 840 nm. There were also differences in how the CC slab was defined,: from 4 to 20 µm below BM in our study (or a 16-µm slab) and from the BM to 10 µm below in the previous study by Nam et al.,[23] both of which were smaller than the 28-µm slab below BM examined in the other study by Nesper et al.[22] In addition, it should be noted that the AMD severity at the individual level (e.g., whether neovascular AMD was present in the fellow eye of the eye analyzed) of the cohort of the study by Nesper et al.[22] was not reported, and previous studies have shown that the extent of CC FDs differs between the non-late AMD eyes of individuals with intermediate AMD and non-late AMD eyes from individuals with late AMD.[50,51] As such, differences in AMD severity at the individual level may have been a significant confounder for their findings, explaining the differences in the findings of Nesper et al.[22] compared to those of this study. In addition, even though regions with drusen were excluded from the analysis of CC FDs in that previous study,[22] another study has shown that CC FDs are more frequently present in the region immediately surrounding drusen than more distal regions without drusen.[52] These observations are supported by the findings in this study, where the extent of FDs increased with increasing drusen volume. The extent of drusen in the eyes of the above previous study[22] may thus have been a significant confounder of CC blood flow. Note that another recent case report showed that CC FDs were present within regions with RPD in an individual with Sorsby macular dystrophy.[53] It is thus unclear why the coexistence of RPD in eyes with large drusen are not associated with a significantly larger extent of CC FDs.

The findings in this study that the presence of RPD was also not significantly associated with a difference in the average size of the individual flow deficits are in contrast to the qualitative observations of a previous study that reported that flow deficits appeared larger in eyes with RPD compared to eyes with drusen only.[22] It is also in contrast to previous observations that eyes with RPD had a larger proportion of the total FD area accounted for by FDs $\geq$ 10,000 µm^2 in one study,[54] or more individual areas of larger FDs in another study.[55] These differences may be attributed to differences in CC flow impairments between eyes with large drusen and coexistent RPD and eyes with only RPD.

Our findings of a non-significant difference in choroidal thickness based on the presence of RPD in individuals with bilateral large drusen replicates our previous findings from an analysis of a different cohort of 297 eyes from 152 individuals also with bilateral large drusen.[35] However, these findings are not consistent with previous studies that reported that eyes with RPD, with or without drusen, have a significantly lower choroidal thickness compared to those without.[24–30] However, AMD severity at the individual level in these studies is not clearly known. As described above for CC FDs, choroidal thickness is also lower in non-late AMD eyes of individuals with late AMD in the fellow eye compared to individuals with the earlier stages of AMD.[56,57] This important confounder may thus account for the differing findings regarding choroidal thickness in eyes with RPD. Nonetheless, several previous studies where the AMD severity at the individual level was unclear also observed an absence of a significant difference in eyes with RPD, with or without drusen, and eyes with drusen only,[32–34,36] lending support to the observations in this study.

The findings of a non-significant difference in choroidal thickness between the eyes with and without coexistent RPD in this study are further reinforced by an absence of a significant difference in the CVI, a robust measure of the choroidal vasculature.[37] This observation is supported by the findings from one recent study reporting a lack of a significant difference in CVI between eyes with only RPD compared to eyes with large drusen.[38] Another study reported that the CVI was higher in non-neovascular AMD eyes with RPD compared to those without.[36] In that study, eyes with RPD also had a significantly lower luminal area (or extent of choroidal vessels) but did not have a significantly lower choroidal thickness.[36] The authors interpreted these findings as representing attenuation of both the stromal and vascular components of the choroid, with a greater attenuation of the former. However, the higher CVI observed in this study is in the opposite direction of effect expected to reflect abnormalities of the choroidal vasculature, given that the CVI is reduced in eyes and individuals with AMD compared to healthy eyes.[37]

This study importantly adds to our knowledge about the potential contribution, or lack thereof, of the CC and choroidal vascular changes in the mechanisms associated with RPD development and their clinical associations in intermediate AMD. However, our observations of a lack of measurable differences in the CC and choroidal parameters may reflect limitations of imaging and analytical techniques rather than the true absence of choroidal vascular insufficiency in eyes with RPD. For instance, the time interval between the repeated scans used to derive the SS-OCTA flow signal in this study has a relatively low dynamic range, and flow velocity cannot be reliably determined. This could be improved through novel acquisition approaches that enhance the resolvable flow signal dynamic range and allows quantification of flow velocities.[58] Furthermore, the CVI measure only captures structural changes and does not provide information about choroidal blood flow, which is challenging to measure on SS-OCTA imaging due to signal attenuation and scattering from the overlying RPE. However,

advances in OCTA acquisition and analytical approaches, such as through the subtraction of CC projection artifacts used in one study,[59] may enable choroidal blood flow to be quantified and examined in AMD cohorts with and without RPD.

A limitation of this study is that it examined CC flow and choroidal vascular characteristics in individuals with bilateral large drusen only. Future studies will benefit from examining SS-OCTA CC and choroidal parameters across a wider spectrum of AMD severities in order to evaluate whether there are severity-dependent differences in these parameters based on the presence or absence of RPD. Strengths of this study include a clear description of the AMD severity of the cohort, compensation of signal attenuation from overlying structures when quantifying CC FDs, and adjustment for the potential confounders of the OCTA parameters including age and drusen volume. These factors enabled a robust assessment of the independent impact of RPD on the CC and choroidal parameters in this study. Note that the findings in this study remain unchanged when evaluating square-root drusen area rather than cube-root drusen volume measurements in this study (data not shown).

Conclusions

We observed that the presence of RPD was not associated with any significant differences in any of the macular CC FD parameters examined (percentage, average size, or number of FDs present) in a cohort of individuals with bilateral large drusen. We also did not observe a significant difference in the macular choroidal vasculature between eyes with and without coexistent RPD in this cohort. These findings highlight how there are likely other factors apart from the CC and choroidal vascular impairments driving the development of RPD, warranting further studies to identify these mechanisms.

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