Quantitative Assessment of Choriocapillaris Flow Deficits in Eyes with Advanced Age-Related Macular Degeneration Versus Healthy Eyes

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• PURPOSE: To compare choriocapillaris (CC) flow deficits in eyes with geographic atrophy (GA) or choroidal neovascularization (CNV) associated with age-related macular degeneration (AMD) and age-matched healthy control subjects.

• DESIGN: Cross-sectional study.

• METHODS: Patients with GA due to AMD, CNV due to AMD, and age-matched healthy subjects presenting to the Doheny-UCLA Eye Centers were enrolled in this cross-sectional institutional review board–approved study. Swept-source optical coherence tomography angiography was performed using a Zeiss PLEX Elite instrument with a 6 × 6-mm scan pattern centered on the fovea. Two repeated volume scans were acquired to allow for image averaging. The instrument predefined en face slab of the CC was used to isolate and display the CC. Both the structural and optical coherence tomography angiography slabs from this location were exported for averaging and signal compensation using Image J. The resultant image was then binarized. The CC flow deficit percentage (FD%) was computed in 4 peripheral 1 × 1-mm squares located at the corners of the images to allow comparison between equidistant regions unaffected by atrophy or CNV.

• RESULTS: Twenty eyes of 20 subjects were enrolled in each of the 3 groups (CNV, GA, normal) for this study. The average CC FD% of the 4 peripheral squares was 17.24% ± 2.86% in GA eyes, 15.55% ± 1.03% in CNV eyes, and 15.31% ± 0.93% in healthy controls of a similar age. The FD% in GA eyes was significantly greater than in both normal eyes and eyes with CNV ($p = 0.012$ and 0.038 respectively). The difference in FD% was not significantly different between CNV eyes and normal eyes for the tested peripheral macular regions ($P = .678$).

• CONCLUSIONS: The CC in peripheral macular regions in eyes with GA shows greater impairment than in eyes with CNV. (Am J Ophthalmol 2019;205:132–139.

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LATE STAGE AGE-RELATED MACULAR DEGENERATION (AMD) may manifest as geographic atrophy (GA), characterized by loss of the photoreceptors and retinal pigment epithelium (RPE) (late "dry" AMD) and/or the development of choroidal neovascularization (CNV) (late "wet" AMD).[1,2] Despite this phenotypic distinction, these 2 manifestations have been shown to have fairly similar systemic, ocular, and genetic risk profiles.[3–12]

Alterations in the choroid, and in particular, the choriocapillaris (CC), have been implicated in aging eyes, as well as in development and progression of AMD in various histopathological and clinical reports.[13–15] The vascular model proposed by Friedman[16] implicating choroidal vascular changes also stems from the fact that atherosclerosis, hypertension, and AMD share a common pathogenic mechanism. Various reports have confirmed the reduction in the average choroidal blood flow in patients with dry AMD.[17,18] The choriocapillaris also has been noted to be attenuated or impaired in CNV and GA eyes in various studies.[19–21] Boltz et al[22] linked the reduced choroidal blood flow with the risk for the development of CNV in the fellow eye in their study.

Investigators have used noninvasive techniques like optical coherence tomography (OCT) to identify and quantify alterations of the choroid as potential structural biomarkers in these eyes.[23] Ferrara et al[24] outlined various structural retinal and choroidal changes seen in OCT as risk factors for progression to advanced AMD. Reliable identification of CC alteration is challenging when using structural OCT alone. OCT angiography (OCTA) provides vascular imaging via motion contrast processing of decorrelation signals.[25] The extensive CC loss in eyes with CNV and GA has been well documented in various studies using this technique.[26–31] Differences in CC flow deficits in eyes with CNV compared with GA have not been well-studied.

In this study, we analyzed the percentage of flow deficits in the CC layer in relatively preserved areas in eyes with

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CNV or GA, and compared them with the corresponding regions in healthy eyes.

METHODS

IN THIS OBSERVATIONAL, PROSPECTIVE, CROSS-SECTIONAL study, patients with treatment-naïve CNV secondary to AMD, GA secondary to AMD, and age-matched healthy controls were recruited at the Doheny-UCLA Eye Centers between May 2018 and November 2018. All patients underwent a comprehensive ophthalmic examination, including best-corrected visual acuity, slit lamp biomicroscopy, intraocular pressure measurement, and dilated ophthalmoscopy. Only 1 eye from each subject was included in this 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. Written, informed consent was obtained from all subjects before image acquisition. The study was approved by the institutional review board of the University of California–Los Angeles (UCLA).

Patients were excluded from the study if they had high myopia with more than 6 diopters, other concomitant macular diseases, a history of intravitreal injections/prior surgeries, or non–AMD-related CNV.

• **IMAGE ACQUISITION AND SCANNING PROTOCOLS:** The swept-source OCTA (SS-OCTA) images were captured using the PLEX Elite 9000 device (Carl Zeiss Meditec Inc, Dublin, CA, USA), which features a swept laser source with a central wavelength of 1050 nm (100,000 A-scans per second). This device provides a full-width at half-maximum resolution of approximately 5 μm (axial) in tissue, and 14 μm (lateral) on the retinal surface. FastTrac motion artifact compensation software was used during image acquisition. Following mydriasis, at least 2 scans 6 × 6 mm each, were acquired centered on the fovea for averaging (described later). Each scan was composed of 500 × 500 A-scans. The OCTA images were generated using the complex optical microangiopathy algorithm, which depends on detection of variation in both the intensity and the phase between successive B-scans acquired at the same location to generate the motion signal. Poor-quality images were excluded from the study (if signal strength index was less than 7 or if there was evidence of motion artifact). The manufacturer's semiautomated retinal layer segmentation algorithm was used to identify different retinal layers. The segmentation boundaries were inspected by certified Doheny Image Reading Center OCT-A graders (AA, AV) and manual correction was performed in 8 healthy subjects and all patients with CNV and GA to ensure accurate and consistent segmentation. A maximum projection was applied on the segmented volumes to generate the en face angiograms.

• **IMAGE PROCESSING:** Signal compensation was used to compensate for the attenuated CC signal resulting from structural alterations in RPE/Bruch's membrane complex as previously reported.[32] The CC slab was segmented from the structural OCT and the corresponding flow slab was then identified from the angiogram. The attenuated signal was enhanced by applying inverse transformation to the en face structural image and the speckle noise was reduced by a Gaussian smoothing filter (3 × 3 pixel kernel). A multiplication was performed between the en face flow image and the inverted, smoothed structural image. The 2 highest-quality OCTA images were selected for use in averaging (Figures 1 and 2) according to the previously published approach by Uji et al.[33]

• **QUANTITATIVE IMAGE ANALYSIS:** For GA eyes, the precise borders of the atrophic lesions were verified by inspection of the en face structural OCT fundus image[34] and the corresponding structural B-scans, with atrophy defined according to the Classification of Atrophy Meetings criteria.[35] For patients with neovascular lesions, we used the outer retina to CC slab to verify the presence of CNV. This slab extends from the outer boundary of the outer plexiform layer to 37 μm posterior to the RPE reference line.[36] In all subjects included in the study, for the analysis of the CC, the en face reconstruction of a 10-μm slab starting 31 μm below the RPE reference was used.[21,37,38] The 2 angiograms from 2 acquisitions were exported and averaged using ImageJ software version 1.50 (National Institutes of Health, Bethesda, MD; available at http://rsb.info.nih.gov/ij/index.html).[39] The resulting image was binarized for quantitative measurement of the signal deficits using the Phansalkar method (radius, 15 pixels) as described previously.[33,40,41] Four 1 mm × 1-mm squares were selected at the 4 corners of the images in order to include equidistant and comparable regions in all eyes outside of areas involved by GA and CNV (Figure 3). The percentage of flow deficits (FD%) in these selected squares was calculated as a percentage of the resulting area using the "Analyze Particles" command and compared among the 3 groups.

• **STATISTICAL ANALYSIS:** Statistical analyses were performed using SPSS Statistics version 20 (IBM, Armonk, NY). A Kruskal-Wallis test was performed to test the difference in FD% among the 3 groups. A P value ≤ .05 was considered statistically significant.

RESULTS

THE FINAL STUDY COHORT CONSISTED OF 20 HEALTHY EYES, 20 eyes with CNV, and 20 eyes with GA (1 eye from each

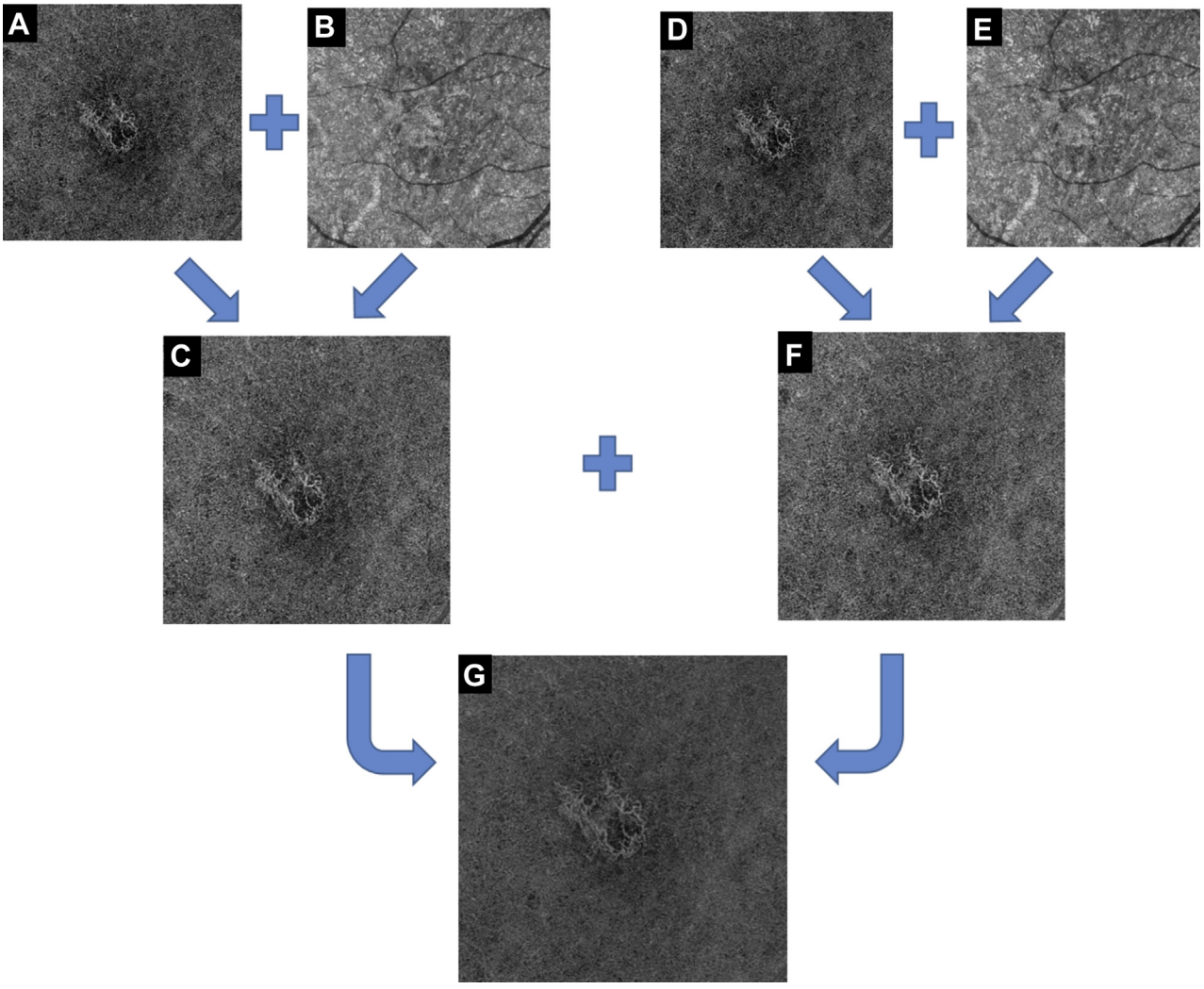

FIGURE 1. Eye with choroidal neovascularization imaged with swept-source optical coherence tomography angiography. The choriocapillaris slab from the first acquisition (A) is compensated for signal attenuation by using the corresponding structural en face slab (B). This same operation is performed for the second acquisition (D, E), the compensated images from the 2 acquisitions (C, F) are then aligned and averaged to yield the final compensated, averaged image (G). ×300 magnification.

subject). The demographic data for each group are shown in the Table. There was no statistically significant difference in age among the groups ($P = .089$). The mean CNV area was 3.68 ± 4.12 mm^2 (0.35–16.47) and the mean GA area was 5.78 ± 4.75 mm^2 (0.73–17.01). Based on the enrolled sample size, the study had power of 84% to detect the 2% of difference in CC FDs between the study cohorts.

The average CC FD% of the 4 peripheral squares was 17.24 ± 2.86 (14.33–24.81) in the GA group, 15.55 ± 1.03 (13.53–17.92) in the CNV group, and 15.31 ± 0.93 (12.89–16.29) in the healthy group (Figure 4).

Kruskal-Wallis test confirmed a statistically significant difference between groups ($P = .027$). To further investigate the differences between the specific group pairs, we performed a Mann-Whitney U test. GA eyes had a statistically significantly higher CC FD% compared with both healthy eyes ($P = .012$) and CNV eyes ($P = .038$), whereas there were no significant differences between CNV eyes and healthy eyes ($P = .678$).

The severity of the CC FD% did not correlate with lesion size of either GA ($r = 0.172$; $P = .468$) or CNV ($r = 0.225$; $P = .33$).

The CNV group did have 2 patients with a region of complete RPE and outer retinal atrophy and 1 patient with a region of incomplete RPE and outer retinal atrophy. When these 3 patients were excluded, the difference in FD % between the CNV and GA eyes grew even wider.

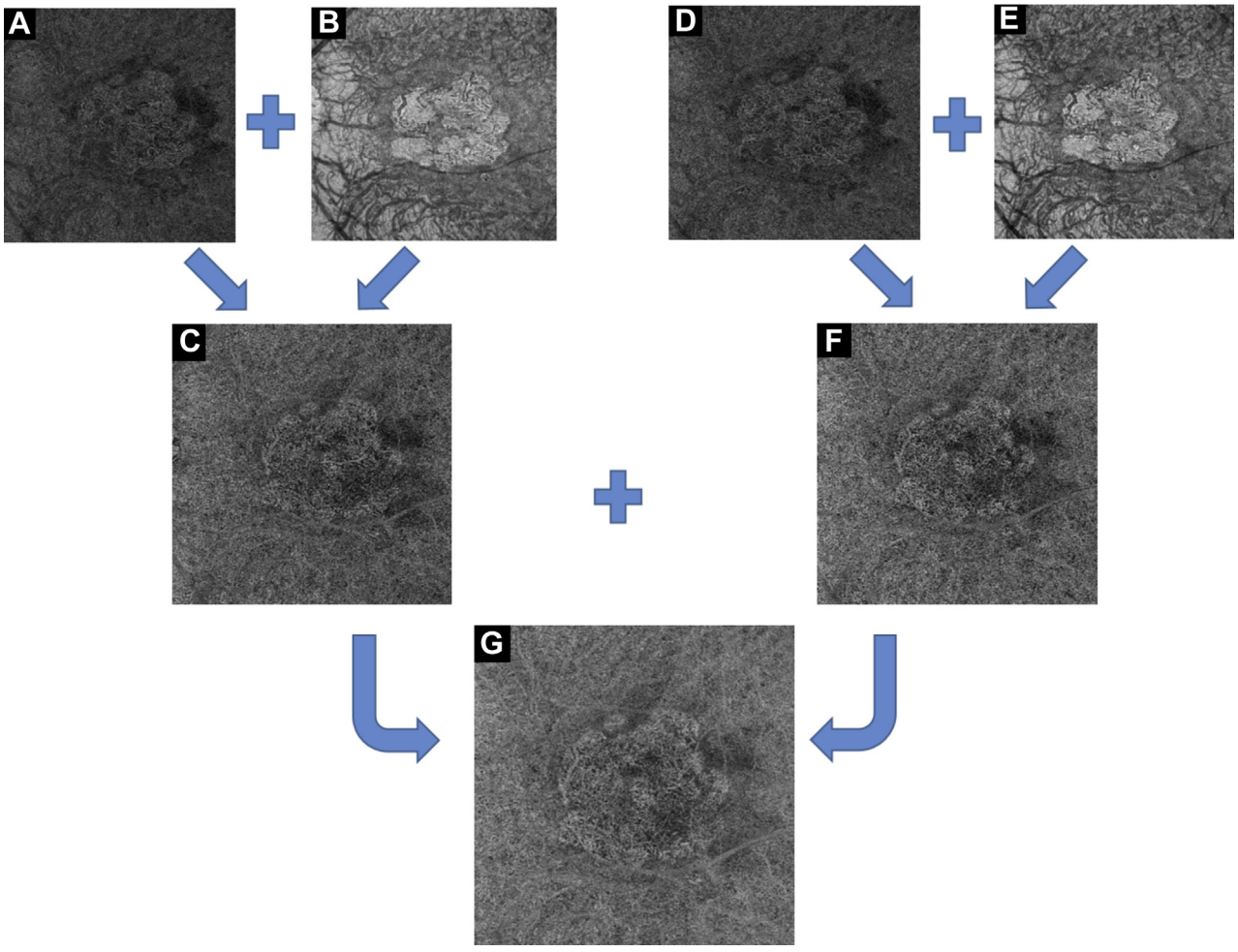

FIGURE 2. Eye with geographic atrophy imaged with swept-source optical coherence tomography angiography. The choriocapillaris slab from the first acquisition (A) is compensated for signal attenuation by using the corresponding structural en face slab (B). This same operation is performed for the second acquisition (D, E), the compensated images from the 2 acquisitions (C, F) are then aligned and averaged to yield the final compensated, averaged image (G). ×300 magnification.

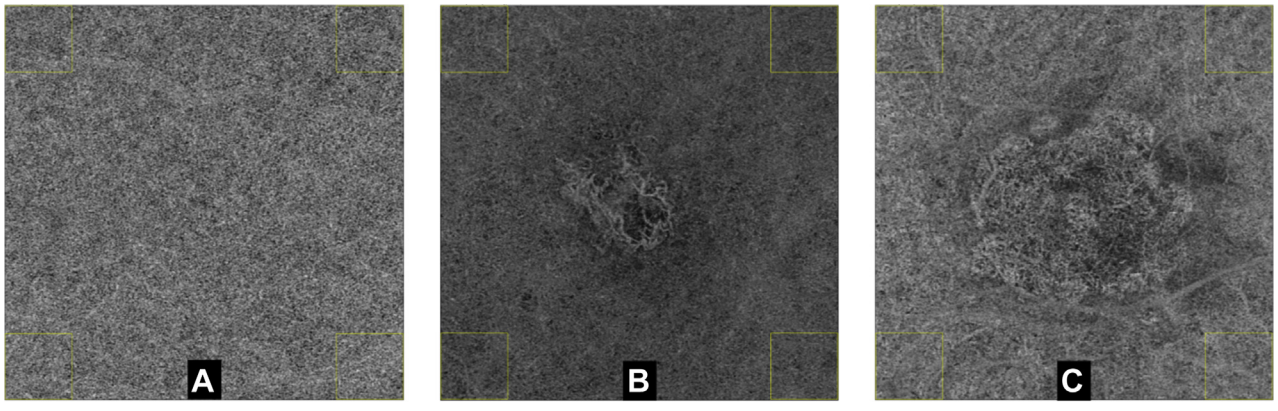

FIGURE 3. Compensated, averaged swept-source optical coherence tomography angiography en face 6 × 6-mm slabs at the level of the choriocapillaris. Four 1 × 1-mm squares (yellow boxes) at the peripheral corners of the macular optical coherence tomography angiography scan, remote from the central lesion, were used for calculation of choriocapillaris flow deficits in healthy eyes (A), choroidal neovascularization eyes (B), and geographic atrophy eyes (C). ×300 magnification.

TABLE. Demographic Data of the Study Cohort

	Healthy	CNV	GA
Mean age ± SD, y (range)	70.95 ± 5.25 (60-80)	74.7 ± 5.18 (64-80)	73.45 ± 5.7 (62-80)
Mean BCVA ± SD, logMAR (range)	0.12± 0.07 (0-0.2)	0.7 ± 0.2 (0.4-1)	0.791± 0.16 (0.5-1)
Gender (F:M)	12:08	8:12	11:09

BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; F = female; GA = geographic atrophy; LogMAR = logarithm of minimum angle of resolution; M = males.

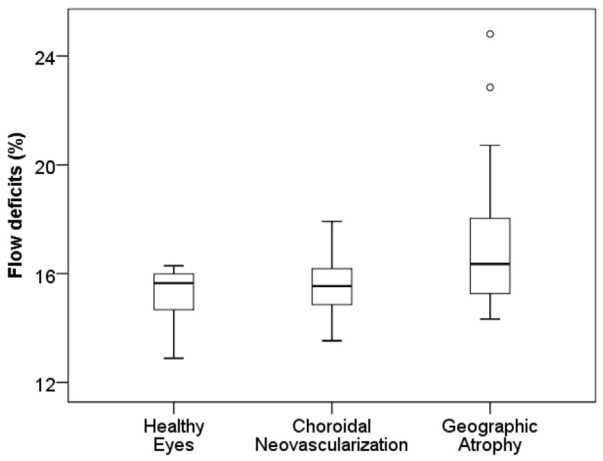

FIGURE 4. Box and whisker plots showing the distributions of flow deficits percentage in the 3 cohorts. The boxes represent the 25th to 75th percentiles, and horizontal lines within the box represent median values. The whiskers represent the lowest and highest value in the 25th percentile minus 1.5 the interquartile range (IQR) and 75th percentile plus 1.5 IQR regions, respectively. The suspected outliers (open circles) are 1.5 IQR or more above the 75th percentile.

DISCUSSION

IN THIS STUDY, WE OBSERVED DIFFERENCES IN THE SEVERITY of CC FDs in the peripheral aspects of the macula in eyes with different manifestations of late AMD. Whereas the peripheral CC FD in eyes with CNV was similar to that of normal/healthy eyes, the CC FD was significantly greater in eyes with GA compared with both normal ($P = .012$) and CNV eyes ($P = .038$).

Although the precise pathogenesis of AMD has eluded investigators over the years, the complex interplay between RPE and CC has been the focus of interest in most of studies. Whether the pathology initiates in RPE or the CC is still a matter of debate. The changes in CC with reduced flow have been consistently shown to occur with aging and in all forms of AMD.[13–21] In fact, this reduced blood flow in CC has been hypothesized to occur due to oxidative stress with age, resulting in ischemia, which may serve as a triggering event in development of early and late forms of AMD.[22,42]

Previously, alterations in choroid have been assessed by various methods, including indocyanine green angiography, Doppler analysis, and histopathological studies that were difficult to quantify precisely or conistently.[1,17,43] High-resolution OCT, and now OCTA, have allowed alterations in the inner choroid to be studied with greater confidence and precision.[17,44]

Recent reports have confirmed the presence of extensive CC disruption in the regions immediately surrounding the lesions in late AMD. Nassisi et al[21] performed a SS-OCTA–based analysis of CC flow around GA and confirmed the presence of significantly greater FD in a 500-μm para-atrophy zone immediately surrounding the GA as compared with a 500-μm peri-atrophy ring just beyond the para-atrophy ring. More recently, Nassisi et al[45] also reported that the severity of FD in these regions surrounding the GA correlates with the rapidity of disease progression or atrophy enlargement. FDs surrounding CNV lesions also have been reported,[46] and appear to be worst in eyes with type 3 CNV.[47] It should be noted that CC FDs are also present in eyes with intermediate AMD, especially in eyes with CNV in the fellow eye.[44] Interestingly, in these intermediate AMD eyes, the severity of the CC FD appears to be most severe directly below drusen and in the regions immediately surrounding the drusen.[38] Of note, in one series, although increased CC FD could be observed around the drusen, there was no overall difference in CC FD between intermediate AMD eyes and healthy controls.[44] The authors speculated that there may have been compensatory increased CC perfusion in a more remote region of the macula (distant from drusen) that may have accounted for this observation. Such a compensatory phenomenon may explain the lack of difference in peripheral macular CC FD between CNV eyes and normal healthy eyes in our series.

The difference in CC FD between AMD and CNV eyes may reflect overall disease severity and stage. Some researchers have speculated that CNV may arise as a compensatory response to underlying CC deficiency as a "last-ditch" attempt to rescue dying RPE and photoreceptors.[48] Thus, eyes that go on to atrophy or fail to mount a CNV response may simply be at more severe or later stage in the disease

process. Hence, it is perhaps not surprising that the CC FD was more severe in GA eyes compared with CNV eyes.

To eliminate bias from the CNV or GA lesion itself, we chose peripheral regions of the macular OCTA scans in all eyes. In addition, as it is known that the CC FD varies depending on the macular region, with a greater FD in the central macula compared with the peripheral macula, we compared equidistant regions among all eyes.[37] We also chose 4 separate peripheral macular regions in order to sample all sectors of the macula and to include a reasonable area of the macular CC for quantification. In addition, as the CC FD is also known to increase with age, we recruited subjects of similar ages into all 3 groups.

Despite our efforts to eliminate potential bias or confounders, some potential issues still remain. First, the GA lesions on average were larger than the CNV lesions. Thus, the sampled CC regions were generally farther from the CNV lesion compared with the GA lesion. As there may be gradient of CC FD that may extend from the border of a lesion, this may have biased the study to find a greater FD in eyes with GA. To assess this potential confounder, we correlated the peripheral macular CC FD% with the lesion area for both GA and CNV lesions. We did not observe any relationship between the lesion size and the FD%. Thus, we believe that lesion size is a not a key factor at all. Second, although we found no statistically significant difference in age among the 3 groups, the CNV subjects were numerically older than the GA subjects who in turn were numerically older than the healthy controls. Although the differences in age were not statistically different, the study may have been underpowered. However, when we further restrict the analyses to subsets of subjects with exactly (numerically) the same age among the groups, the overall findings remain the same.

Despite these potential limitations, our study has many strengths, including the use of deeper-penetrating SS-OCT, signal compensation, and averaging to optimize CC image quality, and the use of certified reading center graders.

Our findings of potential differences in the severity of CC FDs in eyes with CNV compared with eyes with GA warrants further study, particularly with longitudinal follow-up. For example, it is well-established that many eyes treated with anti-angiogenic therapy for neovascular AMD go on to develop macular atrophy over time.[49] Longitudinal OCTA studies of these cases may allow us to determine whether the severity of CC FD predicts which eyes develop macular atrophy and which eyes do not. Such an analysis could further highlight the critical role that the CC plays in the ultimate prognosis of eyes with AMD, and may be of relevance to future therapeutic trials targeting late AMD.

FINANCIAL DISCLOSURES: S.R.S. IS A CONSULTANT FOR ALLERGAN, AMGEN, CENTERVUE, GENENTECH/ROCHE, HEIDELBERG, Novartis, Oxurion, and Optos; and has financial interest in Carl Zeiss Meditec, Centervue, Nidek, Optos, and Topcon. The other authors indicate no financial conflict of interest. All authors attest that they meet the current ICMJE requirements to qualify as authors.

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