Plexus-specific retinal capillary avascular area in exudative age-related macular degeneration with projection-resolved OCT angiography

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The abstract was submitted to and will be presented at the Association for Research in Vision and Ophthalmology 2020 Annual Meeting, Baltimore, USA.

Received 24 July 2020
Revised 2 December 2020
Accepted 8 December 2020
Published Online First 22 December 2020

To cite: Gao L, Wang J, You Q, *et al*. *Br J Ophthalmol* 2022;**106**:719–723.

ABSTRACT

Objective To detect the plexus-specific retinal capillary avascular area in exudative age-related macular degeneration (EAMD) with projection-resolved optical coherence tomography angiography (PR-OCTA).

Methods and analysis In this prospective cross-sectional single centre study, eyes with treatment-naïve EAMD underwent macular 3×3 mm OCTA with AngioVue system. OCTA scans were analysed and processed including three-dimensional projection artefact removal, retinal layer semi-automated segmentation and en face angiogram generation. Automated quantification of extrafoveal (excluding the central 1 mm circle) avascular area (EAA) were calculated on projection-resolved superficial vascular complex (SVC), intermediate capillary plexus (ICP) and deep capillary plexus (DCP), respectively.

Results Nineteen eyes with EAMD and 19 age-matched healthy control eyes were included. There was no significant difference between the EAMD and control eyes in terms of age, sex, axial length and mean ocular perfusion pressure (all p>0.05). Compared with control eyes, EAMD eyes had significantly larger EAA in SVC (median 0.125 vs 0.059 mm^2, p=0.006), ICP (0.016 vs 0.000 mm^2, p=0.004) and DCP (0.033 vs 0.000 mm^2, p < 0.001).

Conclusion PR-OCTA showed that EAMD is associated with focal avascular area in all the three retinal vascular plexuses.

INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of blindness and vision impairment worldwide.[1 2] Exudative AMD (EAMD) and geographic atrophy (GA), also known as advanced AMD, can damage central retina and result in irreversible severe central vision loss. Although EAMD accounts for only 10% to 15% of patients with AMD, it is responsible for the 90% of severe vision loss related to the disease due to the development of choroidal neovascularisation (CNV).[3]

The exact pathogenesis of AMD remains to be elucidated. Microvascular abnormality in retina and choroid has been reported to be associated with AMD.[4–6] Quantitative and qualitative ocular blood flow abnormalities have been consistently reported using different techniques such as fluorescein and indocyanine green angiography, laser Doppler flow metre and colour Doppler imaging.[6 7] In EAMD, ischaemia is thought to promote release of vascular endothelial growth factor (VEGF), which subsequently induces chorioretinal neovascularisation.[8 9] It has been well established that choroidal ischaemia plays a driving role in AMD development.[10] However, vascular abnormality might not be limited to choroid during the ageing and degeneration of macula. Several population based epidemiological studies have reported an association between retinal vascular abnormality and incident AMD.[11–13] Additionally, histopathological studies have demonstrated significant reduction in functioning retinal capillaries in advanced AMD, suggesting possible association between retinal vasculature abnormalities and AMD.[14 15]

The development of optical coherence tomography angiography (OCTA) makes it possible to visualise CNV and associated choroidal perfusion defects.[16] Recently developed projection-resolved OCTA (PR-OCTA) significantly suppress projection artefacts and allow us to visualise three distinct retinal plexuses described in histological studies: superficial vascular complex (SVC), intermediate capillary plexus (ICP) and deep capillary plexus (DCP).[16–21] With this novel technology, it is now possible to evaluate the inner retinal circulation of eyes with AMD in vivo. Using PR-OCTA, we recently demonstrated retinal vessel density significantly decreased in GA.[22] However, it remains unclear whether there is perfusion abnormality in retinal vasculature in EAMD on OCTA. The purpose of the study was to detect the plexus-specific retinal capillary abnormalities in eyes with EAMD using PR-OCTA.

METHODS

Patients and age-matched healthy controls were recruited from the Casey Eye Institute at Oregon Health & Science University. A written informed consent was obtained from each participant.

Inclusion criteria for EAMD were age ≥50 years and treatment-naïve EAMD diagnosed with fluorescein angiography and structural OCT. Inclusion criteria for healthy control were age ≥50 years, lack of any history of retinal diseases, corrected visual acuity ≥20/20, intraocular pressure ≤21 mm Hg and without any abnormality findings on clinical fundus examination and structural OCT scans. We excluded participants who had diabetes mellitus, previous intraocular surgery except cataract extraction and intraocular lens implantation. We also excluded participants who had epiretinal membrane, complete retinal pigment epithelium

(RPE) and outer retinal atrophy, incomplete RPE and outer retinal atrophy,[23] refractive error greater than −6 or +3 diopters, significant media opacity or poor OCTA image quality with severe shadows or defocus. Type 3 CNV or retinal angiomatous proliferation were also excluded.

Each participant underwent a full ophthalmological examination which included measurement of best-corrected visual acuity, intraocular pressure (IOP), axial length, dilated fundus examination, colour fundus photography and OCTA. Fluorescein angiography was performed in patients with EAMD. Systolic and diastolic blood pressure (BP) were measured and recorded. The mean ocular perfusion pressure was calculated using the formula of 2/3 [diastolic BP + 1/3 (systolic BP – diastolic BP)] – IOP.

OCTA scans were obtained using a 70 kHz commercial OCT system (RTVue-XR Avanti Optovue, Inc, Fremont, California) with a centre wavelength of 840 nm. The eyes were scanned using 3×3 mm^2 macular scan pattern with 304 A line in each B-scan and 304 B-scans in each volume. Retinal flow signal was evaluated using the commercial version of the split-spectrum amplitude-decorrelation angiography on two repeated B-scans at the same location. One X-fast and one Y-fast scans were obtained, registered to suppress miscrosaccadic motion artefacts. Retinal layers were segmented using our in-house OCTA processing software equipped with the directional graph search-based retinal layers segmentation algorithm.[19] Boundaries of the inner limiting membrane (ILM), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer and RPE/Bruch membrane were identified. Segmentations were reviewed and adjusted manually to ensure accuracy. PR-OCT was used to remove projection artefacts and divide retinal vasculature of the macular region into three distinct layers: SVC, ICP and DCP. SVC was defined as the inner 80% of the ganglion cell complex, which includes all structures between the ILM and IPL/INL border; ICP was defined as the outer 20% of the ganglion cell complex to the inner 50% of the INL; DCP was defined as the outer 50% of the INL and the OPL.

Avascular area was measured using our deep learning-based algorithm, which was able to detect the avascular area ignoring scan quality variation.[24] Both the slab-specific angiogram and structural en face reflectance were fed into the custom convolution neural network, detected avascular area was unaffected by signal reduction and miscrosaccadic motion artefacts.[24] The extrafoveal avascular area (EAA) in each individual plexus were shown separately. EAA was defined as before, the avascular area outside the 1.0 mm central circle to reduce the effect of normal variation of the foveal avascular zone size among individuals.[20 21] The macular fluid volume was automatically detected using a validated algorithm. The regions of intraretinal fluid that overlapped with regions of EAA were excluded. The EAAs after exclusion of intraretinal fluid were compared between EAMD eyes and controls. The area of CNV membrane was quantified on OCTA, as reported previously.[16]

All statistical analyses were performed using Statistical Package for Social Sciences software (SPSS for Windows, V.25.0; IBM SPSS Inc, Chicago, USA). Descriptive statistics included mean, SD, range, median and percentages were presented where appropriate. The normality of data distribution was assessed using Shapiro-Wilk test. Independent sample t-test was used to compare age, axial length, intraocular pressure, diastolic blood pressure, systolic blood pressure and ocularperfusion pressure between eyes with EAMD and eyes of healthy control. χ^2 test was used to compare the proportion of sex and history of hypertension between EAMD and control groups. The Mann-Whitney U test was used to compare the difference of EAAs on each of the three plexuses between the two groups. The Pearson correlation was used to analyse the association between CNV size and the EAAs, and the association between the macular fluid volume and the EAAs. Significance was set at $p < 0.05$, and all p values were two-sided.

Table 1 Clinical characteristics of study participants with exudative age-related macular degeneration and age-matched controls

Characteristics	Mean±SD		P value
	Control, n=19	EAMD, n=19	
Age, years	72.7±5.3	75.6±7.6	0.17
Range	63 to 85	65 to 85	
Male, No. (%)	11 (57.9)	8 (42.1)	0.33
History of hypertension (%)	9 (47.4)	8 (42.1)	0.74
BP, mm Hg			
Systolic	128.1±17.9	124.4±16.3	0.51
Diastolic	76.4±9.7	75.0±14.5	0.72
IOP, mm Hg	16.0±3.2	14.2±3.3	0.11
Axial length, mm	24.29±1.11	24.48±1.16	0.63
MOPP, mm Hg	47.5±9.5	46.7±9.4	0.81
SSI	70±5.6	59±9.3	<0.001

BP, blood pressure; EAMD, exudative age-related macular degeneration; ; IOP, intraocular pressure; MOPP, mean ocular perfusion pressure; SSI, signal strength index.

RESULTS

A total of 19 eyes with treatment-naïve EAMD and 19 eyes of age-matched controls were included in the study. Clinical characteristics of the included participants and eyes are summarised in table 1. The age was similar between the EAMD and healthy controls (75.6±7.6 vs 72.7±5.3 years, p=0.17). There were no significant differences in sex, history of systemic hypertension, systolic blood pressure, diastolic blood pressure, intraocular pressure, mean perfusion pressure and ocular axial length between the two groups (all $p>0.05$). With regards to the types of EAMD, 13 eyes were classified as type 1 CNV and 6 eyes were classified as type 2 CNV.

In each plexus, the automated algorithm detected avascular areas in EAMD eyes (figure 1). EAAs in EAMD eyes were significantly larger in SVC (median 0.125 vs 0.059 mm^2, p=0.006),

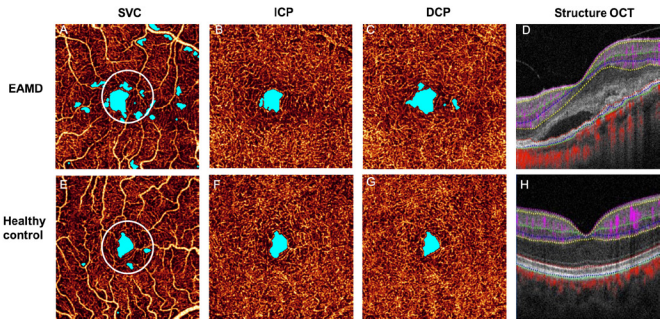

Figure 1 Eyes with exudative age-related macular degeneration (EAMD) have greater areas of avascular area (top panel) compared with age-matched healthy controls (lower panel). A to C and E to G show avascular area (light blue) at superficial vascular complex (SVC), intermediate capillary plexus (ICP) and deep capillary plexus (DCP). The white circle label central 1 mm. The avascular areas outside this circle were measured and compared between EAMD and controls. D and H show horizontal cross-sectional images of the central foveal with blood flow signal overlaid. OCT, optical coherence tomography.

Table 2 Extrafoveal avascular area in eyes with exudative age-matched controls EAMD and control eyes

	Control, n=19		EAMD, n=19		
Plexus	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	P value
SVC	0.075±0.063	0.059 (0.025 to 0.121)	0.211±0.296	0.125 (0.086 to 0.235)	**0.006**
ICP	0.004±0.007	0.000 (0.000 to 0.006)	0.019±0.024	0.016 (0.000 to 0.025)	**0.004**
DCP	0.004±0.007	0.000 (0.000 to 0.002)	0.075±0.101	0.033 (0.003 to 0.083)	**<0.001**
Inner	0.0003±0.0006	0.000 (0.000 to 0.001)	0.024±0.065	0.000 (0.000 to 0.019)	0.20

DCP, deep capillary plexus; EAMD, exudative age-related macular degeneration; EAMD, Exudative age-related macular degeneration; ICP, intermediate capillary plexus; IQR, Interquartile range; SD, Standard deviation; SVC, superficial vascular complex.

ICP (0.016 vs 0.000 mm^2, p=0.004) and DCP (0.033 vs 0.000 mm^2, p < 0.001), but not in total inner retinal layer (0.000 vs 0.000 mm^2, p=0.20), compared with EAAs of the control eyes. (table 2).

The EAA on SVC (p=0.70), ICP (p=0.15) and DCP (p=0.33) was not significantly associated with CNV membrane area. There was no difference in median EAA in eyes with type 1 CNV compared with eyes with type 2 CNV: SVC (median 0.111 vs 0.140 mm^2, p=0.63), ICP (0.010 vs 0.020 mm^2, p=0.86), DCP (0.042 vs 0.016 mm^2, p=0.73) and inner retinal layer (0.000 vs 0.000 mm^2, p=1.00).

The EAA on SVC (p=0.97), ICP (p=0.88) and DCP (p=0.57) was not significantly associated with the macular fluid volume. After the regions of intraretinal fluid that overlapped with regions of EAA were excluded, EAAs in EAMD eyes remained significantly larger in SVC (p=0.003), ICP (p=0.007) and DCP (p=0.001), but not in total inner retinal layer (p=0.42),compared with that of healthy controls (figure 2).

DISCUSSION

Our results demonstrated that retinal capillary avascular area detected with PR-OCTA in SVC, ICP and DCP of treatment-naïve EAMD eyes with type 1 or type 2 CNV were significantly larger compared with that of age-matched healthy controls, suggesting retinal microvascular abnormality is associated with EAMD. These results are consistent with previous histopathological studies.[14 15] Kornzweig *et al* examined 166 postmortem eyes and found significantly higher number of atrophic or occluded capillaries in perifoveal region in eyes with advanced senile macular degeneration compared with normal aged eyes.[14] Histopathologically, these occluded capillaries appeared as inter-capillary strands with a diameter of 2 to 3 µm without any red blood cells within them.[14] Areas covered by these occluded capillaries (lack of blood cells flowing inside) will appear as non-perfusion areas on OCTA, since OCTA produces angiograms depending on detection of flowing blood.[17 25]

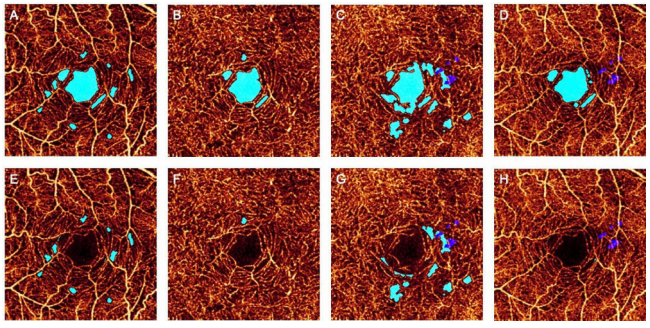

Figure 2 Extrafoveal avascular area in an eye with exudative age-related macular degeneration. A to D show avascular area (light blue) at superficial vascular complex (SVC), intermediate capillary plexus (ICP), deep capillary plexus (DCP) and inner retina, respectively. The dark blue labels intraretinal fluid. E to H show extrafoveal avascular area (excluding central 1 mm circle) at SVC, ICP, DCP and inner retina, respectively. The overlapped areas of light blue (avascular area) and dark blue (intraretinal fluid) were excluded from statistical analysis to eliminate the impact of intraretinal fluid.

Our results of reduced retinal perfusion in EAMD detected with OCTA also agree with previous studies on retinal perfusion using other clinical techniques in vivo. Colour Doppler imaging demonstrated central retinal arteries in patients with AMD had lower velocities compared with controls.[26 27] Reduced blood flow velocity in retinal arteries was reported in patients with EAMD by Retinal Function Imager.[28] Further studies on retinal oxygen metabolism revealed smaller arteriovenous difference in patients with EAMD, implying reduced oxygen extraction by retinal vessels. These studies indicate that the vascular abnormalities in EAMD may extend beyond the level of the choroidal vasculature to retinal vascular system, which supplies the inner retinal layers.

It remains unclear whether the reduced retinal perfusion is secondary to EAMD lesions or plays a driving role in EAMD pathogenesis. Previous structural OCT study demonstrated significantly thinner ganglion cell complex in treatment-naïve EAMD eyes than in normal controls.[29 30] Histopathological studies also reported that, in addition to photoreceptor loss, eyes with EAMD had 47% fewer ganglion cell layer neurons than aged normal eyes.[15 31] Because subretinal haemorrhage, exudation and fibrosis often results in photoreceptor loss, we deduce the decreased retinal perfusion detected by OCTA is more likely resulting from EAMD lesions, rather than playing a driving role in EAMD pathogenesis. The loss of inner retinal neurons might cause secondary reduced retinal perfusion.[29] Another possible explanation is that the reduced retinal perfusion change may be secondary to the reduced inner retinal activity due to reduced signal transferring from outer retina after photoreceptor damage in EAMD.

Our automated algorithm of detecting the avascular areas on PR-OCTA not only visualised retinal microvascular networks with retinal capillary loss but also quantified the avascular area automatically in three retinal capillary plexuses. Retinal capillary avascular was detected in SVC, ICP, DCP and inner layers in eyes with EAMD. EAAs in EAMD eyes were significantly larger in SVC, ICP, DCP, whereas EAA of inner retina in EAMD eyes did not differ significantly from that observed in healthy control eyes. The reason for larger EAA detected in individual plexus but not in the inner retina measured as a whole is mainly due to the overlapping effect. When the inner retina is measured as a whole, the vessels of different plexuses overlap with each other. This overlap reduces the EAA detection sensitivity. Similar results were also found in our recently

published studies on diabetic retinopathy.[20] The results indicated that the automated algorithm for quantification of avascular with PR-OCTA may be more sensitive and reliable in evaluating the reduced retinal perfusion than commercially available vessel density measurements. Another advantage of measuring avascular area for assessment of retinal microvasculature abnormality is it is less dependent on signal strength index than vessel density measurement.[20 21]

This study is associated with some limitations. First, as a cross-sectional study, it is impossible to determine whether there is a causal relationship between the reduced retinal perfusion and EAMD. Second, the sample size is relatively small. Some potential systemic confounding factors, such as cigarette smoking, hyperlipidaemia and renal functions, were not available in the current study. A longitudinal study with a larger sample size including more potential systemic confounding factors on this issue is warranted. Third, the intraretinal fluid may confound the avascular area measurements due to displacement of inner retinal vessels. This is an inherent issue in any case of retinal oedema, and it is unclear how significant is the impact. To reduce the potential impact of intraretinal fluid, we excluded cases with extensive intraretinal fluid, and include 5 EAMD eyes with only minimal intraretinal fluid and 14 eyes with subretinal fluid only. The same methodology has been used and accepted in diabetic retinopathy literatures.[20 32] Furthermore, we excluded the overlapped intraretinal fluid area from EAAs (figure 2), the results demonstrated the EAAs remained significantly larger in EAMD eyes after eliminating the impact of intraretinal fluid on EAA measurements. Despite the limitations, to the best of our knowledge, we provide the first study of visualisation and quantification retinal capillary avascular area in each of the three retinal capillary plexuses in EAMD eyes using OCTA. This finding will increase our understanding of the disease.

In conclusion, retinal capillary avascular was automatically detected in all three retinal plexuses (SVC, ICP and DCP) using PR-OCTA in eyes with EAMD. Greater EAA was found in each of the three individual plexuses in eyes with EAMD compared with controls. PR-OCTA showed that EAMD is associated with focal avascular in all the three retinal vascular plexuses.

Contributors LG: Assembly of data, data analysis and interpretation and manuscript writing. JW: Assembly of data, data analysis and interpretation and manuscript preparation. QSY: Conception and design, assembly of data, data analysis and interpretation and manuscript writing. YG: Assembly of data, data analysis and interpretation and manuscript preparation. CF: Collection of data and manuscript preparation. TSH: Collection of data and manuscript preparation. DH: Data analysis and interpretation and manuscript preparation. YJ: Conception and design, collection and/or assembly of data, data analysis and interpretation and manuscript writing. SB: Conception and design, collection and/or assembly of data, data analysis and interpretation and manuscript writing.

Funding The study was supported by grants R01 EY024544, R01 EY027833 and P30 EY010572 from the National Institutes of Health, an unrestricted departmental funding grant and William & Mary Greve Special Scholar Award from Research to Prevent Blindness, New York.

Disclaimer The funding source had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests Oregon Health & Science University (OHSU) and Drs Huang and Jia have a significant financial interest in Optovue, a company that may have a commercial interest in the results of this research and technology. These potential conflicts of interest have been reviewed and managed by OHSU.

Patient consent for publication Not required.

Ethics approval The study was approved by the institutional review board at Oregon Health & Science University and performed in accordance with the tenets of the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Not applicable.

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