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CORRESPONDENCE

Differences in macular microvascular changes between eyes with central retinal vein occlusion and proliferative diabetic retinopathy

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To the Editor:

Both proliferative diabetic retinopathy (PDR) and central retinal vein occlusion (CRVO) affect the macular microvasculature. Whilst diabetic retinopathy is a gradual process and predominantly affects the venous end of capillaries, CRVO causes acute back pressure from larger veins into the microvasculature. However, both have clinically similar endpoints in terms of macular ischaemia and macular oedema. In this study, we evaluated the similarities and differences in microvascular changes at the macula in these two conditions using multimodal imaging. In particular, optical coherence tomography angiography (OCTA) was used to quantify changes in the architecture of different vascular plexi of retina [1]. On OCT, the disorganisation of inner retinal layers (DRIL) has been reported as a marker of ischaemia in both these conditions and is associated with poor visual prognosis [2, 3]. We hypothesise that as the inciting stimuli in these two conditions vary, these conditions may affect the macular microvasculature differently.

This retrospective observational study was performed at the Moorfields eye Hospital. Imaging was performed as part of standard clinic procedure. Institutional review board approval was not required.

Eyes with treated stable PDR or non-ischaemic CRVO with no macular oedema were included. Only eyes with PDR had prior history of pan retinal photocoagulation laser. We excluded eyes with any co-existent pathology and those with significant macular haemorrhages that can mask the changes in the microvasculature. The OCTA images were captured on Zeiss Cirrus HD-OCT 5000 or RTVue XR 100 Avanti (Optovue, Inc., Fremont, CA, USA) device from June 2017 to September 2018. Only images with good quality (signal strength >50 on Optovue, >7 on Zeiss Cirrus Angioplex) were considered for analysis. Motion artefact corrected $3 \times 3\,mm^2$ enface OCTA centred on the fovea were selected. The boundaries for superficial and deep vascular plexi (SVP, DVP) analysis were manually adjusted to match both devices. The inner boundary of SVP was set at 3 µm beneath the internal limiting membrane and outer boundary at 15 µm beneath the inner plexiform layer, while the DVP enface image was segmented considering inner boundary at 15 µm below the inner plexiform layer and an outer boundary at 70 µm below the inner plexiform layer. The foveal avascular zone (FAZ) was delineated manually for both superficial and deep vascular plexus on ImageJ software [http://rsb.info.nih.gov/ij/index.html] (Fig. 1). The FAZ area and perimeter was calculated using the formula: FAZ area in $pixel^2 \times 9\,mm^2$/area of the whole image in $pixel^2$. Vessel density was obtained by binarization of original image using the threshold obtained using Otsu's method, which minimises the intra-class variance of the resulting vessel and background distributions [4]. The vessel density metric was computed as ratio between vessel area and total image area and value obtained using Matlab 2019a [4]. All eyes included in the study also underwent Spectral domain OCT (Heidelberg Engineering, Germany) scans ±14 days of their OCTA imaging. Central subfield thickness, integrity of ellipsoid zone (EZ) and presence or absence of DRIL were also recorded.

All study parameters are reported as mean and standard deviation. Independent- samples *t* or Mann–Whitney *U* test was used to compare between groups. Linear regression analysis was used to study the strength of relationship of these markers with either retinal pathology. *P* values of <0.05 were considered as statistically significant. Statistical analysis was performed with SPSS software version 22 (SPSS, Inc., Chicago, IL, USA).

A total of 59 eyes were included, 29 eyes with stable PDR and 30 eyes with CRVO. Table 1 shows the differences between these two study groups. The mean vessel

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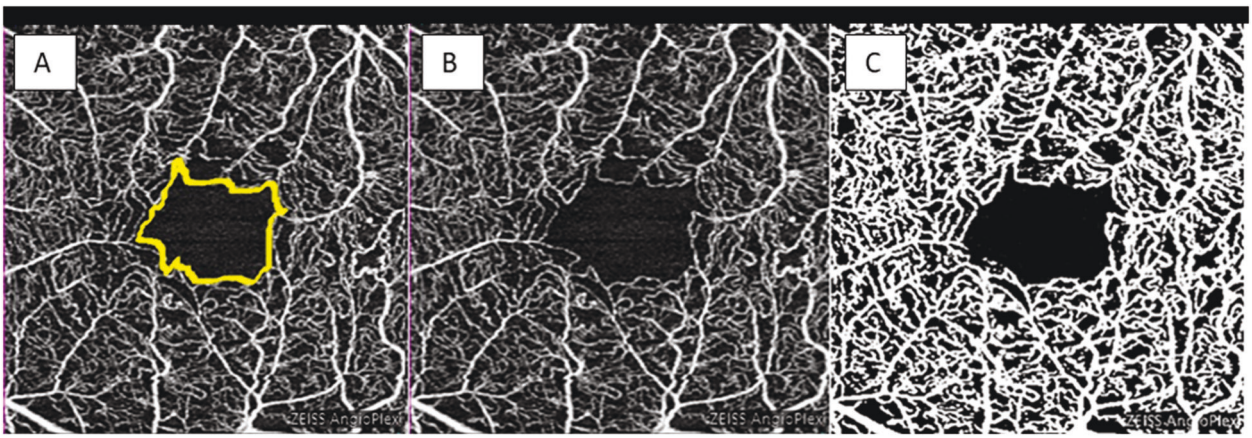

Fig. 1 OCT angiogram of left eye of patient with stable proliferative diabetic retinopathy showing foveal avascular zone (FAZ) at superficial vascular plexus (SVP). (**A**) FAZ determined using manual tracing (marked yellow), (**B**) original en face image of SVP, (**C**) en face image after binarization.

Table 1 Optical coherence tomography (OCT) and OCT-angiography derived measurements.

	PDR Mean (SD) $n = 29$	CRVO Mean (SD) $n = 30$	p value[a]
VA (ETDRS letters)	78.41 (8.13)	74.10 (14.50)	0.47
Age (years)	52.86 (10.61)	56.4 (17.62)	0.36
SVP density, %	42.45 (8.86)	52.32 (7.67)	**0.001**
DVP density, %	48.14 (7.48)	53.11 (8.87)	**0.03**
FAZ SVP area (mm^2)	0.54 (0.22)	0.49 (0.23)	0.32
FAZ DVP area (mm^2)	0.62 (0.26)	0.79 (0.39)	0.05
FAZ perimeter	3.48 (1.12)	2.96 (0.70)	**0.04**
Proportion with DRIL	21 (72.41%)	10 (33.33%)	**0.002**
CST (μm)	249.10 (33.37)	253.17 (36.62)	0.41
Proportion with loss of integrity of ellipsoid layer	3 (10.34%)	6 (20%)	0.31
Patients received Anti-VEGF treatment for macular oedema	8	16	0.05

PDR proliferative diabetic retinopathy, *CRVO* central retinal vein occlusion, *VA* visual acuity, *ETDRS* early treatment diabetic retinopathy study, *SVP* superficial vascular plexus, *DVP* deep vascular plexus, *FAZ* foveal avascular zone, *DRIL* disorganisation of the inner retinal layers, *CST* central subfield thickness, *VEGF* vascular endothelial growth factor.

[a]Statistical comparison using independent-samples t test or Mann–Whitney U test.

p values <0.05 indicated in bold.

density in both the superficial and deep capillary plexus were significantly reduced and proportion of DRIL were higher in PDR compared to CRVO. Although FAZ areas were no different between the two conditions, FAZ perimeter was significantly higher in PDR patients ($p = 0.04$). The outer retinal change represented by integrity of EZ were similar in PDR and CRVO eyes. Regression analysis showed FAZ perimeter is estimated to be 0.52 mm (95% CI 0.33, 1.005) higher in PDR eyes than CRVO. Vessel density of superficial plexus is expected to be 10% (95% CI 5.6, 14.1%) and that of deep plexus 5% (95% CI 0.7, 9.3%) higher in CRVO eyes.

Our study shows that stable treated PDR have more signs of ischaemia in both the superficial and deep plexi than non-ischaemic CRVO. Reductions of density of superficial and deep plexi have been shown to precede overt clinical diabetic retinopathy, highlighting the slow course of the capillary drop out [5]. It usually takes years to develop PDR. The reduction in density of superficial plexus in PDR may also relate to higher proportions of DRIL, as a secondary neurodegenerative change. As DRIL was less common in CRVO, it suggests that DRIL is more common in chronic ischaemia or that a threshold of loss of density of superficial vascular density is required before DRIL develops. In contrast, CRVO is associated with capillary drop out even in eyes that are clinically diagnosed as non ischaemic [6].

Previous studies have shown that FAZ size increases with severity of diabetic retinopathy [7] and CRVO eyes also have larger FAZ than healthy eyes [8]. However, the mean FAZ area was not different between the two conditions in our cohort. Tan et al. suggested FAZ size may not be a reliable marker for foveal health as it is affected by inter individual variation as well as axial length [9]. Disruption of terminal capillary ring specified by FAZ perimeter would be better indicator of ischaemic damage when comparing microvascular conditions. In our study population, FAZ perimeter was larger among PDR eyes. One could argue that the two conditions are not comparable. However, both these conditions are end-stage of acute or chronic events and so comparing them is more valid than comparing CRVO to any severity of diabetic retinopathy or comparing PDR to ischaemic CRVO only. It is also very

challenging to obtain good OCTA images in eyes with ischaemic CRVO. We conclude that although PDR and CRVO may result in severe capillary non-perfusion, there are differences in severity of microvascular changes, which may at least in part be explained mainly by the nature of onset of the conditions.

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Compliance with ethical standards

Conflict of interest SS reported receiving research grants from Novartis, Bayer, Allergan, Roche, Boehringer Ingelheim, and Optos Plc, travel grants from Novartis and Bayer, speaker fees from Novartis, Bayer, and Optos Plc, and attending advisory board meetings for Novartis, Bayer, Allergan, Roche, Boehringer Ingelheim, Optos Plc, Oxurion, Opthea, Apellis, Oculis and Heidelberg Engineering.

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