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Comparison between post treatment vascular density, fractal dimension and choriocapillaris flow in ischemic and non-ischemic retinal vein occlusion using optical coherence tomography angiography

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***Abstract*---**The aim of the study was to compare vascular density (VD), fractal dimension (FD), foveal avascular zone (FAZ) and choriocapillaris flow and using optical coherence tomography angiography (OCTA) before and after Bevacizumab therapy in patients with macular edema associated with ischemic and non-ischemic retinal vein occlusion (RVO). 15 eyes with ischemic RVO and 20 with non-ischemic RVO were included. Each patient had 3 consecutive intravitreal injections of Bevacizumab every month. Best-corrected visual acuity (BCVA), central macular thickness (CMT) and retinal microvasculature were measured using OCTA before and one month after the third injection. The BCVA and FAZ area improved significantly after treatment in both ischemic and non-ischemic cases. Although, in ischemic group, FD, superficial and deep capillary VD decreased with no statistically significant change in the choriocapillaris flow. In the non-ischemic group, there was an increase in the FD, superficial parafoveal, perifoveal VD and choriocapillaris flow with insignificant increase in the DCP VD while the foveal VD showed a statistically significant decrease. In conclusion, anti-VEGF therapy improved the BCVA, retinal FD, VD in

non-ischemic case but despite improvement in BCVA it reduced the VD in the ischemic cases.

***Keywords*---**retinal vein occlusion, optical coherence tomography angiography, anti–vascular endothelial growth factor, macular edema, retina

Introduction

Retinal vein occlusion (RVO) is a common retinal vascular disorder that is complicated by retinal hemorrhage, retinal ischemia, and macular edema lead to severe visual impairment or even blindness (Lumbroso et al. 2015). Macular edema is induced by increased intraocular vascular endothelial growth factor (VEGF) and the introduction of anti-VEGF therapy has revolutionized the management of RVO. Multiple reports have shown the effectiveness of the anti-VEGF in reducing macular edema, however, post treatment changes in retinal vasculature and perfusion varied between the studies and few have divided the patients into ischemic vs non ischemic RVO (Suzuki et al., 2016; Winegarner et al. 2018; Deng et al., 2019; Ghasemi et al., 2017; Sellam et al., 2017; Nicolai et al., 2019). Ischemic RVO is characterized by extensive retinal capillary non perfusion leading to significant visual impairment, while non ischemic RVO entitle a less severe non perfusion with mild to no visual dysfunction (Lumbroso et al. 2015).

Reported visual outcomes after anti-VEGF therapy were different. Some reports showed complete visual recovery while other showed less improvement in the visual acuity, an effect that was related to the status of post treatment retinal perfusion and retinal ischemia. (Sellam et al., 2017; Nicolai et al., 2019). Therefore, understanding the effects of anti-VEGF therapy on the retinal perfusion would provide better management of RVO.

Optical coherence tomography angiography (OCTA) is a noninvasive test that allow imaging and differentiation of the retinal vascular layers up to the capillary level in comparison to conventional fluorescein angiography (FA). It can delineate area of capillary drop-out precisely and capture the foveal avascular zone (FAZ) without dye leakage as in FA. OCTA can also accurately and quantitatively measure the fractal dimension (FD and vascular density (VD), especially in the macular area, without human interference, in a reproducible manner (Lumbroso et al. 2015).

The aim of the study was to compare the short-term changes in FAZ, retinal VD and choriocapillaris flow using OCTA in patients with ischemic vs non ischemic RVO after 3 months of consecutive intravitreal injection of anti-VEGF therapy and investigate their relationship with visual outcomes.

Material and Methods

Our prospective comparative analytic study was performed according to the declaration of Helsinki and was approved by the Institutional Review Board and

ethical committee at Cairo University. All patients received a thorough explanation of the study design and aims. Before inclusion in the study, written informed consent was obtained from all study participants.
The study included all consecutive patients who presented to the outpatient ophthalmology clinic of Kasr El Aini Hospital, Cairo, Egypt from October 2017 to April 2019; with central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) of recent onset within 3 months who had macular edema more than 250 micrometers.

We excluded patients with macular edema secondary to other causes such as diabetic retinopathy, age-related macular degeneration, vitreomacular traction or epiretinal membrane, patients with ocular conditions that may affect macular perfusion (e.g. uveitis, vasculitis), patients with history of old retinal vein occlusion of more than 3 months duration, patients with history of previous vitreoretinal surgery, patients with significant media opacity preventing good image quality and patients who had previous intravitreal Anti-VGEF injection.
All patients underwent FA (Topcon TRC-50DX, Topcon Medical System Inc., 2015), spectral domain optical coherence tomography (SD-OCT) (Optovue RTVue ™, Optovue inc., Fremont, CA) and OCTA using RTVue XR Avanti (AngioVue; optovue Inc, Fremont, California, USA) in a 6x6 mm protocol before starting the treatment.

FA was used to establish the diagnosis of RVO with qualitative evaluation of abnormal vascular permeability in addition to delineation of non-perfused areas to differentiate ischemic from non- ischemic RVO, besides assessing the degree of capillary dilatation. Patients were classified as ischemic CRVO if the FA showed more than 10-disc areas of capillary non perfusion in addition to visual acuity of less than 6/6, relative afferent pupillary defect (RAPD) and fundus examination with extensive cotton wool spots. Similar criteria were used for ischemic BRVO but only with FA showing more than 5-disc areas of capillary non perfusion. Patients with visual acuity more than 6/60, no RAPD, had less than 10 (for CRVO) or 5 (for BRVO) disc areas of capillary non perfusion were classified as non-ischemic RVO.

SD-OCT was used to quantify the macular edema, while OCTA was used evaluate the choriocapillaris flow, the FAZ and the vascular density map at the level of the superficial capillary plexus (SCP) and deep capillary plexus (DCP). All patients had consecutive intravitreal VEGF injections of 2.5 mg/0.1 ml Bevacizumab each month for total of 3 months. Patients were assessed within 3 days of injections and then after 1 month following each injection. FFA, SD-OCT and OCTA were repeated one month after the third injection.

Retinal microvasculature imaging by OCTA

A 6 x 6 mm scan protocol with fovea in the center was used for all patients using RTVue XR Avanti (AngioVue; optovue Inc, Fremont, California, USA) OCTA. This protocol allowed imaging of a wider area including the perifoveal capillary network. Automated segmentation was done by the machine. Full thickness retinal slab extended from the internal limiting membrane (ILM) to 9 µm below the outer plexiform layer (OPL) - outer nuclear layer (ONL) junction. The SCP

extended from the ILM to 9 µm above the inner plexiform layer (IPL) - inner nuclear layer (INL) junction, while the DCP extended from 9 µm above the IPL-INL junction to 9 µm below the OPL-ONL junction.
Scans were repeated if there was poor fixation or low signal strength index (SSI; < 5), 1 or more blink artifacts were present, areas of localized signal loss due to media opacity obscuring the view of part of the vasculature, or major segmentation errors. The patient was excluded if the any of the above criteria persisted on repeat imaging. Built in machine software was used to manually correct any minor segmentation errors. The 2 parallel segmentation lines were placed at the appropriate depth using the corresponding structural OCT B-scans as a guide (Figure 1).

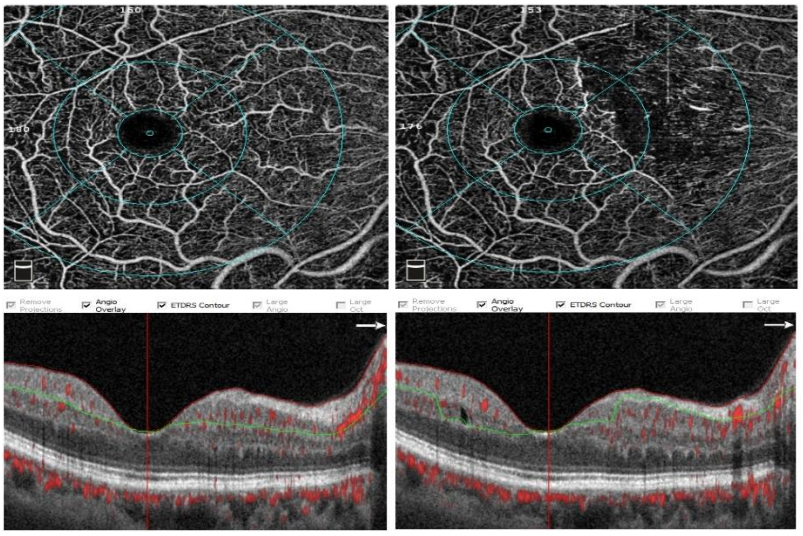

Figure 1: An Example of Manual Correction of a Segmentation Error. A Segmentation Error in The Superficial Capillary Plexus (Lt Photo) was Corrected Manually Using The Built-In Machine Software Which Resulted in Visualization of Missing Vasculature (Rt Photo).

OCTA parameters, including the flow area, FAZ, vessel density, and differences between pre and post treatment measurements, were calculated using OCTA built-in software. Associations between these parameters and BCVA and retinal thickness were then evaluated.

FAZ parameters were automatically quantified on a retina slab from the Angio Retina scan, extending from ILM to 9 µm below the OPL. We quantitatively evaluated VD, defined as the percentage area occupied by OCTA-detected vasculature in the selected regions. The software automatically measured the VD in percentage in the fovea, different sectors of parafovea and perifovea at the superficial and deep en-face slabs, which is an ETDRS grid overlay, that is centered on the FAZ of the SCP and DCP. Data were quantitatively displayed in tables and qualitatively in color coded vessel density maps, where dark blue representing the areas of severe ischemia.

A software generated retinal map scan was used to quantify the full retinal thickness of the scanned area, including the foveal region, parafoveal region and perifoveal region. Full retinal thickness extended from the ILM to the retinal pigment epithelium (RPE). The area occupied by the vasculature in a 1-mm radius circle centered on the fovea in the choriocapillaris, was defined as the vascular flow area FD provides an index of the branching complexity of the retinal capillary network which is a description of blood vessel tortuosity. FD was calculated manually by segmenting the blood vessels from a full OCTA image, producing a binary black and white image. First, an area within the FAZ was selected manually 3 times to establish a baseline signal-to-noise ratio for the global thresholding step. A global threshold was used to set to zero all the pixels below that threshold. The binary image was then skeletonized by reducing all the continuous white segments to a line with a single pixel width using the skeleton plugin of ImageJ software (Figure 1).

Statistical analysis

Analysis was done using the statistical package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). Mean, standard deviation, median, minimum, and maximum was used to summarize quantitative data while frequency (count) and relative frequency (percentage) was used for categorical data. Comparison between data measured before and after within same patients was done using Wilcoxon signed rank test while comparison between different patients was done using Mann-Whitney test (Chan YH, 2003). Spearman correlation coefficient was used to correlate between quantitative variables. P-values less than 0.05 were considered as statistically significant (Chan YH, 2003).

Results

Total of 40 eyes of 40 patients with RVO were eligible during the study period and were enrolled initially. 2 patients were lost to follow up and 3 patients were excluded due to inability to obtain high quality images in the follow-up scans. Total of 35 eyes of 35 patients were included in the final analysis. The 35 patients included 14 men (40%) and 21 women (60 %). The mean age of the patients was 54.5 ± 9.9 years old ranging from 30 to 70 years old.

Regarding the type of RVO and according to FA images, 15 (43 %) eyes had ischemic RVO (CRVO in 6 eyes and BRVO in 9 eyes) while 20 (57%) eyes had non-ischemic RVO (CRVO in 7 eyes and BRVO in 13 eyes). The mean IOP was 13.86 ± 4.47 mmHg across all patients. The pre-treatment logMAR BCVA in the non-ischemic group was statistically significantly higher than the pre-treatment BCVA in the ischemic group (P value <0.001). However, there were no statistical difference between both groups as regards of pre-treatment FAZ area, SCP VD, DCP VD and choriocapillaris flow. In the non-ischemic group, there was statistically significant negative correlation between pre-treatment LogMAR BCVA and pre-treatment FD ($r = -0.515$, $p = 0.041$). No significant correlations were found between pre-treatment LogMAR BCVA and pre-treatment FAZ area, pre-treatment SCP VD, DCP VD, pre-treatment choriocapillaris flow and CMT, respectively.

In ischemic RVO, there was statistically significant positive correlation between pre-treatment logMAR BCVA and pre-treatment central macular thickness (CMT) ($r = 0.780$, $p = 0.037$) while no significant correlation was found between pre-treatment LogMAR BCVA and pre-treatment FAZ area, pre-treatment SCP VD, DCP VD, pre-treatment choriocapillaris flow and FD, respectively.
Table 1 shows the quantitative analysis of the pre- and post-treatment results of the ischemic RVO group.

Table 1: Quantitative Analysis and Comparison of The Pre- And Post- Treatment Results of The Ischemic Group.

	Pre-treatment	**Post-treatment**	**P-value[a]**
LogMAR BCVA (mean ± SD)	1.44 ± 0.29	0.91 ± 0.34	0.005
CMT (mean ± SD), µm	727 ± 238	327 ± 162	0.003
FAZ area (mean ± SD), mm2	0.25 ± 0.21	0.37 ± 0.28	0.012
VD SCP Whole image (mean ± SD)	44.53 ± 4.34	40.23 ± 4.31	0.003
VD SCP parafovea (mean ± SD)	44.55 ± 5.07	39.45 ± 4.00	0.003
VD SCP perifovea (mean ± SD)	44.17 ± 4.18	40.27 ± 4.68	0.003
VD DCP Whole image (mean ± SD)	43.16 ± 4.04	39.32 ± 3.80	0.008
VD DCP Parafovea (mean ± SD)	46.78 ± 5.44	43.43 ± 4.16	0.016
VD DCP Perifovea (mean ± SD)	42.84 ± 3.45	40.17 ± 3.65	0.005
Superficial foveal density (mean ± SD)	35.85 ± 12.22	20.51 ±13.76	0.004
Deep foveal density (mean ± SD)	35.54 ± 13.15	28.65 ±11.02	0.012
FD (mean ± SD)	1.70 ± 0.04	1.64 ± 0.05	0.028
Choriocapillaris flow (mean ± SD)	1.78 ± 0.22	1.86 ± 0.26	0.400

a: Comparison between data measured before and after was done using Wilcoxon signed rank test. BCVA: Best correct visual acuity, CMT: Central macular thickness, DCP: Deep capillary plexus, FAZ: Foveal avascular zone, FD: Fractal dimension, SCP: Superficial capillary plexus, SD: Standard deviation, VD: Vascular density

In ischemic RVO group, statistically significant improvement in the BCVA (mean change -0.53 ± 0.28) with decrease in the CMT (mean change -399 ± 264.8). However, there were statistically significant decrease in all vascular perfusion parameters that may indicate decrease in macular perfusion secondary to intravitreal injections. The mean size of the FAZ area (mean change + 0.12 ± 0.2) increased post treatment, while there was decrease in the SCP VD (mean change of the whole image vascularity -4.3 ± 3.4, mean change of the foveal vascularity -15.09 ± 11.02, mean change of the parafoveal vascularity -5.09 ± 3.85 and of the perifoveal vascularity -3.9 ± 3.43), DCP VD (mean change of the whole image -3.84 ± 3.3, mean change of the foveal vascularity -6.89 ± 4.82, mean change of the parafoveal vascularity -3.35 ± 3.78 and of the perifoveal vascularity -2.66 ± 2.24) and FD (mean change -0.06 ± 0.03). No statistically significant change was noted in the flow at the choriocapillaris (mean change 0.08 ± 0.2). Figure 2 demonstrate example findings in a patient with right ischemic CRVO.

Table 2 shows the quantitative analysis of the pre- and post-treatment results of the non-ischemic RVO group.

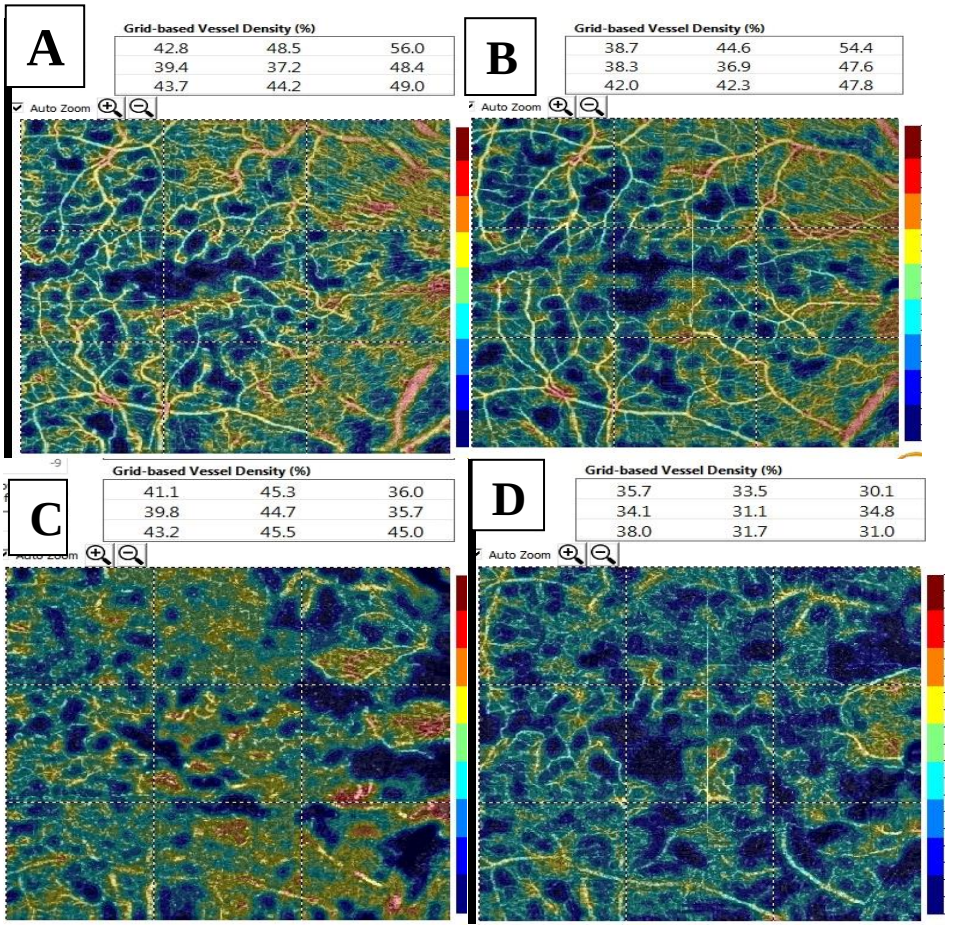

Figure 2: Changes in Retinal Microvasculature in The SCP and DCP of A Patient With Ischemic CRVO. The SCP Before (A) and After Treatment (B). The DCP Before (C) and After Treatment (D).

Table 2: Quantitative Analysis and Comparison of The Pre and Post- Treatment Results of The Non- Ischemic Group.

	Pre-treatment	**Post-treatment**	**P-value[a]**
LogMAR BCVA (mean ± SD)	0.89 ± 0.22	0.38 ± 0.24	< 0.001
CMT (mean ± SD), µm	554 ± 164	263.65 ± 62	< 0.001
FAZ area (mean ± SD), mm2	0.21 ± 0.11	0.35 ± 0.12	< 0.001
VD SCP Whole image (mean ± SD)	43.25 ± 4.85	45.65 ± 4.97	0.011
VD SCP parafovea (mean ± SD)	42.80 ± 5.50	44.92 ± 5.51	0.049
VD SCP perifovea (mean ± SD)	43.76 ± 5.07	46.07 ± 5.22	0.030
VD DCP Whole image (mean ± SD)	42.31 ± 5.21	42.99 ± 4.22	0.410
VD DCP Parafovea (mean ± SD)	44.95 ± 4.30	46.64 ± 4.59	0.127
VD DCP Perifovea (mean ± SD)	43.29 ± 6.65	44.10 ± 5.05	0.272

Superficial foveal density (mean ± SD)	33.00 ±7.95	15.62 ± 6.64	< 0.001
Deep foveal density (mean ± SD)	35.56 ± 10.99	25.55 ± 5.42	0.008
FD (mean ± SD)	1.70 ± 0.04	1.64 ± 0.05	0.028
Choriocapillaris flow (mean ± SD)	1.61 ± 0.24	1.98 ± 0.12	< 0.001

a: Comparison between data measured before and after was done using Wilcoxon signed rank test. BCVA: Best correct visual acuity, CMT: Central macular thickness, DCP: Deep capillary plexus, FAZ: Foveal avascular zone, FD: Fractal dimension, SCP: Superficial capillary plexus, SD: Standard deviation, VD: Vascular density

In non-ischemic RVO group, statistically significant improvement in the BCVA (mean change -0.52 ± 0.9) with decrease in the CMT (mean change -290 ± 162) was also noted. There were statistically significant changes in some of the vascular perfusion parameters indicating possible improvement of macular perfusion secondary to treatment, where we found an increase in the SCP VD (mean change of the whole image 2.3 ± 4.5, mean change of the parafoveal vascularity 2.12 ± 3.82 and mean change of the perifoveal vascularity 2.32 ± 3.58), choriocapillaris flow (mean change 0.37 ± 0.2) and FD (mean change 0.08 ± 0.1).

The DCP VD increased but it was statistically insignificant (mean change of the whole image 0.68 ± 3.9, parafovea 1.69 ± 4.26 and mean change of the perifoveal vascularity 0.81 ± 3.85). However, there was a statistically significant increase in the size of the FAZ area (mean change 0.14 ± 0.1). Figure 3 demonstrate example findings in a patient with right non-ischemic CRVO.

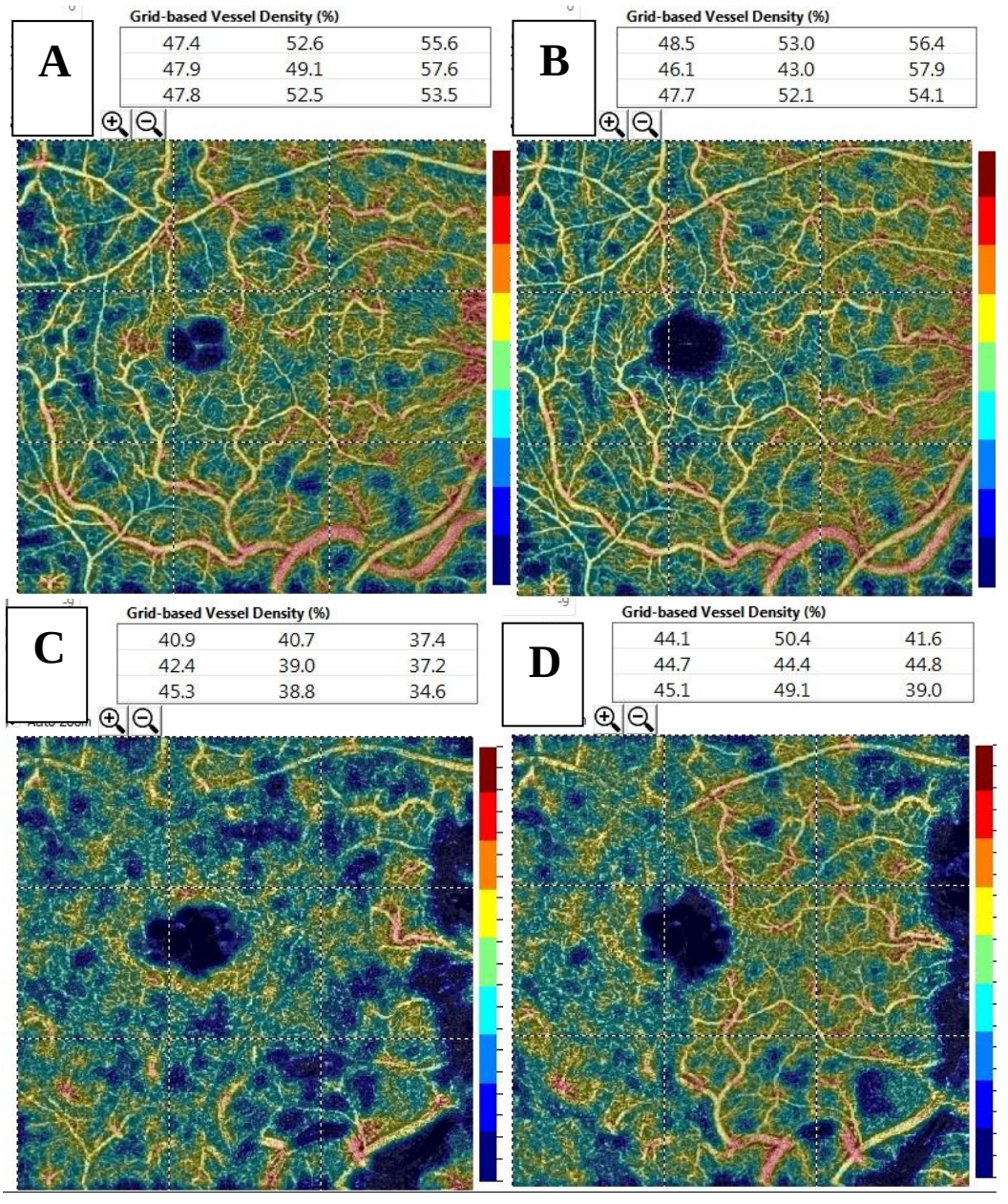

Figure 3: Changes in Retinal Microvasculature in The SCP and DCP Of A Patient With Non-Ischemic CRVO. The SCP Before (A) and After Treatment (B). The DCP Before (C) and After Treatment (D).

No significant correlations were found between post treatment LogMAR BCVA and post treatment FAZ area, SCP VD, DCP VD, CMT, choriocapillaris flow or FD in both ischemic and non-ischemic group. No significant correlations were found between pre-treatment SCP VD and change in SCP VD, pre-treatment DCP VD and change in DCP VD, pre-treatment CMT and change in SCP and DCP VD, pre-

treatment FAZ and change in SCP and DCP VD and pre-treatment SCP VD, DCP VD and change in the BCVA.

Discussion

Our study demonstrated improvement of LogMAR BCVA and CMT in both ischemic and non-ischemic types of RVO. Literature search showed conflicting evidence regarding the effect of anti-VEGF therapy on retinal microvasculature and retinal flow. While some showed adverse effects on retinal perfusion (Papadopoulou et al., 2009; Micieli et al., 2012; Sacu et al., 2011), others showed improvement of retinal perfusion following anti-VEGF therapy (Sophie et al., 2013; Mir et al., 2016).

Despite improvement in LogMAR BCVA and CMT there was decrease in all vascular perfusion parameters (SCP VD, DCP VD and FD) indicating a likely decrease in macular perfusion following intravitreal anti-VGEF injections. This can be secondary to continuous increase of vascular non-perfusion over time due to nonreversible ischemic damage of the retinal vessels or as a part of disease progression, as seen in progression of non-ischemic to ischemic CRVO, however, our study did not have a control group to assess whether the decrease is more or less with the anti-VGEF therapy (Sellam et al., 2017; Glacet-Bernard et al., 2016). Some studies showed that intravitreal anti-VGEF therapy can halt but does not completely block retinal capillary closure (Jia et al., 2012). Masked retinal nonperfusion could have been originally present at the early stages of the RVO and was only revealed after treatment induced cysts regression. Areas with slow capillary blood flow that fall below the OCTA detection limit of 0.3 mm/second can appear to be non-perfused (Boyd et al., 2002).

Boyd et al. suggested that initial transient elevation of VEGF occurs immediately after the onset of ischemic CRVO, that can have a beneficial effect and likely represent retinal cells immediate response to hypoxemia (Boyd et al., 2002). In such cases, VEGF can play a beneficial role, leading to capillary remodeling and revascularization of the ischemic areas with insufficient retinal oxygenation. Hence, anti-VEGF therapy could cause blockage of those protective effects, leading to deleterious effects in the acute phase of CRVO. Anti-VEGF can also delay the development of VEGF-mediated retinal venogenesis and retino-ciliary collateral formations from pre-existing venous channels, that can help in bypassing the venous occlusion.

Similar effect of VEGF is seen patient with myocardial infarction, were the expression of VEGF lead to growth of coronary collateral vessels, helping in the reduction of infarct size in the ischemic tissue (Sun et al., 2003). Regarding the non-ischemic RVO, improvement was noted in some of the vascular perfusion parameters (SCP VD and FD) indicating possible improvement of macular perfusion. In a retrospective study done by Suzuki et al in 2016, a decrease in the non-perfused areas were noted following anti-VGEF treatment, especially in the deep capillary layer claiming that the deep layer is rich of capillaries. They also found an increase in the choriocapillaris flow with increase in the FAZ area (Suzuki et al., 2016). These results coincide with the results in our study, in the non-ischemic group; however, we found that the VD increased more in the

superficial capillary layer after injection.

In another study, no statistical differences were found between VD and FAZ after 12 months of repeated anti-VEGF therapy (mean of 3.7 injection). In addition to that, no significant correlation was found between the number of the anti-VEGF injections and the changes in the VD and FAZ area, The authors of the study concluded that repeated anti-VEGF therapy may not have a positive or negative effect on the macular area blood flow in most eyes with RVO although better BCVA was associated with higher VD and a smaller FAZ (Winegarner et al. 2018). Other reports showed no significant changes of macular VD after treatment (Deng et al., 2019; Ghasemi et al., 2017; Sellam et al., 2017).

In a study done by Nicolai et al, they studied the papillary and peripapillary VD changes after intravitreal anti VGEF injection, showing significantly improved BCVA with increase in inside disc and peripapillary VD after 4 months follow up (Nicolai et al., 2019). Several explanations could account for the increased macular perfusion in non-ischemic RVO detected by OCTA in our study. In one study, reappearance of retinal microvasculature after anti-VEGF treatment was noticed and the authors suggested that this could be secondary to re-perfusion of poorly perfused vessels or perhaps the de-masking of retinal vessels after resolution of cystoid spaces secondary to anti-VEGF treatment (De Carlo et al., 2016).

In contrast, Spaide et al. showed that despite resolution of edema following anti-VEGF therapy no changes were noted in the non-perfusion area. Cystoid spaces were noted at sites of disturbed vascular flow in the SCP, and absent or severely disturbed vascular flow in the DCP. After treatment, no changes were noted in the pattern of the SCP or DCP and cystoid spaces reformed in the same areas as previously affected, in case of recurrence (Spaide et al., 2016). Same suggestion was made by Mané et al. where they suggested that reperfusion is unlikely to occur after anti-VEGF treatment, and the documented effects are just due to capture of capillaries that became visible after resolution of cystoid spaces in patient with DME (Mané et al., 2016).

On the other hand, many authors believe that improvement of VD after anti-VGEF injection is attributed to actual reperfusion of the occluded capillaries in addition to prevention of progression of non-perfusion areas. It is thought that VEGF mediated increased intercellular adhesion molecule-1 (ICAM-1) in the retinal endothelial cells, leads to ICAM-1–mediated leukocytes binding to the vasculature, their entrapment in the retinal microcirculation and eventually downstream non-perfusion. Given that, anti-VEGF therapy is thought that administration of intravitreal anti-VEGF injections can improve or at least maintain retinal perfusion in patients with RVO (Mir et al., 2016; Kim et al., 2001).

In our study, we also found significant increase in the choriocapillaris flow, but as mentioned before, the shadowing effect of fluid secondary to macular edema may have caused initial attenuated OCT signal, and the increase in choriocapillaris flow after treatment can be secondary to reduction of that shadowing effect (Novais et al., 2016; Mastropasqua et al., 2016).

Conclusions

- Reported visual outcomes after anti-VEGF therapy were different. Some reports showed complete visual recovery while other showed less improvement in the visual acuity, an effect that was related to the status of post treatment retinal perfusion and retinal ischemia.
- Despite improvement in logMAR BCVA in all patients, our study showed that there was a discrepancy in the effect of three-monthly intravitreal bevacizumab injections for treatment of macular edema among ischemic and non-ischemic cases
- Further studies are needed to investigate the effect of anti-VEGF agents on retinal perfusion in patients with RVO

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Consent for publication: Patient signed informed consent regarding publishing their data and images.
Availability of data and material: Raw data were generated at Cairo University. Derived data supporting the findings of this study are available from the corresponding author [D.A] on request.
Disclaimer: The views expressed in the submitted article is the author's own and not an official position of the institution or funder.

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