

Evaluation of Microvascular Network with Optical Coherence Tomography Angiography (OCTA) in Branch Retinal vein Occlusion (BRVO)

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Abstract

Purpose: To evaluate changes of microvascular network of macular and peripapillary regions and to provide a quantitative measurement of foveal avascular zone (FAZ) in unilateral BRVO patients.

Methods: Forty-seven unilateral BRVO patients were enrolled. A 3*3 mm scan centered on fovea followed by a 4.5*4.5 mm scan centered on optic nerve head (ONH) were obtained in BRVO eyes and fellow eyes of each individual using OCTA (Optovue Inc., Fremont, CA, USA). Vessel density (VD) in superficial (SVC) and deep vascular complex (DVC) of macula and radial peripapillary capillary (RPC) were automatically calculated. Parameters of FAZ region including size, perimeter, acircularity index (AI) and foveal density 300 (FD-300) were measured.

Results: VDs of SCV and DVC were significantly lower, especially in affected regions, in BRVO eyes compared with fellow eyes ($P < 0.05$). BRVO affected eyes has larger FAZ size, FAZ perimeter, AI and lower FD-300 compared with fellow eyes (all $P < 0.05$). The average vessel density in whole area and peripapillary area in BRVO eyes were significantly lower compared with fellow eyes ($P < 0.05$).

Conclusions: OCTA provided quantitative information of vascular changes in BRVO. FAZ in BRVO eyes showed significant morphological alterations and decreases of VD in surrounding area. Decreases of VD existed not only in SVC and DVC in macular region but also in RPCs in BRVO eyes.

Key words: optical coherence tomography angiography, retinal vasculature, foveal avascular zone, radial peripapillary capillary, branch retinal vein occlusion

Background

Retinal vein occlusion (RVO) is the second most common retinal disease after diabetic retinopathy and is considered to be one of the major causes of vision loss[1].

Systemic conditions, especially hypertension, hyperlipidemia and diabetes mellitus have been considered to be predisposing to the development of RVO [2, 3]. Retinal vein occlusion was divided into central (CRVO), hemi-, and branch retinal vein occlusions (BRVO) based on the veins affected[4]. Fluorescein angiography (FA) is the gold standard for evaluating structural and functional status of retinal vasculature in retinal vascular diseases, especially in diabetic retinopathy and RVO. However, this invasive procedure may lead to some side effects[5] such as allergic reaction and it can be difficult to observe details of retinal vascular because of dye leakage and pooling. It is also difficult to differentiate retinal vessels by layer, and deeper retinal vessels are not visualized in FA images. Spectral-domain optical coherence tomography (SD OCT) has been widely used in clinical practice to evaluate retinal and choroidal structures because of its ability to provide high resolution images noninvasively. Optical coherence tomography angiography (OCTA), a more recent imaging modality, has enabled us to visualize microvascular in different layers of retina and choroid, as well as quantify perfusion status of macular and peripapillary regions. Using OCTA, many studies have found microvascular changes such as

microaneurysms, telangiectasia, retinal capillary nonperfusion and disruption of the foveal avascular zone after RVO occurred[6–8]. Decreased microvascular density in different vessel layers of macula and peripapillary region was also reported with quantitative analysis[8–11].

Recent research about FAZ mainly focused on the enlargement of its size and perimeter in diseased eyes, however, acircularity index (AI) has been proved to be a useful parameter depicting the asymmetry of FAZ area in retinal vascular diseases especially in diabetic retinopathy[12, 13]. Another parameter, foveal vessel density 300 (FD–300) is a new metric evaluating vessel density of the area closely surrounding FAZ and is useful in quantitative analysis. To our knowledge, AI and FD–300 have not been used to evaluate FAZ asymmetry and perfusion states in BRVO patients.

The radial peripapillary capillary (RPC) layer is the most superficial capillary layer surrounding the optic nerve head (ONH). Cross sectional studies using OCTA has found a decreased RPC density in retinal vascular diseases such as branch and central retinal artery occlusions[14, 15]. Reports about RPC density from literature cannot differentiate RPCs and large retinal vessels around the disc[16], and quantitative data is currently not available on microvascular alterations in the peripapillary area in patients with unilateral BRVO.

In this study, we measured AI and FD–300 as well as RPC density in BRVO eyes and fellow eyes in unilateral BRVO patients and compared these parameters between the two groups to present a thorough evaluation of microvascular changes in BRVO.

Methods

Patients

This retrospective observational study enrolled 47 eyes of 47 patients with unilateral BRVO who were examined at the Department of Ophthalmology of Peking Union Medical College Hospital (PUMCH), Beijing, China between January 2018 and December 2018. Treatment naïve patients and patients who have been treated with intravitreal medication were included. The exclusion criteria were patients with poor-quality images on OCTA (quality index lower than 5) because of significant eye movements or lens opacities, previous retinal surgery, pathologic myopia, ocular trauma, and the presence of other retinal diseases such as diabetic retinopathy or age-related macular degeneration. Eyes with CRVO or hemicentral retinal vein occlusion (HRVO) were excluded.

The clinically unaffected eyes of the patients with unilateral RVOs served as the control groups if there was no history of any ocular disease or ocular surgery and with an unremarkable result of the ophthalmologic examination, including a normal appearance of the anterior segment and posterior segment of the eye, an intraocular pressure within the normal range.

The following data were obtained from the medical records of our enrolled patients: age, gender, best corrected visual acuity (BCVA, logMAR), slit lamp-assisted biomicroscopy of the anterior segment,

intraocular pressure, fluorescein angiography (FA), SD-OCT (Spectralis Heidelberg Engineering, Heidelberg, Germany), and OCTA using the AngioVue OCTA system version 2017.1 (Optovue Inc., Fremont, CA, USA).

Macular microvascular OCTA imaging

Macular OCT angiograms were acquired using the AngioVue OCTA system version 2017.1 (Optovue Inc., Fremont, CA, USA) with the Angio Retina mode. The software includes the 3D projection artifact removal (PAR) algorithm, which removes projection artifacts from the OCTA volume and uses information from the OCT and OCTA volume to differentiate in situ OCTA signal from projection artifacts.

For each eye, a 3 × 3-mm volume image centered on the fovea was obtained. The scan pattern was a 304 B-scan raster with 304 A-scans per B-scan. Two orthogonal volumes were acquired at each scanning location. The AngioVue software automatically segmented the vascularized tissue into four layers: the superficial vascular complex (SVC), the deep vascular complex (DVC), the outer retinal layer, and the choriocapillaris layer. Based on these default settings, the boundaries of the superficial network extended from the internal limiting membrane to 10 μm above the inner plexiform layer (IPL). The deep capillary network extended from 10 μm above the IPL to 10 μm below the outer plexiform layer (OPL) there was no overlap between the 2 slabs.

We also measured FAZ metrics including size, perimeter and foveal acircularity index (i.e., the ratio between the measured perimeter and the perimeter of the same size circular area: a perfectly circular FAZ has an acircularity index equal to 1, with deviations from a circular shape leading to an increase in this metric). Foveal vessel density 300 (FD-300; i.e., VD in a 300-μm wide zone around the FAZ combining the SVC and the DVC), automatically calculated by the software, was also evaluated (Figure 3). Vessel density measurement in this area avoids to incorporate FAZ, whose area is highly variable among individuals. The values of FD-300 are complimentary to FAZ metrics and have been previously used to detect early signs of diabetic retinopathy[17].

Radial peripapillary capillary measurement

A 4.5*4.5mm rectangle scan centered on ONH was obtained for each eye with AngioVue OCTA system using Angio-Disc mode. The software automatically fits a 2.0mm diameter circle centered on the ONH and the 2.0mm wide round annulus extending from the optic disc 2.0mm circle was defined as the peripapillary region. The software divides the peripapillary region into eight regions automatically based on Garway-Heath method[18], designated as nasal superior (NS), nasal inferior (NI), inferior nasal (IN), inferior tempo (IT). Tempo inferior (TI), tempo superior (TS), superior tempo (ST) and superior nasal (SN). Vessel densities of the whole image, inside disc and each sector of peripapillary area were generated by the software automatically.

We divided our patients into two sub groups according to the location (superior or inferior) of the affected vein and compared vessel density in each sector of the superficial and deep vascular plexus and RPC in

each group.

All scans were reviewed by two experts for correctness of automated layer segmentation, as well as for FAZ delineation. In case of segmentation errors, manual correction was performed by the examiners until agreement achieved.

Statistical analysis

Statistical analysis was performed using a commercially available statistical software program (SPSS for Mac, version 25.0; IBM/SPSS, Chicago, IL, USA). Continuous variables are presented as mean and SD. Paired t test was used to compare the demographics and evaluate the significance of the difference in macular metrics, FAZ parameters and peripapillary vessel densities between the eyes with BRVO and the clinically unaffected fellow eyes.

Results

Patients' Demographic and Clinical Characteristics

Out of 57 primarily enrolled patients, 7 patients were excluded due to poor quality of the OCTA images, 1 patient was excluded due to lack of FAZ zones in both eyes, 2 patients were excluded due to diabetic retinopathy, so that the study eventually included 47 eyes of 47 patients (22 men) with a mean age of 55.0 ± 11.0 years (median, 55.0 years; range, 25–82 years). All patients had unilateral involvement. The right-eye to left-eye ratio was 30×17 . The superior temporal branch vein was occluded in 38 patients, the inferior temporal branch vein was occluded in 8 patients, and the superior nasal branch vein was occluded in 1 patient. The mean presenting BCVA was $\log\text{MAR } 0.440 \pm 0.324$. The mean duration of the symptoms of BRVO was 8.3 ± 14.7 months (0.5–46 months). The mean BCVA for the contralateral eyes was $\log\text{MAR } 0.096 \pm 0.143$ (Table 1). The foveal retinal thickness was significantly ($P < 0.001$) thicker in eyes affected with BRVO than in the contralateral unaffected eyes. (Table 2).

Macular Vessel Density

Eyes affected by BRVO had significantly lower vessel density in both the SVC ($P < 0.05$) and DVC ($P < 0.05$) compared with the contralateral unaffected eyes in OCTA images. In the BRVO group, the FAZ deviated from the gently undulating perimeter seen in the contralateral eyes. The size ($P < 0.05$) and perimeter of FAZ ($P < 0.05$) were significantly larger in BRVO eyes than fellow eyes. The AI was higher ($P < 0.05$) and foveal vessel density 300 was lower ($P < 0.05$) in BRVO eyes compared with the contralateral unaffected eyes (Table 2).

In sub group analysis, we found vessel density was significantly lower in all sectors ($P < 0.05$) except foveal region in SVC and DVC in eyes with superior vein occlusion. Vessel density was significantly lower in inferior ($P < 0.05$) and nasal ($P < 0.05$) sectors in SVC and in all sectors except foveal region in DVC in eyes with inferior vein occlusion. (Fig. 1)

Fig.1 Vessel density of SVC and DVC (a-b) in macular region of superior vein occlusion group and (c-d) inferior vein occlusion group. *, $P < 0.05$; SVC, superficial vascular complex; DVC, deep vascular complex

Peripapillary vessel density

The average vessel density of the whole, inside disc and peripapillary region were 47.7 ± 4.0 – 46.8 ± 6.2 – 49.9 ± 4.2 in BRVO eyes, and 49.9 ± 2.3 – 47.7 ± 5.6 – 52.7 ± 3.0 in contralateral eyes. BRVO eyes has lower vessel density in whole area and peripapillary area compared with contralateral eyes ($P < 0.05$)(Table 3).

In eyes with superior vein occlusion, vessel density in inferior tempo, tempo superior, superior tempo and superior nasal sectors were significantly lower than contralateral eyes ($P < 0.05$). In eyes with inferior vein occlusion, vessel density in inferior nasal, inferior tempo and tempo inferior sectors were significantly lower than contralateral eyes ($P < 0.05$)(Fig. 2).

Fig.2 Vessel density of RPC in (a) superior vein occlusion group and (b) inferior vein occlusion group. RPC, radial peripapillary capillary; s-hemi, superior -hemi; i-hemi, inferior-hemi TS, tempo superior; ST, superior tempo; SN, superior nasal; IT, inferior tempo; TI, tempo inferior; IN, inferior nasal; *, $P < 0.05$

Discussion

In this study, we quantified vessel density in macular region using OCTA. Our study revealed that vessel density in BRVO eyes was significantly lower in affected and adjacent sectors in superficial retinal layer and in all regions except for the foveal region in deep retinal layer compared with contralateral unaffected eyes.

The decrease of vessel density in macular region agreed with previous studies that applied OCTA to measure vessel densities in retinal vein occlusion patients[7, 19–22]. In a previous BRVO study by Samara's group, vessel densities in macular region were measured by sector and researchers found vessel density in affected sector of BRVO eyes was lower than fellow eyes in both superficial and deep network, while vessel density in the unaffected sector of BRVO eyes was also lower than fellow eye in deep network[23]. What's more, affected sector was defined as superior or inferior quadrant of a circular grid in Samara's study, so they only compared superior and inferior sectors in their research. Changes in nasal and temporal regions were not discussed in their work. Coscas et al. found that none perfusion areas were more frequent in deep capillary plexus[7], suggesting that DCPs were more vulnerable to ischemic attack. Freund et al. discovered that collateral vessels mainly existed in deep vascular complex, supporting a serial arrangement of the superficial vascular complex and deep vascular complex with venous drainage coursing through deep vascular complex[24]. Agreed with previous study, our result suggested DCP was more vulnerable to ischemic changes and BRVO may cause a more global vascular alteration.

Recent studies found enlarged FAZ in superficial and deep retinal layer in BRVO eyes[23, 25, 26], which was negatively correlated with visual acuity[23, 25, 27]. In our study, FAZ area and perimeter were larger in

BRVO eyes compared with fellow eyes, which agreed with previous reports. Besides, we also found a larger AI and lower FD-300 in BRVO affected eyes compared with fellow eyes. Wons et al. measured the angle between the maximum FAZ diameter and the papillomacular plane in RVO eyes and contralateral unaffected eyes and found a significant difference between the two groups. According to their research, eyes with RVO showed an asymmetrical FAZ and an unorganized capillary structure[28]. FAZ size according to previous studies, may vary considerably in normal individual and causing a significant overlap among healthy and diseased individual[29, 30], making it difficult to recognize difference between study groups. Recently, a new parameter AI was described by Tam et al. to quantify the irregularity of FAZ[13], which has been proved to be a useful parameter evaluating the asymmetry of the FAZ, providing information about the ischemic status of diseased eyes[12]. Our result agreed with Won's study and showed that BRVO affected eyes have a more irregular shape compared with fellow eyes. This was the first study, to the best of our knowledge, to describe the asymmetry of FAZ in BRVO eyes with AI. FD-300 has been proved to be a useful parameter to detect vascular drop out around foveal region in diabetic retinopathy[17]. No significant difference was found in foveal vessel density in superficial or deep vessel complex in our study. This could be the caused by the scarcity of vessels in FAZ region. However, when the quantified area skipped FAZ and extend to 300 μ m area surrounding FAZ, vascular drop out became obvious.

Peripapillary radial peripapillary capillary dropout was another important discovery in our study. Wang et al. measured flow velocity of veins merging from optic disc and found a slower flow velocity in the occluded hemisphere[31]. Recent studies found a reduction of peripapillary choroidal thickness in BRVO affected and nonaffected eyes in unilateral BRVO patients, suggesting BRVO may be associated with a hypoxic insult on the peripapillary choroid[11, 32]. Shin et al. found that the peripapillary vessel density and perfusion density were decreased in the fellow eyes of unilateral BRVO patients[16], suggesting RVO may cause structural abnormality even in fellow eyes. However, Wang's study only measured large vessels around optic disc while Shin's research measured both large vessels and radial peripapillary capillaries. In our study, we measured radial peripapillary capillaries around optic nerve head with the installed software and found a significant decrease of peripapillary radial peripapillary capillary density in the affected sectors of BRVO eyes. To our knowledge, this is the first report to quantify radial peripapillary capillary change in BRVO affected eyes.

In normal eyes of human, blood flow of the ONH is supplied by the posterior ciliary artery and central retinal artery, which is also the blood supply of superficial RNFL layer of ONH. RPCs are straight, oriented vessels which pursue a paralleled path to each other and arched up steeply to supply RNFL around the ONH[33–35]. Fluorescein angiography (FA) has been used to evaluate ONH perfusion for several decades. However, FA requires dye injection and it is difficult to observe RPCs with this traditional method. OCTA, as a non-invasive method, is advantageous for evaluating ONH perfusion. With OCTA, we can easily visualize the RPCs and quantify the vascular perfusion status. RPC drop out has been reported in glaucoma[36] and diabetes mellitus[37] patients, and has been considered as a useful parameter evaluating vascular dysfunction. Current research has found a correlation between mean RPC density and mean RNFL thickness[34]. Decreasing of RNFL thickness was found with OCT in RVO eyes[32, 38,

39], suggesting retinal nerve fiber atrophy may be the result of RVO as the disease progressed. In our study, PRC was lower in BRVO eyes compared with fellow eyes, especially in the affected sectors. However, no significant thinning of RNFL was observed in either the affected sector or the unaffected sector (data not shown), which disagreed with previous studies. This could be explained by the discrepancy of patients included in our research since we included both treatment naïve patients and those who has been treated. ONH swelling is usually observed in treatment naïve patients at the early stage of BRVO and this can influence the average RNFL thickness. However, the underlying swelling of RNFL may have little impact on RPC and the decrease of RPC density was prominent in our research.

There are a few limitations in this study. First, the study is a retrospective study and lacks longitudinal data. A longitudinal study is necessary to elucidate vascular changes with treatments. Besides, there is likely a selection bias due to the limited sample size. In addition, we did not measure vessel density of choriocapillaris in macular and ONH region. Artifacts such as projection and shadow may influence the accuracy of the measurement of choriocapillaris[40]. We scanned a 3*3mm² area of the foveal and 4.5*4.5mm² area of the ONH and these regions were relatively small. A larger scanning region with high accuracy may bring out more information of perfusion status. Future studies may be able to evaluate a thorough status of perfusion and vascular changes in a larger scale in BRVO eyes with the updated OCTA techniques.

Conclusions

In conclusion, our study demonstrated OCTA with upgraded software enhanced with 3D PAR provides high-resolution images and quantitative information of microvascular parameters of not only macular, but also peripapillary vascular in BRVO eyes. Vascular density of SVC and DVC in macular region was much lower in BRVO eyes compared with fellow eyes. SVC was significantly lower in affected sectors while all sectors in DVC were decreased in affected eyes. In addition to enlarged FAZ area and perimeter, larger AI and lower FD-300 are prominent in BRVO eyes and can be used to evaluate the asymmetry and ischemic status of foveal region. More importantly, lower RPC density was another feature of BRVO affected eyes and RPC density can be a useful parameter to evaluated perfusion status of ONH in BRVO.

Abbreviations

RVO: Retinal vein occlusion; FAZ: foveal avascular zone; ONH: optic nerve head; VD: Vessel density; SVC: superficial vascular complex; DVC: deep vascular complex; RPC: radial peripapillary capillary; AI: acircularity index; FD-300: foveal vessel density 300; CRVO: central retinal vein occlusion; SD-OCT: spectral-domain optical coherence tomography; HRVO: hemicentral retinal vein occlusion; BCVA: best corrected visual acuity; FA: fluorescein angiography; IPL: inner plexiform layer; OPL: outer plexiform layer; NS: nasal superior; NI: nasal inferior; IN: inferior nasal; IT: inferior tempo; TI: tempo inferior; TS: tempo superior; ST: superior tempo; SN: superior nasal.

Declarations

Ethics approval and consent to participate:

The study adhered to the tenets of the Declaration of Helsinki and was approved by PUMCH. Written informed consent was obtained from all subjects (and the parents/guardians of any minors included as participants). The research was approved by the institutional review board of PUMCH (approval number: S-K631).

Consent for publication:

Written informed consents were obtained from all participants for the publication of clinical information and images.

Availability of data and materials:

The datasets presented in this study is available from the corresponding author upon request.

Competing interests:

The authors declare that they have no conflict of interest.

Funding:

Not applicable.

Authors' contributions:

CLL interpreted data, drafted this manuscript and reviewed the literature. YMZ, WYL and SL collected the data. YMZ reviewed the manuscript. CYX final approval. All authors have read and approved the final manuscript.

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Tables

Table 1 Demographics and clinical characteristics of patients with BRVO

Variables	Mean \pm Standard Deviation
BRVO eyes	47
Age, y , mean \pm SD	55. 0 \pm 11.0 (range, 25–82)
Sex, male/female	22/25
Affected eye, OD/OS	30 \square 17
BCVA of BRVO eyes	0.440 \pm 0.324
BCVA of fellow eyes	0.096 \pm 0.143
Symptom duration of BRVO	8.3 \pm 14.7(range 0.5–46 months)
Superior/inferior, no	39/8

Table 2 Macular measurements in BRVO eyes and fellow eyes

Variables	Eyes with BRVO (n=47)	Contralateral unaffected eyes (n=47)	<i>P</i> value (paired t test)
BCVA	0.440 ± 0.324	0.096±0.143	<0.001
Foveal retinal thickness(μm)	321±113	248±20	<0.001
Vascular density in SVP (%)			
whole	40.4±4.0	45.6±3.5	<0.001
foveal	15.5±5.0	15.5±5.9	0.960
tempor	41.3±5.3	47.3±3.5	<0.001
superior	42.2±7.5	50.1±3.9	<0.001
nasal	42.7±6.0	47.5±4.0	<0.001
inferior	44.6±5.5	49.8±4.0	<0.001
Vascular density in DVP (%)			
whole	42.9±5.0	50.0±3.0	<0.001
foveal	28.2±9.3	29.8±8.0	0.158
tempor	44.0±7.1	52.7±3.0	<0.001
superior	41.1±8.8	52.0±3.6	<0.001
nasal	46.2±6.4	52.8±3.2	<0.001
inferior	46.0±7.4	52.2±3.8	<0.001
FAZ [mm ²]	0.394±0.260	0.325±0.136	0.046
FAZ perimeter [mm]	2.589±1.108	2.255±0.503	0.031
AI	1.23±0.13	1.14±0.04	<0.001
FD-300 [%]	45.66±6.04	49.21±4.46	<0.001

Table 3 Peripapillary vessel density in BRVO eyes and fellow eyes

Variables	Eyes with BRVO (n=47)	Contralateral unaffected eyes (n=47)	<i>P</i> value
whole(%)	44.7±4.0	49.9±2.3	<0.001
Inside disc(%)	46.8±6.2	47.6±5.4	0.390
Peripapillary(%)	47.8±5.6	52.8±3.1	<0.001
nasal superior(%)	44.1±5.6	48.9±4.7	0.159
nasal inferior(%)	47.2±5.8	47.9±4.8	0.410
inferior nasal(%)	49.4±9.1	52.5±4.2	0.035
inferior tempo(%)	52.9±9.3	58.4±4.5	<0.001
tempo inferior(%)	52.4±6.4	53.3±5.0	0.337
tempo superior(%)	54.4±4.2	56.7±3.7	0.005
superior tempo(%)	49.0±7.9	56.6±4.1	<0.001
superior nasal(%)	47.4±7.4	51.3±4.5	<0.001

Figures

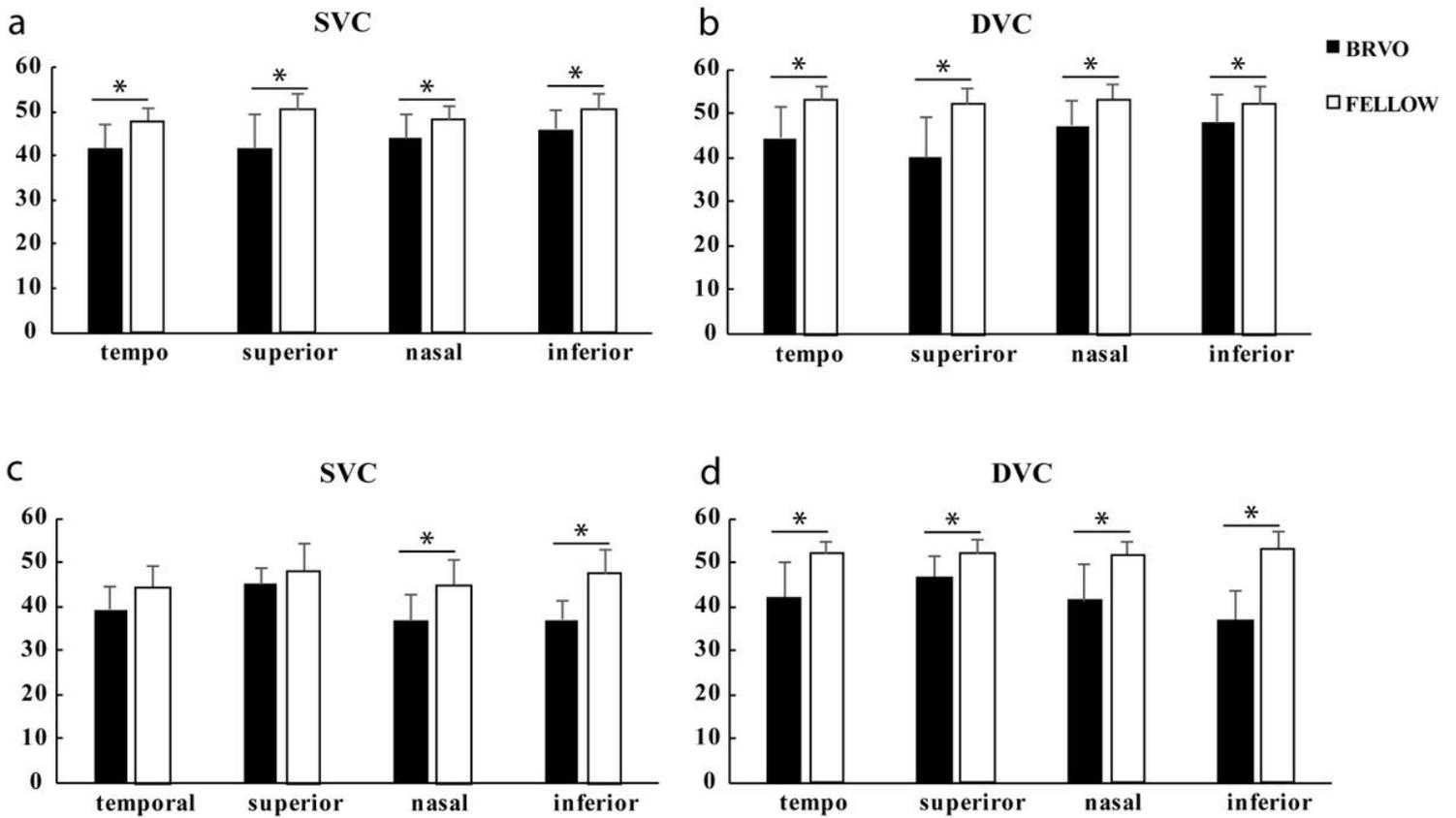


Figure 1

Vessel density of SVC and DVC (a-b in macular region of superior vein occlusion group and c-d inferior vein occlusion group. *, $P < 0.05$; SVC, superficial vascular complex; DVC, deep vascular complex

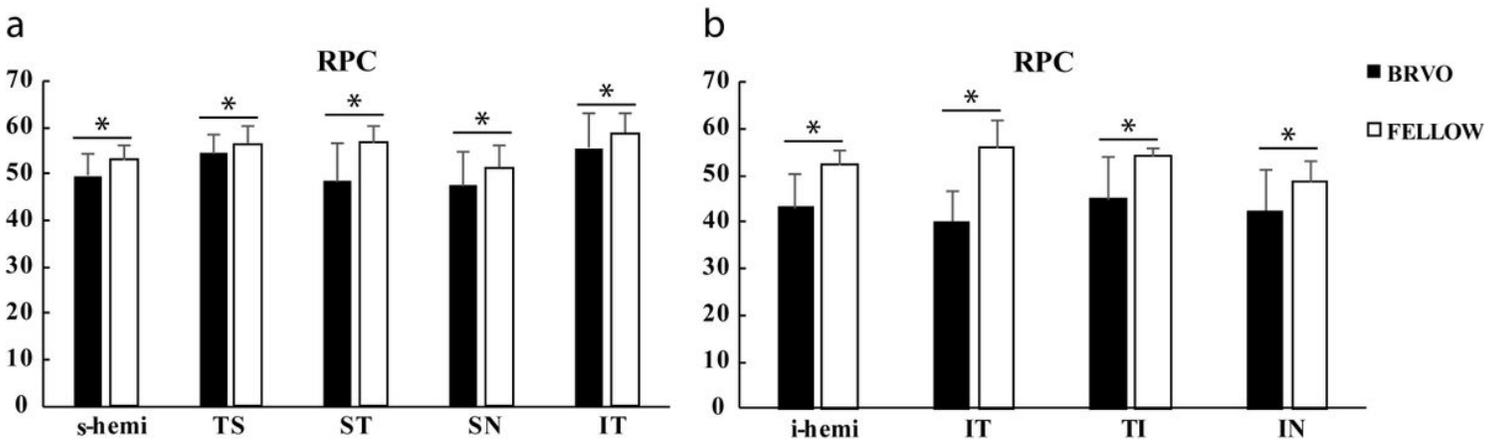


Figure 2

Vessel density of RPC in (a) superior vein occlusion group and (b) inferior vein occlusion group. RPC, radial peripapillary capillary; s-hemi, superior -hemi; i-hemi, inferior-hemi TS, tempo superior; ST, superior tempo; SN, superior nasal; IT, inferior tempo; TI, tempo inferior; IN, inferior nasal; *, $P < 0.05$