·Clinical Research·

Peripheral retinal non-perfusion and treatment response in branch retinal vein occlusion

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Abstract

• AIM: To evaluate the association between the size of peripheral retinal non-perfusion and the number of intravitreal ranibizumab injections in patients with treatment-naive branch retinal vein occlusion (BRVO) and macular edema.

• METHODS: A total of 53 patients with treatment-naive BRVO and macular edema were included. Each patient underwent a full ophthalmologic examination including optical coherence tomography (OCT) imaging and ultra wide-field fluorescein angiography (UWFA). Monthly intravitreal ranibizumab injections were applied according to the recommendations of the German Ophthalmological Society. Two independent, masked graders quantified the areas of peripheral retinal non-perfusion.

• RESULTS: Intravitreal injections improved best-corrected visual acuity (BCVA) significantly from 22.23±16.33 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters to 36.23±15.19 letters (P<0.001), and mean central subfield thickness significantly reduced from 387±115 μm to 321±115 μm (P=0.01). Mean number of intravitreal ranibizumab injections was 3.61±1.56. The size of retinal non-perfusion correlated significantly with the number of intravitreal ranibizumab injections (R=0.724, P<0.001).

• CONCLUSION: Peripheral retinal non-perfusion in patients with BRVO associates significantly with intravitreal ranibizumab injections in patients with BRVO and macular edema.

• **KEYWORDS:** angiography; branch retinal vein occlusion; non-perfusion; retina; wide-field
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INTRODUCTION

Branch retinal vein occlusion (BRVO) is the second most common major retinal vascular disease after diabetic retinopathy[1]. The prevalence of BRVO has been estimated to range from 0.6% to 1.1%[2-4]. The major risk factors for BRVO include increasing age, hypertension, and concomitant cardiovascular diseases[5-6]. The pathogenesis of BRVO is believed to involve both retinal vein compression, *e.g.* by an adjacent atherosclerotic artery, as well as damage to the vessel wall through the trophic changes of venous endothelium as well as intima or media possibly resulting in thrombus formation[7]. BRVO may be asymptomatic or associated with blurring in the visual field corresponding to the involved retinal quadrant. Common vision-threatening complications are cystoid macular edema, macular ischemia and vitreous hemorrhage[8-9]. Macular edema is the most common cause of visual loss in these patients, and intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents is one of the generally accepted and often used treatment options. It has been suggested that the clinical course of retinal vein occlusion may be affected by the extent of retinal ischemia, including ischemia occurring in the periphery[10].

Fluorescein angiography (FA) is able to determine whether the vision loss is due to macular edema or ischemia[2]. On the other hand, FA can also be an important tool to detect peripheral ischemia. However, imaging of the peripheral retina by common methods of FA is not optimal and often accompanied by difficulties to depict peripheral pathophysiological retinal alterations. This may be due to the field of view of the traditional fundus cameras, which is varying from 30 to 60 degrees; in addition, images of different areas are not taken concurrently and comparison is therefore not precise[11-12]. Furthermore, with traditional fundus

cameras, the far periphery of the retina or the underlying choroid cannot be visualized. With the advent of the commercial ultra wide-field fluorescein angiography (UWFA; Optos Panoramic 200; Optos PLC, Dunfermline, Scotland, United Kingdom), simultaneous imaging of the posterior pole and periphery of up to 200 degrees is possible[13-14].

The aims of this study were to investigate the relationship between peripheral retinal non-perfusion in patients with BRVO and macular edema and the number of intravitreal injections using UWFA.

SUBJECTS AND METHODS

Patient Selection Fifty-three consecutive patients were included in this prospective interventional study which was conducted in the Department of Ophthalmology at Ludwig Maximilians University, Munich, Germany between June 1, 2012 and February 1, 2014. The Institutional Review Board approved the study design and patients' care was conformed to the tenets of the World Medical Association Declaration of Helsinki. All patients gave written informed consent for both participation in the study and for FA. Inclusion criteria were diagnosis of BRVO (as revealed by superficial hemorrhages in a defined sector of the retina along a retinal vein) with active macular edema. Center-involving macular edema was defined and confirmed by macular leakage seen in FA and central subfield thickness (CST) >250 μm in cross-sectional spectral-domain optical coherence tomography (SD-OCT) images.

Patients without macular edema, previous focal or panretinal photocoagulation and degenerative disorders of the posterior pole and/or retinal periphery were excluded. Enrolled patients received three intravitreal injections of 0.50 mg ranibizumab (Lucentis™, Genentech, Inc., South San Francisco, CA, USA and Novartis Pharma AG, Basel, Switzerland) every four weeks according to the recommendation of the German Ophthalmic Society. Additional monthly injections were given at the presence of retinal hemorrhage or macular edema as determined by CST>250 μm. All included patients had a thorough ophthalmologic examination including visual acuity evaluation using the Early Treatment of Diabetic Retinopathy Study (ETDRS) refraction protocol, slit-lamp biomicroscopy, applanation tonometry, indirect ophthalmoscopy and SD-OCT before treatment and at each monthly follow-up visit. UWFA was obtained for each patient before treatment.

Image Acquisition SD-OCT volume scans [20°×15° with 19 horizontal sections, automatic real time (ART) mean value of 9, SD-OCT, Heidelberg Engineering, Heidelberg, Germany] of the macula were obtained for each study eye to measure the CST in μm by Heidelberg SD-OCT software, double checked for accuracy and significant macular ischemia was ruled out by UWFA. Ultra wide-field images were acquired using the Optos 200Tx scanning laser ophthalmoscope (Optos PLC) after standard intravenous infusion of 5 mL of sodium fluorescein 10% by one experienced technician for all included cases. Images were taken of the posterior portion of the eye, and peripheral images were taken in four cardinal directions (nasal, superior, inferior, temporal).

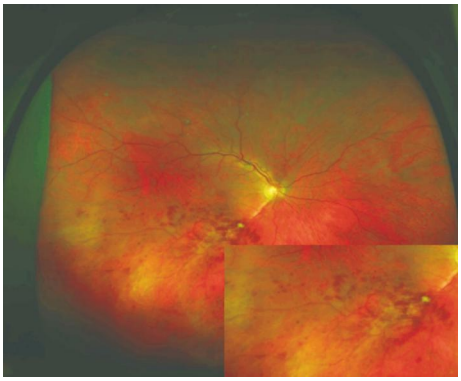

Figure 1 En face wide-field fundus image of the right eye with BRVO.

Image Processing and Analysis Images were digitally captured using the Optos V^2 Vantage Review Software. This allowed quality improvement and high resolution zoom for the analysis of all acquired images. Images taken approximately one minute (arteriovenous phase) and 4-5min (late venous phase) after intravenous injection of fluorescein were compressed into high-quality JPEG files (*e.g.* Figures 1, 2) and analysed for retinal non-perfusion by two experienced ophthalmologists. For quantification of the non-perfused areas, a standardized pattern grid with square fields of the size of the optic disc was laid over the obtained images and the non-perfused fields were counted (Figure 3). Retinal non-perfusion was defined as hypofluorescence (representing retinal non-perfusion or capillary dropout) or areas of microvascular pathology (multiple microaneurysms and significant perivascular leakage). In cases of extensive intraretinal haemorrhage, the area of non-perfusion was evaluated by comparing the UWFA images with the results of the fundus examination.

Data Collection Collected parameters included number of ischemic pattern fields of each included patient before treatment, CST before and during therapy, demographic information of all included patients, previous ocular history, number and dates of intravitreal injections, best-corrected visual acuity (BCVA) in ETDRS letters and intraocular pressure throughout the observational period and the occurrence of any complications. Regarding the quantified peripheral retinal non-perfusion, all patients were divided into two groups: 1) no peripheral retinal non-perfusion and a mild to moderate peripheral retinal non-perfusion from 0 to 49 fields; 2) severe peripheral retinal non-perfusion from 50 to more than 100 fields of peripheral retinal non-perfusion.

Table 1 Baseline and final visual acuity, CST and the number of intravitreal injections for two groups with various extents of peripheral retinal non-perfusion

Fields of peripheral retinal non-perfusion	Baseline BCVA (ETDRS letters)	Final BCVA (ETDRS letters)	Baseline CST (μm)	Final CST (μm)	No. of intravitreal injections
0-49 (n=25)	29.93±16.67	40.63±13.83	373±102	294±42	2.12±1.19
50- >100 (n=28)	19.66±16.21	34.76±15.63	564±178	342±113	5.10±1.93
P	0.02	0.01	<0.001	<0.001	0.001

BCVA: Best-corrected visual acuity; CST: Central subfield thickness; ETDRS: Early Treatment of Diabetic Retinopathy Study.

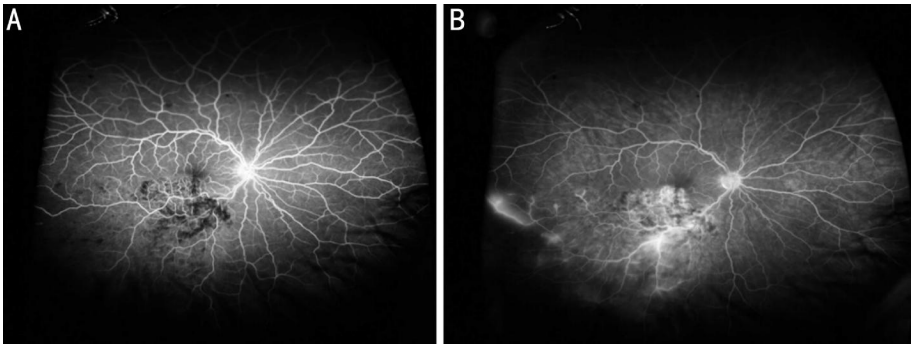

Figure 2 Optos fluorescein angiogram of the same patient at arterio-venous (A) and late venous (B) phases The late phase image reveals central fluorescein leakage inferior to the fovea and extensive areas of non-perfusion in the infero-temporal part of the peripheral fundus.

Statistical Analysis Data were collected and analysed using SPSS software (version 20.0, IBM Corporation, Armonk, NY, USA). Each obtained variable was tested for normal distribution. Nonparametric Mann-Whitney U test was used for ordinal variables. Spearman's rho test was used for correlation analysis. A P -value of < 0.05 was considered statistically significant.

RESULTS

Mean age of all enrolled 53 treatment-naive BRVO with center-involving macular edema was 71.18±10.56y (range: 34-92y). Twenty-nine patients (55%) were male, twenty-four (45%) were right eyes. Four patients (7.5%) had the additional ophthalmic diagnosis of glaucoma, 35 patients (66%) had systemic hypertension and 18 patients (34%) were pseudophakic. Cut off time for follow-up was 18mo.

Regardless of peripheral perfusion status, mean BCVA was 22.23±16.33 ETDRS letters and increased to 36.23±15.19 letters after therapy (P<0.001). Mean CST was 387±115 μm and decreased to 321±115 μm after treatment (P=0.01). Mean number of intravitreal injections was 3.61±1.56 during the study period. Table 1 shows the baseline and final BCVA, CST and the number of intravitreal injections in each group. The median number of intravitreal injections was significantly different between the two study groups (P=0.001, Mann-Whitney U test). The size of retinal non-perfusion correlated significantly with the number of intravitreal ranibizumab injections (R=0.724, P<0.001, Spearman's rho test).

Panretinal photocoagulation was not performed during the study because no case of anterior or posterior segment neovascularization happened. Injection-related adverse events such as retinal detachment or endophthalmitis did not occur.

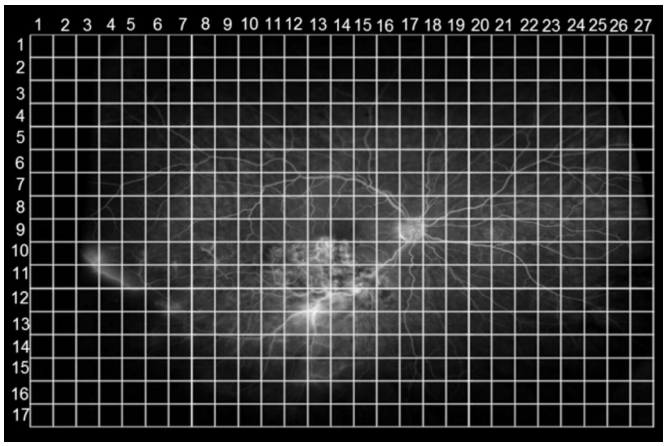

Figure 3 Quantification of the amount of non-perfused areas using the grid with 27×17 square fields approximately the size of the optic disc.

DISCUSSION

Occlusion of a branch retinal vein results in leakage from the capillary beds. A possible resulting irreversible damage of the affected capillary beds in the retinal periphery may be permanent non-perfusion of the retinal tissue with retinal hypoxia causing the release of vasoproliferative chemicals such as VEGF[15].

The relationship between peripheral retinal ischemia, elevated VEGF levels and persistent macular edema is not fully understood. It has been suggested that the clinical course of retinal vein occlusion may be affected by the extent of retinal ischemia, including ischemia occurring in the periphery[10].

Since retinal ischemia is associated with higher levels of VEGF, detecting the extent of the retinal non-perfusion is important in patient management[16]. Little is known about the

development of retinal peripheral non-perfusion because of the limitation of available imaging technologies. A major limitation of current studies is the difficulty to visualize the peripheral fundus and pathophysiologic changes using the common imaging devices.

UWFA is able to image the retina up to 200 degrees of the ocular fundus [17-18]. By applying UWFA, we evaluated the association between the frequency and amount of intravitreal ranibizumab injections and the extent of non-perfused areas in patients with BRVO and macular edema in the peripheral retina. To our knowledge, this is the first study to apply an invented grid for quantification of non-perfused areas of UWFA in patients with BRVO. In this study, treatment with ranibizumab resulted in a significant improvement in BCVA and reduction in mean CST of the treated eyes. However, patients with peripheral retinal non-perfusion received more intravitreal injections for treatment of the macular edema.

In our study, baseline CST was significantly lower in patients without peripheral retinal non-perfusion. Similar findings have been reported by Singer *et al* [19]. They evaluated 32 patients with retinal vein occlusion and refractory macular edema and found that mean CST was higher in patients with more non-perfused areas. Prasad *et al* [10] investigated UWFA angiograms from 80 eyes of 78 patients with a diagnosis of BRVO (86%) or hemi-central retinal vein occlusions (CRVOs) (14%). Untreated non-perfusion at any location was associated with macular edema. They suggested that areas of untreated retinal non-perfusion could be the source of production of biochemical mediators that promote neovascularization and macular edema. Campochiaro *et al* [20] evaluated a total of 392 (397) patients with macular edema due to CRVO and BRVO. Treatment with ranibizumab did not worsen retinal non-perfusion in their patients. They concluded that the initial vein occlusion is a precipitating event resulting in ischemia and release of VEGF, which then promotes the progression of retinal non-perfusion and worsening of ischemia. They hypothesized that aggressive blockade of VEGF prevents an exacerbation of retinal non-perfusion, thus eliminating the positive feedback loop. In a randomized clinical trial, Rehak *et al* [21] evaluated 22 patients with CRVO and suggested the selective laser photocoagulation of peripheral areas of non-perfusion may further improve the visual outcome and decrease the number of ranibizumab re-injection in CRVO patients, not using wide-field imaging in their study.

One limitation of our study was the relatively small number of 53 patients, which is due to the fact that many patients are being treated and followed up by office based ophthalmologists. Another limitation was that we performed UWFA for each patient at only a single time point, we were not able to demonstrate potential angiographic changes during the follow-up time.

In conclusion, UWFA is suitable to evaluate the peripheral retina. In patients with BRVO and macular edema, the size of retinal non-perfusion associates with applied intravitreal ranibizumab injections. Further studies are needed to evaluate whether treatment of peripheral non-perfused retina with early peripheral photocoagulation may alter the number of needed intravitreal injections.

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Conflicts of Interest: Abri Aghdam K, None; **Reznicek L,** None; **Soltan Sanjari M,** None; **Framme C,** None; **Bajor A,** None; **Klingenstein A,** None; **Kernt M,** None; **Seidensticker F,** None.

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