Peripheral Microvascular Abnormalities Detected by Wide-Field Fluorescein Angiography in Eyes with Branch Retinal Vein Occlusion.

Yusuke Yasuda, MD, Yoshio Hirano*, MD, PhD, Yuya Esaki, MD, Taneto Tomiyasu, MD, Norihiro Suzuki, MD, Tsutomu Yasukawa, MD, PhD, Munenori Yoshida, MD, PhD, and Yuichiro Ogura, MD, PhD

From the Department of Ophthalmology & Visual Science, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

Correspondence and reprint request: *Yoshio Hirano, MD, PhD, Department of Ophthalmology & Visual Science, Nagoya City University Graduate School of Medical Sciences, 1-Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan. Phone: +81-52-8538251; Fax: +81-52-8419490; E-mail: yoshio.hirano@gmail.com

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Running head: Peripheral Microvascular Abnormalities in BRVO

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ABSTRACT

Purpose: To evaluate the location of microvascular abnormalities using wide-field fluorescein angiography (WFFA) and investigate the impact on visual outcomes in eyes with branch retinal vein occlusion (BRVO).

Methods: Forty of 39 patients (24 male and 15 female, average age of 71 years) were retrospectively reviewed. One patient had BRVO bilaterally. WFFA was performed in all patients to evaluate perfusion status and detect microvascular abnormalities. The areas on WFFA images were divided into three groups; Zone 1: posterior pole, Zone 2: mid periphery, and Zone 3: far periphery to document the presence of microvascular abnormalities. Scatter retinal photocoagulation (PC) was performed for retinal neovascularization (NV) and/or widespread NPAs.

Results: The incidence of microvascular abnormalities in Zone 3 was significantly (P<0.0001) less than those in Zone 1 and Zone 2. The presence of larger NPAs in Zone 1, but not Zone 3, was associated with the incidence of NV and vitreous hemorrhage. Both the presence of peripheral lesions and application of PC did not affect the visual outcomes.

Conclusion: The presence of peripheral abnormalities or scatter PC for NPAs did not affect the visual outcomes in eyes with BRVO.

Introduction

Recent developed wide-field fluorescein angiography (WFFA) (Optos200Tx and Optos California, Optos DLC, Dunfermline, Scotland, UK) enabled evaluation of wider retinal peripheral lesions in several retinal diseases [1-3]. In these papers, it was reported that peripheral lesions were associated with increased risk of diabetic retinopathy progression [1]. In eyes with branch retinal vein occlusion (BRVO), several microvascular abnormalities were observed [4, 5]. However, to our knowledge, no any reports have been published about the association of peripheral microvascular abnormalities with visual outcomes in eyes with BRVO.

The Branch Vein Occlusion Study Group (BVOS) established that retinal scatter laser photocoagulation (PC) was effective to prevent retinal neovascularization (NV) and vitreous hemorrhage (VH) [6]. Moreover, Tomomatsu et al [7] reported that retinal scatter PC for peripheral nonperfused areas (NPAs) prevented recurrence of macular edema (ME) in BRVO. On the other hand, Campochiaro et al [8] reported that retinal scatter PC did not reduce ME in BRVO. In fact, retinal scatter PC is essential when NV is observed in eyes with BRVO to prevent VH or tractional retinal detachment. However, whether PC itself really reduces ME in BRVO or not is still controversial.

In the current study, we aimed to detect peripheral microvascular abnormalities using WFFA, compare the incidence of peripheral lesions with those of the other areas, and investigate the impact of peripheral lesions and retinal scatter PC on visual outcomes in eyes with BRVO.

Methods

Patients

This was a retrospective, observational, and consecutive case series conducted at Nagoya City University (NCU) Hospital from March 2008 through August 2016. The Institutional Review Board of NCU approved the study protocol (No. 60160087). The clinical trial was registered in UMIN-CTR (UMIN-ID: UMIN000028920). All experiments were performed in accordance with the Declaration of Helsinki. All patients provided written informed consent to participate in this study.

Eyes with BRVO, eyes with NPAs larger than 5 disc diameters on WFFA, and patients who agreed with the current study were included. Eyes with macular BRVO, other retinal diseases, and poor-quality images were excluded.

All patients underwent ophthalmic examinations including measurement of best-corrected visual acuity (BCVA), indirect ophthalmoscopy, fundus photography,

optical coherence tomography (OCT) (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA, USA), and WFFA (Optos200Tx and Optos California, Optos DLC). Two retinal specialists (YH and YY) diagnosed and determined the perfusion status using WFFA images.

Assessments

Central retinal thickness (CRT) was measured on the OCT system automatically. ME was defined as CRT exceeded 250 micrometer and/or exudative change on a color map of OCT. Persistent ME was defined as residual and recurrent ME longer than 1 year.

WFFA images were used to determine each Zone; e.g. Zone 1 had a radius of approximately 5.4 mm (3 disc diameters) and roughly corresponded to the posterior pole. Zone 2 extended from the edge of Zone 1 anteriorly with a radius of 16.2 mm (9 disc diameters) and overlapped the vortex veins. Zone 3 was the region anterior to Zone 2 (Fig 1) as previously reported [3]. The presence and the location of microaneurysm (MA) and retinal NV were evaluated by the retinal specialists (YH and YY) with WFFA images and compared among the three Zones. Moreover, the impacts of the peripheral abnormalities on visual outcomes also were evaluated.

Treatments

Intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents [ranibizumab (Lucentis, Novartis, Bülach, Switzerland)] (IVR) was performed to treat ME secondary to BRVO. Patients who did not want anti-VEGF therapy because of the cost or previous cerebral and/or cardiovascular events received sub-Tenon's capsule injection of triamcinolone acetonide (Kenacort, Bristol-Myers, Tokyo, Japan) (STTA). Additional injections were applied for the recurrent or residual ME with the CRT exceeded 250 micrometer and/or exudative change on a color map of OCT. Retinal scatter PC was performed for retinal neovascularization and/or NPAs larger than 5 disc diameters using pattern scanning laser photocoagulator (PASCAL Streamline 577, Topcon Inc., Tokyo, Japan). In addition, vitrectomy was performed for VH and/or epiretinal membrane secondary to BRVO, but not for ME. Moreover, the impacts of the application of PC on visual outcomes also were evaluated.

Statistical Analysis

BCVA was measured using Landolt C charts and converted to the logarithm of the minimal angle of resolution (logMAR) for statistical analyses. Independent chi-

squared test was used to compare the incidence of microvascular abnormalities in each Zone. Unpaired *t*-test was used to compare the differences with and without far peripheral lesion or scatter PC. Paired *t*-test was used to compare the logMAR VA and the CRT. $P < 0.05$ was considered as statistically significant.

Results

Patient Characteristics, Functional / Anatomical Outcomes, and Treatments

Forty eyes of 39 patients (24 men and 15 women; mean age, 70.7 ± 11.3 years) were enrolled. One patient had BRVO bilaterally. The patient baseline characteristics are shown in Table 1. The mean follow-up period was 41.8 ± 28.9 months. The mean logMAR VA significantly ($P < 0.001$**) improved from 0.279 ± 0.334 at baseline to 0.0509 ± 0.267 at final visit. Twenty-two eyes out of 40 eyes (55 %) had a Snellen equivalent BCVA of 20/20 or better. The mean CRT significantly ($P < 0.0001$**) decreased from 430 ± 169 at baseline to 265 ± 54.9 at final visit. The mean injection number of STTA and IVR was 1.08 ± 2.03 and 2.13 ± 3.07, respectively. Retinal scatter PC was applied in 33 eyes (83 %). Five eyes (13 %) had VH; 2 eyes at initial visit, 2 eyes before PC, and 1 eye after PC, respectively. All of the 5 eyes with VH underwent a vitrectomy with scatter PC. The other 2 eyes underwent scatter PC, but VH was not observed at all. Twenty eyes (50 %) had persistent ME longer than 1 year. No eyes had neovascular glaucoma.

Incidence of Microvascular Abnormalities in Each Zone

Fig 2 shows the incidence of microvascular abnormalities seen in each Zone. In Zone 3, MA was significantly less observed compared with the other Zones and NV was not observed at all. In all of the eyes with MAs in Zone 3 (25 %: black bar in Fig 2), MAs were observed in the other Zone as well; i.e., no eyes had only MAs in Zone 3. Fig 3 shows WFFA images from a representative case. NV was observed in Zone 2. On the other hand, MA and NV were not observed in the far periphery, although the NPAs spread over a wide range from the posterior pole through the far periphery.

Impact of Peripheral Abnormalities or Scatter PC on Visual Function and Macular Morphology

Baseline characteristics of the patients with and without far peripheral microvascular abnormalities are shown in Table 2. There were no significant differences except the ages. Fig 4 shows the changes of logMAR VA and CRT in eyes with and without far peripheral lesions. The presence of peripheral lesions did affect

neither the changes of logMAR VA nor the CRT. In addition, there were no significant differences in injection number and the incidence of persistent ME or VH (Table 3).

The data of the eyes with PC and without PC also are shown in Table 4, 5, and Fig 4. Similar to the results of the far peripheral lesions, any significant differences were not detected (Table 5 and Fig 4). In the current study, scatter PC reduced neither the injection number of STTA and IVR nor the incidence of persistent ME (Table 3).

Impact of the Nonperfused Areas in the Posterior Pole on Visual Function and Complications

Baseline characteristics of the patients with and without NPAs larger than 5 disc diameters in Zone 1 are shown in Table 6. There were not any significant differences. Fig 5 shows the incidence of microvascular abnormalities in eyes with and without NPAs larger than 5 disc diameters in Zone 1. In Zone 3, MAs were more frequently observed in eyes with smaller Zone1 NPA. We speculate that it was because larger NPAs in the periphery might cause MA in the far periphery. However, MAs in the far periphery usually does not threaten a central vision. Interestingly, NV was not observed in the far periphery at all and was significantly frequently observed in eyes with larger NPAs in Zone 1 (Fig 5). In addition, VH was significantly more frequently developed in eyes with larger NPAs in Zone 1 (Table 7). However, there were no significant differences in the final logMAR VA and the CRT between the eyes with and without NPAs larger than 5 disc diameters in Zone 1 (Table 7).

Discussion

In the current study, we found that microvascular abnormalities in far periphery in eyes with BRVO were significantly less observed compared with those in posterior pole and mid-periphery. BRVO occurs due to venous occlusion at the arteriovenous crossings, which is usually observed at the posterior pole. Therefore, it is obvious that the incidence of peripheral lesions which are far from the occlusion site was less and the impact of peripheral lesions on visual outcomes and complications such as ME and VH was not significant.

The BVOS reported that 61 % of untreated eyes with NV developed VH and scatter PC reduced the incidence of VH to 29 % [6]. In the current study, 5 eyes (71 %) out of 7 eyes with NV had VH. Thus, untreated NV in eyes with BRVO has a high risk of VH. Therefore, scatter PC should be applied when NV develops in eyes with BRVO.

The BVOS also established laser PC as the gold standard for treating ME associated with BRVO prior to injection of anti-VEGF agents [9]. Tomomatsu et al [7] reported that retinal scatter PC for peripheral NPAs prevented recurrence of ME in BRVO. On the other hand, Campochiaro et al [8] reported that scatter PC did not reduce ME in BRVO or injection number of anti-VEGF agents. As the current results showed, if any microvascular abnormalities were less observed in the far periphery and scatter PC did not affect the visual outcomes and not reduce the injection number or frequency of persistent ME, scatter PC application for peripheral lesions in eyes with BRVO might be fruitless. On the other hand, the presence of NPAs larger than 5 disc diameters in Zone 1 was significantly associated with the incidence of NV and VH. Therefore, PC should be applied for the NPAs larger than 5 disc diameters in the posterior pole, but not in the peripheral lesions.

The current study had several limitations. First, the study design was retrospective and the application of scatter PC was not randomized. A prospective, randomized, controlled study is needed. Second, the treatment drugs differed in each patient. Third, the period of WFFA after disease onset also differed.

In conclusions, the current results showed microvascular abnormalities in far periphery were less observed and not associated with the visual outcomes in eyes with BRVO. Laser application also was not associated with the visual outcomes. However, the NPAs larger than 5 disc diameters in posterior pole should be treated because of high risk of development of NV and VH. A future prospective, randomized, controlled study with larger samples is needed to confirm the current results.

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Competing Financial Interests

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Additional Information

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Figure Legends

Figure 1. Zone grading on a wide-field fluorescein angiogram. Zone 1 has a radius of 3 disc diameters and roughly corresponded to the posterior pole. Zone 2 extends from the edge of Zone 1 anteriorly with a radius of 9 disc diameters and overlapped the vortex veins. Zone 3 is the region anterior to Zone 2 as previously reported [3]. A white dotted circle indicates a vortex vein.

Figure 2. Incidence of microvascular abnormalities in each Zone. Fig 2 shows the percentages of microvascular abnormalities observed in each Zone. Microaneurysm (MA) was significantly less observed in Zone 3 and retinal neovascularization (NV) was not observed in Zone 3. In all of the eyes with MAs in Zone 3 (25 %: black bar), MAs were observed in the other Zone as well, i.e., no eyes had only MAs in Zone 3. MA = microaneurysm, NV = retinal neovascularization. ** $P < 0.01$

Figure 3. Representative wide-field fluorescein angiograms of an eye with branch retinal vein occlusion. (**A**), early phase, (**B**), late phase. Retinal neovascularization (arrows) was observed in Zone 2. Retinal nonperfused areas (asterisks) spread over a wide range from the posterior pole through the far periphery.

Figure 4. Changes of best-corrected visual acuity and central retinal thickness. (**A, B**), logarithm of the minimal angle of resolution visual acuity (logMAR VA) (**A**) and central retinal thickness (CRT) (**B**) with and without peripheral abnormalities at baseline and final visit. In both eyes with and without peripheral abnormalities, the mean logMAR VA significantly improved and the mean CRT significantly decreased. (**C, D**), logMAR VA (**C**) and CRT (**D**) with and without retinal laser photocoagulation (PC) at baseline and final visit. In both eyes with and without PC, the mean logMAR VA significantly improved and the mean CRT significantly decreased. ** $P < 0.01$

Figure 5. Incidence of microvascular abnormalities in each Zone as related to posterior ischemia. Fig 5 shows the percentages of microvascular abnormalities in eyes with and without nonperfused area (NPA) larger than 5 disc diameters (DD) in Zone 1. There were not significant differences between the incidences of microaneurysm (MA) in Zone 1 and Zone 2, but was significant in Zone 3. Retinal neovascularization (NV) was not observed in Zone 3. In Zone 1 and Zone 2, NV was significantly more

frequently observed in eyes with larger NPA in Zone 1. NS = not significant, ** $P < 0.01$, * $P < 0.05$.

Table 1. Patient characteristics

Age(year, mean±SD)	70.7 ± 11.3
Gender(male/female))	24/15
Hypertension(yes/no)	20/19
Diabetes Mellitus(yes/no)	2/37
Initial logMAR VA(mean±SD)	0.279±0.334
Initial CRT(μm, mean±SD)	430±169
Time of WFFA measurement from disease onset(month, mean±SD)	18.6±30.2
Follow-up period(month, mean±SD)	41.8±28.9
Treatment(anti-VEGF/STTA/PC alone/none)(n, eyes)	13/15/11/1
Vitrectomy(yes/no)(n, eyes)	5/35
Retinal PC(yes/no)(n, eyes)	33/7

SD = standard deviation, logMAR = logarithm of the minimal angle of resolution, VA = visual acuity, CRT = central retinal thickness, WFFA = wide-field fluorescein angiography, VEGF = vascular endothelial growth factor, STTA = sub-Tenon's capsule injection of triamcinolone acetonide, PC = photocoagulation.

Table 2. Patient characteristics as related to presence or absence of peripheral abnormalities

	Peripheral Abnormalities(+)	Peripheral Abnormalities(-)	*P* value
Patients	11(11 eyes)	28(29 eyes)	-
Age(year, mean±SD)	75.5±12.3	68.8±10.4	0.04*
Gender(male/female)	8/3	16/12	0.36
Follow-up(month, mean±SD)	31.8±31.4	45.5±27.9	0.09
Initial logMAR VA(mean±SD)	0.20±0.21	0.30±0.36	0.15
Initial CRT(μm, mean±SD)	397±140	443±179	0.22
Hypertension(yes/no)	5/6	15/13	0.72
Diabetes Mellitus(yes/no)	0/11	2/26	0.37

SD = standard deviation, logMAR = logarithm of the minimal angle of resolution, VA = visual acuity, CRT = central retinal thickness. *$P < 0.05$

Table 3. Treatments and complications as related to presence or absence of peripheral abnormalities

	Peripheral Abnormalities(+)	Peripheral Abnormalities(-)	*P* value
STTA(n, mean±SD)	0.36±0.67	1.34±2.30	0.08
IVR(n, mean±SD)	2.81±3.70	1.86±2.82	0.19
PC(yes/no)	10/1	23/6	0.38
Final logMAR VA(mean±SD)	-0.04±0.10	0.08±0.30	0.09
logMAR change(mean±SD)	0.24±0.16	0.22±0.38	0.43
Final VA>20/20(yes/no)	8/3	14/15	0.16
Final CRT(μm, mean±SD)	256±27.8	269±62.5	0.26
CRT change(%, mean±SD)	-28.7±22.1	-30.7±25.8	0.40
Persistent ME(yes/no)	5/6	15/14	1.00
VH(yes/no)	1/10	4/25	0.69

STTA = sub-Tenon's capsule injection of triamcinolone acetonide, SD = standard deviation, IVR = intravitreal injection of ranibizumab, PC = retinal photocoagulation, logMAR = logarithm of the minimal angle of resolution, VA = visual acuity, CRT = central retinal thickness, ME = macular edema, VH = vitreous hemorrhage.

Table 4. Patient characteristics as related to presence or absence of retinal photocoagulation

	PC(+)	PC(-)	*P* value
Patients	32(33 eyes)	7(7 eyes)	-
Age(year, mean±SD)	71.0±10.7	69.4±14.4	0.37
Gender(male/female)	20/12	4/3	0.74
Follow-up(month, mean±SD)	46.9±30.8	33.1±19.2	0.19
Initial logMAR VA(mean±SD)	0.30±0.36	0.26±0.13	0.46
Initial CRT(μm, mean±SD)	468±179	323±55.1	0.06
Hypertension(yes/no)	17/15	2/5	0.21
Diabetes Mellitus(yes/no)	1/31	1/6	0.21

SD = standard deviation, logMAR = logarithm of the minimal angle of resolution, VA = visual acuity, CRT = central retinal thickness, PC = retinal photocoagulation.

Table 5. Treatments and complications as related to presence or absence of retinal photocoagulation

	PC(+)	PC(-)	*P* value
STTA(n, mean±SD)	1.28±2.20	0.71±0.75	0.30
IVR(n, mean±SD)	1.60±3.11	3.14±2.85	0.17
Final logMAR VA(mean±SD)	0.07±0.28	0.008±0.12	0.32
logMAR change(mean±SD)	0.22±0.36	0.26±0.14	0.38
Final VA>20/20(yes/no)	19/14	3/4	0.16
Final CRT(μm, mean±SD)	266±54.3	266±61.8	0.48
CRT change(%, mean±SD)	-32.0±22.1	-21.6±15.0	0.15
Persistent ME(yes/no)	17/16	3/4	0.67
VH(yes/no)	4/29	1/6	0.88

STTA = sub-Tenon's capsule injection of triamcinolone acetonide, SD = standard deviation, IVR = intravitreal injection of ranibizumab, logMAR = logarithm of the minimal angle of resolution, VA = visual acuity, CRT = central retinal thickness, ME = macular edema, VH = vitreous hemorrhage, PC = retinal photocoagulation.

Table 6. Patient Characteristics as related to presence or absence of nonperfused areas larger than 5 disc diameters in Zone 1

	Zone1NPA>5DD	Zone1NPA<5DD	*P* value
Patients	19(20 eyes)	20(20 eyes)	-
Age(year, mean±SD)	68.3±11.5	73.1±10.7	0.08
Gender(male/female)	14/5	10/10	0.10
Follow-up(month, mean±SD)	48.6±29.5	34.9±28.0	0.07
Initial logMAR VA	0.31±035	0.23±0.31	0.29
Initial CRT(μm, mean±SD)	465±200	397±120	0.10
Hypertension(yes/no)	8/11	12/8	0.20
Diabetes Mellitus(yes/no)	1/18	1/19	1.00

SD = standard deviation, logMAR = logarithm of the minimal angle of resolution, VA = visual acuity, CRT = central retinal thickness, NPA = nonperfused area, DD = disc diameters.

Table 7. Treatments and complications as related to presence or absence of nonperfused areas larger than 5 disc diameters in Zone 1

	Zone1NPA>5DD	Zone1NPA<5DD	*P* value
STTA(n, mean±SD)	1.30±2.34	0.85±1.69	0.24
IVR(n, mean±SD)	1.80±2.94	2.45±3.23	0.25
Final logMAR VA(mean±SD)	0.08±0.26	0.02±0.26	0.23
logMAR change(mean±SD)	0.23±0.33	0.21±0.34	0.42
Final VA>20/20(yes/no)	10/10	12/8	0.75
Final CRT(μm, mean±SD)	266±62.6	265±48.7	0.47
CRT change(%, mean±SD)	-31.6±29.7	-28.9±18.8	0.48
Persistent ME(yes/no)	10/10	10/10	1.0
VH(yes/no)	5/15	0/20	0.01*

STTA = sub-Tenon's capsule injection of triamcinolone acetonide, SD = standard deviation, IVR = intravitreal injection of ranibizumab, logMAR = logarithm of the minimal angle of resolution, VA = visual acuity, CRT = central retinal thickness, ME = macular edema, VH = vitreous hemorrhage, NPA = nonperfused areas, DD = disc diameters. *$P < 0.01$.