Angiographic Risk Features of Branch Retinal Vein Occlusion Onset as Determined by Optical Coherence Tomography Angiography

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Purpose. Examine associations between the vasculature at arteriovenous (AV) crossings and the onset of branch retinal vein occlusion (BRVO).

Methods. We included 78 patients with major BRVO, 35 patients with macular BRVO, and 110 controls without BRVO and determined the vessel positions at AV crossings, where the first- or second-order branches of the retinal veins associate, using a viewing angle of 12 × 12 mm² in optical coherence tomography angiography (OCTA).

Results. We reviewed 1349 and 1276 AV crossings in BRVO patients and control subjects, respectively. The proportions of venous overcrossing were 26.5%, 28.6%, and 26.8% at non-causative crossings in BRVO eyes, non-BRVO fellow eyes, and unaffected control eyes, respectively; however, the rate of venous overcrossings at the causative crossings was 45.1%. In OCTA analyses, we divided the branches into macular- or non-macular veins. The rate of venous overcrossing was 52.5% at causative crossings in major BRVO but was 28.6% in macular BRVO. Odds ratios for whether venous overcrossing was a risk factor for BRVO were 3.09 (95% confidence interval [CI], 1.96–4.88) and 0.94 (95% CI, 0.44–2.00) for non-macular veins and macular veins, respectively. The patients with major BRVO caused by venous overcrossing were younger than patients for whom the cause was arterial overcrossing (P < 0.001). The onset of macular BRVO did not differ between crossing patterns at causative crossings (P = 0.60).

Conclusions. In eyes with BRVO, venous overcrossing was a common angiographic feature at causative crossings and might be a risk factor for major BRVO onset.

Keywords: branch retinal vein occlusion, arteriovenous crossing, venous overcrossing, optical coherence tomography angiography

Branch retinal vein occlusion (BRVO) is the second most frequent retinal vascular disease.1–3 The clinical characteristics of BRVO determined using conventional methods, including ophthalmoscopy, color fundus photography (CFP), and fluorescein angiography (FA), have been reported previously.4,5 These methods have revealed that BRVO frequently occurs at arteriovenous (AV) crossings where retinal arteries and first- or second-order branches of the retinal veins associate.1–7

Generally, the anatomical vessel position of AV crossings can be categorized into one of two patterns: arterial overcrossings, where the artery courses over the adjacent vein, or venous overcrossings, where the vein courses over the adjacent artery.6,8 Previous reports using conventional imaging methods have also revealed that arterial overcrossings are predominant, whereas venous overcrossings are very rare at causative crossings of eyes with BRVO, for reasons that are not clear.7,9

Compared to the older imaging modalities, optical coherence tomography (OCT) and OCT angiography (OCTA) enable detailed evaluation of the retinal vasculature parallel or perpendicular to the retinal plane.11–21 Our recent investigations using OCT or OCTA have indicated that BRVO caused by venous overcrossing might be more prevalent than previously reported and that these cases involve more highly narrowed veins at the causative crossings and a larger retinal non-perfusion area than cases caused by arterial overcrossing. However, the viewing angle of OCT and OCTA used in these investigations might not have been sufficiently large to allow evaluation of retinal vasculature other than at causative crossings. Therefore, the clinical relevance of venous overcrossing remains undetermined.

To elucidate precise vessel positions at AV crossings and their associations with the pathogenesis of BRVO, we reviewed the detailed anatomy at their respective causative and non-causative crossings in consecutive patients with either macular or major BRVO subtypes, as well as in control eyes without BRVO, using a larger OCTA viewing angle.
Methods

Patients

The present observational study was approved by the institutional review board of Kyoto University Graduate School of Medicine (Kyoto, Japan) and adhered to the tenets outlined in the Declaration of Helsinki. Written informed consent was obtained from each participant during the initial visit prior to the initiation of the study.

The present study included patients with unilateral BRVO involving the temporal sector. The duration from onset was more than 3 months, by which time the retinal hemorrhages had been substantially absorbed. Patients with BRVO in which the occluded site was located within the optic disc or on the disc margin were excluded. We excluded eyes with multiple occlusions of the retinal veins, central retinal vein occlusion (CRVO), hemispherical CRVO, coexisting ocular diseases (diabetic retinopathy, retinal arterial occlusion, retinal macroaneurysm, history of retinopathy of prematurity, or familial exudative vitreoretinopathy), high myopia (more severe than –6 diopters), or high astigmatism (more severe than ±5 diopters). Additionally, eyes for which poor-quality OCTA (signal strength index < 50) images had been obtained due to eye movement or media opacities were excluded.

Finally, a total of 113 patients with BRVO who had visited the Department of Ophthalmology, Kyoto University Hospital, between January 2017 and December 2018 met these criteria for eligibility. As an age-adjusted control group, we studied CFP and OCTA data in the records of 110 consecutive subjects diagnosed with conditions other than retinal circulatory diseases. These eyes were analyzed in exactly the same way as the diseased and fellow eyes of patients with BRVO. The recruitment period and subjects for the current study and our previously published studies did not overlap.

Classification of AV Crossing Pattern at the Causative AV Crossing

We captured images by means of 45° digital CFP (TRC-50LX, Topcon, Tokyo, Japan; 3216 × 2136 pixels) and swept-source OCTA (Plex Elite 9000, Carl Zeiss Meditec, Inc., Dublin, CA), with a scanning area of 12 × 12 mm², on the same day and centered on the fovea. In both types of imaging, we defined the major trunk veins (superotemporal or inferotemporal arcade veins) as a first-order branch and veins draining the retinal periphery beyond the vascular arcades.6 We defined major BRVO as a retinal vein occlusion limited to a smaller venous tributary draining only a sector of the macula located between the superior and inferior temporal arcades, and non-macular veins were defined as veins draining the retinal periphery beyond the vascular arcades.6 We defined major BRVO as a retinal vein occlusion beyond the retinal vascular arcades and macular BRVO as an occlusion limited to a smaller venous tributary draining a section of the macula, located between the superior and inferior temporal arcades.

Statistical Analysis

Statistical analysis was performed using PASW® Statistics 18 (SPSS, Chicago, IL). Values are presented as the mean ± standard deviation. Comparisons between the two groups were performed using unpaired t-tests. The importance of a vessel position in which the vein was anterior to the artery (venous overcrossing) as a risk factor for BRVO onset was evaluated by calculating the odds ratios (ORs) and 95% confidence intervals (CIs). Significant differences in the sampling distributions were determined using χ² tests. The level of statistical significance was set at P < 0.05.

Results

We examined vessel positions for 1349 and 1276 AV crossings in 113 patients with BRVO and 110 non-BRVO subjects, respectively. Table 1 shows their clinical characteristics. The numbers of patients with major BRVO and macular BRVO were 78 and 35, respectively.

Distribution of AV Crossing Patterns as Determined via CFP

Figure 2 shows the distribution of AV crossings as classified by CFP. The rates of venous overcrossing were 30.9%, 36.7%, and 35.9% at non-causative crossings of eyes with

| Table 1. Characteristics of Included Subjects with or without Branch Retinal Vein Occlusion |
|-----------------------------------------------|---------------------|---------------------|
| Characteristic                                 | BRVO    | Non-BRVO |
| Total number of patients included              | 113     | 110      |
| Women                                         | 61      | 55       |
| Men                                           | 52      | 55       |
| Mean age at OCTA examination, y (range)        | 68.9 ± 10.2 (38–92) | 69.2 ± 12.8 (40–93) |
| Mean age at onset, y (range)                   | 65.2 ± 10.2 (38–90) | NA        |
| Patients with systemic hypertension, n         | 63      | 48       |
| Patients with diabetes mellitus, n             | 14      | 19       |
| Mean number of arteriovenous crossings examined, n/person | 11.9 ± 2.5 | 11.6 ± 2.6 |

NA, not applicable.
Risk Features of Branch Retinal Vein Occlusion

FIGURE 1. Evaluations of retinal arteriovenous crossing patterns using (A) color fundus photography and (B) optical coherence tomography angiography. (C) In the common viewing angle of both images, we judged crossing patterns at all AV crossings where retinal arteries and first- and second-order branches of retinal veins were associated. We excluded AV crossings located more nasal to the optic disc and tiny AV crossings involving third-order branches of retinal veins, from the evaluations (dashed line box, C). CFP and OCTA classified the vessel position at each crossing as an arterial overcrossing (C, a–c) or a venous overcrossing (C, d and e), consistently, in evaluations of eyes without branch retinal vein occlusion.

FIGURE 2. Distributions of arteriovenous crossings patterns in color fundus photography. Graphs show the distribution of AV crossings classified by CFP. The rates of venous overcrossing (black) were 30.9%, 36.7%, and 36.9% at non-causative crossings of eyes with branch retinal vein occlusion, crossings of fellow eyes, and crossings of control eyes, respectively. However, the rate of venous overcrossing (black) at causative crossings of eyes with BRVO was about one-half (17.7%) of these rates.

Distribution of AV Crossing Patterns as Determined via OCTA

The high-depth resolution and three-dimensional observation of OCTA demonstrated narrowed veins and capillary vessels even in eyes with BRVO (Supplementary Figs. S1–S3). In OCTA, the rates of venous overcrossings were 26.5%, 28.6%, and 28.8% at non-causative crossings of eyes with BRVO, crossings of fellow eyes, and crossings of control eyes, respectively, which had similar values and were nearly equivalent to those examined by CFP (Figs. 1–3). However, the rate of venous overcrossings at the causative crossing was 45.1% (51/113), which was markedly more frequent compared with other venous overcrossings (Fig. 3).

AV Crossing Patterns of Major BRVO and Macular BRVO

In OCTA analyses, we divided the first- and second-order venous branches into macular or non-macular veins, which could be causative vessels of macular BRVO and major BRVO, respectively. Figure 4 shows the rates of venous overcrossings at the causative crossings of major BRVO and macular BRVO. The rate of venous overcrossing was 52.5% at the causative crossings of major BRVO; in contrast, the rate of venous overcrossing was 28.6% at the causative crossings.
of macular BRVO, which was as frequent as those at other crossings. We determined differences in the distributions of AV crossing patterns at the causative crossings; the \( P \) values were <0.001 for the causative crossings of eyes with major BRVO and 0.785 for those with macular BRVO.

To study whether venous overcrossing could be a risk factor for BRVO onset, we calculated ORs for non-macular veins and for macular veins by evaluating 2625 AV crossings of the 223 subjects included. The ORs were 3.09 (95% CI, 1.96–4.88) and 0.94 (95% CI, 0.44–2.00) for non-macular veins and macular veins, respectively.

The mean age of patients with macular BRVO did not differ between the vessel positions of the causative crossings (\( P = 0.60 \)); however, patients with major BRVO caused by venous overcrossing were significantly younger than patients with major BRVO caused by arterial overcrossing (\( P < 0.001 \)) (Table 2).

**DISCUSSION**

In this study, we used OCTA to image the posterior poles of the included subjects and examined the vessel positions of AV crossings at the causative and non-causative crossings of BRVO eyes, crossings of fellow eyes, and crossings of control eyes. We found that venous overcrossing at the causative crossings, which had, to date, been considered to be a very rare pattern,\(^7,9,10,26\) was in fact a common angiographic feature rather than a risk factor for the onset of major BRVO.

Because BRVO mostly occurs at AV crossings, underlying arterial disease is considered to play a causative role.\(^1,5\) For example, advanced age, hypertension, and arteriosclerosis are known to be representative risk factors for the onset of BRVO. Previous histological studies have suggested that the major arteries and veins share a common adventitial sheath at the AV crossing.\(^27,28\) Previous studies using conventional imaging modalities, prior to the advent of OCT or OCTA, showed that, although venous overcrossing was a common finding (22%–40%), this pattern rarely occurred at the sites of occlusion (1%–12%).\(^6,7,9,10\) Based on these findings, many ophthalmologists had speculated that a vessel position in which the artery is anterior to the vein might be involved in the pathogenesis of BRVO.\(^8,29–32\)

In OCTA examinations in the present study, the rates of venous overcrossing ranged from 26.5% to 28.6% at non-causative crossings of eyes with BRVO, crossings of fellow eyes, and crossings of control eyes and were equivalent to those of previous reports involving conventional imaging modalities\(^7,9,33\) and those obtained by CFP in the present study (Figs. 1–3). However, our study showed that the rate of venous overcrossings at causative crossings was 45.1%, which was different from the rates previously reported\(^7,9,10,26\) as well as from the current CFP-based findings (Figs. 2 and 3). But, this rate was consistent with our recent OCTA investigation using another BRVO cohort.\(^14\)

The discrepancy in causative crossing findings between the modalities used in this study may be related to the classification of 93 sites (82.3%) as arterial overcrossings by CFP, whereas OCTA examinations with high depth-resolution and three-dimensional observation accurately classified 31 of the 93 sites as venous overcrossings (Fig. 3, Supplementary Figs. S1–S5). Overall, the rates of disagreement between CFP and OCTA were 7.6%, 10.4%, and 11.3% at non-causative crossings of eyes with BRVO, crossings of fellow eyes, and crossings of control eyes, respectively. However, the rate of disagreement at the causative crossing site was 27.4%, which was markedly more frequent than that at the other sites.

**Table 2.** Comparison of Age Difference Between Causative Arteriovenous Crossing Patterns Determined via Optical Coherence Tomography Angiography

|                | Major BRVO (n = 78 eyes) | Macular BRVO (n = 35 eyes) |
|----------------|-------------------------|---------------------------|
| Age at onset, y (range) | Arterial Overcrossing (37 eyes) | Venous Overcrossing (41 eyes) | \(P\) | Arterial Overcrossing (25 eyes) | Venous Overcrossing (10 eyes) | \(P\) |
|                | 68.4 ± 7.9 (50–85) | 61.9 ± 8.8 (45–86) | <0.001 | 64.7 ± 12.8 (41–90) | 67.4 ± 14.0 (38–85) | 0.60 |

**FIGURE 3.** Distributions of arteriovenous crossing patterns in optical coherence tomography angiography. The graphs show the distribution of arterial overcrossing (white) and venous overcrossing (black) for all subjects. In OCTA examinations, rates of venous overcrossings are 26.5%, 28.6%, and 26.8% at non-causative crossings of eyes with branch retinal vein occlusion, crossings of fellow eyes, and crossings of control eyes, respectively; these rates are equivalent. However, the rate of venous overcrossing at causative crossings was 45.1%, which is greater than the rates of venous overcrossing at the other sites.
FIGURE 4. Differences in rates of vessel positions at causative crossings between non-macular veins and macular veins. The graphs show the distributions of arterial overcrossing (white) and venous overcrossing (black) in the (A) non-macular vein and (B) macular vein as examined by OCTA. The rate of venous overcrossing was 52.5% at the causative crossings of major branch retinal vein occlusion; however, the rate of venous overcrossing was 28.6% at the causative crossings of macular BRVO, which is equivalent to that at other crossings.

Using OCT B-scans, Muraoka et al.\textsuperscript{22} reported that the venous lumen at an arterial overcrossing was relatively preserved at causative crossings, with the affected vein approaching the retinal pigment epithelium level. In contrast, the venous lumen at a venous overcrossing was more severely compressed between the inner limiting membrane and the rigid arterial wall (Supplementary Fig. S3).\textsuperscript{22} Using OCTA to image causative crossings, Iida et al.\textsuperscript{14} recently reported that the affected veins, which coursed anterior to the artery, were more severely narrowed in parallel to the retinal plane than when the affected vein coursed posterior to the artery. We considered that the disparity in the frequencies of venous overcrossings between previous studies\textsuperscript{7,9,10,14,26} and more recent investigations using OCT\textsuperscript{22} or OCTA\textsuperscript{14} may be due to the failure of previously used imaging modalities to capture the narrowed veins at the causative crossings in cases where the vein coursed anterior to the artery. A very recent study using only OCT-B scan for imaging causative crossings reported that venous overcrossings occurred at 50.5% of causative crossings in a case series of 111 patients with BRVO,\textsuperscript{34} a finding that was highly consistent with the current study’s OCTA findings.

In this study, venous overcrossing at causative crossings was more frequent than that observed in normal fundi.\textsuperscript{7,33} If BRVO occurs randomly among all AV crossings, the rate of venous overcrossing should be equivalent for causative crossings and for the fundus overall. Therefore, we considered that venous overcrossing at the causative crossings might rather serve as a risk factor for BRVO onset, although this notion is in contradiction to previous speculations about vessel position at causative crossings.\textsuperscript{7,9,10,26} We thus calculated ORs based on the evaluations of 2625 AV crossings of the 223 included subjects. Interestingly, the ORs were 2.15 (95% CI, 1.46–3.18) and 3.09 (95% CI, 1.96–4.88) for all veins and for non-macular veins, respectively, but decreased to 0.94 (95% CI, 0.44–2.00) for macular veins. These results indicate that the venous overcrossing was not associated with the onset of macular BRVO but might be significantly associated with the onset of major BRVO. It is unclear why the risk differs between the scales of the venous branches; however, we have considered that intravascular lesions,\textsuperscript{22,35,36} such as endothelial damage, shear stress change, or clot formation, secondary to the vasculature changes that are suggested to differ partially among crossing patterns,\textsuperscript{14,22} may be more prevalent when non-macular veins drain an area beyond the vascular arcades than when macular veins drain only a macular area.

Staurenghi et al.\textsuperscript{24} previously performed FA for 65 patients with BRVO and found that arterial overcrossing was not significantly important in the first-order branches (mostly non-macular veins). This finding might be contrary to the results of other previous reports using conventional imaging modalities\textsuperscript{7,9,10,26} but was consistent with our current OCTA findings showing that venous overcrossing may be a risk factor for major BRVO. In this study, patients with major BRVO caused by a venous overcrossing were significantly younger than those for whom the onset was caused by an arterial overcrossing (P < 0.001) (Table 2). In contrast, the onset of macular BRVO did not differ between crossing patterns at the causative crossing (P = 0.60) (Table 2).

Most recently, we reported that the retinal non-perfusion area of eyes with BRVO caused by a venous overcrossing was larger\textsuperscript{14} and tended to enlarge longitudinally.\textsuperscript{25} Additionally, the incidence of neovascular changes was higher
in eyes where BRVO was caused by venous overcrossing than in eyes where BRVO was caused by arterial overcrossing. Therefore, the angiographic features associated with BRVO may aid in the development of appropriate management strategies or an optimized treatment protocol for each patient.

The present study has some notable limitations. First, the number of study subjects was limited. Second, we did not include BRVO patients with occlusions at the optic disc (although the prevalence is considered to be relatively lower than that of BRVO occurring at AV crossings)75 or patients with poor visual function due to severe BRVO. Therefore, the current findings may not be generalizable to all types of BRVO. Third, the associations between causative crossing patterns and clinical features, such as collateral vessel formations, were not elucidated. Fourth, because we analyzed data of BRVO patients who visited our university’s referral retinal practices, it is likely that our study may have been biased to include relatively severe cases. Finally, we could not compare OCTA findings to FA results because FA examinations were not always performed for the control eyes.

Despite these shortcomings, however, our findings demonstrated an association between the angiographic features of AV crossings and the onset of BRVO. Because the criteria used in this study were objective and applicable to most cases of BRVO occurring at AV crossings, these results might provide insights into the pathogenesis of BRVO, which may differ depending on the clinical subtypes.

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