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FUNDUS CHANGES IN BRANCH RETINAL VEIN OCCLUSION

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Abstract

Purpose—To investigate systematically the retinal changes in branch retinal vein occlusion (BRVO) and their natural history.

Methods—The study comprised 214 consecutive BRVO patients (144 major BRVO and 72 macular BRVO eyes) seen within 3 months of onset, Ophthalmic evaluation at initial and follow-up visits included recording visual acuity, visual fields, and detailed anterior segment and fundus examinations and fluorescein fundus angiography.

Results—Initially retinal hemorrhages were moderate to severe in the perifovea and macula in at least 65% in major and 52% in macular BRVO; at the fovea it was 51% in major and 36% in macular BRVO. Initially macular edema was more marked in major BRVO than in macular BRVO ($p=0.007$). Major BRVO had a significantly higher rate of development of serous macular detachment ($p=0.002$), epiretinal membrane ($p=0.008$), serous retinal detachment ($p=0.002$), perivenous sheathing ($p<0.0001$), optic disc pallor ($p<0.0001$), and lipid deposit ($p<0.0001$) compared to macular BRVO. Retinal and disc neovascularization was seen only in major BRVO. The time to resolution of BRVO was significantly longer for major BRVO compared to macular BRVO ($p=0.0002$).

Conclusion—Major and macular BRVOs are two distinct clinical entities Initial and final fundus findings in the two types differ markedly.

Keywords

Branch retinal vein occlusion; Epiretinal membrane; Fluorescein fundus angiography; Macular edema; Macular pigmentary degeneration; Retina; Retinal hemorrhages; Retinal vein occlusion; Retinal veins

The clinical entity of branch retinal vein occlusion (BRVO) has been known since 1896¹, and is a common retinal vascular occlusive disorder. Yet, a Medline literature search revealed little comprehensive scientific data on all the fundus changes and their natural history, from any study with large cohort of eyes with BRVO. There are review articles,

dealing either with BRVO alone²⁻⁴ or as a part of all types of retinal vein occlusion^{5,6}; these primarily give the well-known general description of the fundus lesions in BRVO, without giving any detailed scientific data about all the fundus lesions and their evolution. Moreover, our studies⁷⁻⁹ have shown that BRVO actually consists of two distinct clinical entities: major BRVO and macular BRVO. There was no information about all the fundus changes separately in the two types of BRVO in the literature except in one study¹⁰ which gives information about serous macular detachment and macular edema only. In view of that, we investigated various fundus changes as well as their natural history separately for major and macular BRVO.

Patients and Methods

We investigated various aspects of BRVO systematically in the Ocular Vascular Clinic at the Tertiary Care University of Iowa Hospitals and Clinics from 1973 till 1999 (when SSH retired), as part of a large prospective study on ocular vascular occlusive disorders funded by the National Institute of Health (RO1 grant), approved by the Institutional Review Board. In our study on BRVO, 214 patients (216 eyes: 144 eyes with major and 72 eyes with macular BRVO) fulfilled the following strict inclusion and exclusion criteria:

Inclusion criteria

1. Only those patients who had a definite diagnosis of major or macular BRVO were included. Following are the definitions of the two types of BRVO:

Major BRVO is due to occlusion of one of the four major branch retinal veins (Fig. 1). It involves the entire segment of the retina drained by the vein extending all the way up to the peripheral retina.

Macular BRVO is due to occlusion of one of the veins from the macular region (a part of the retina between the superior and inferior vascular arcades) only (Fig. 2).

2. Only those patients who at the initial visit gave a definite history of onset of visual symptoms within 3 months were included. It is known that with longer interval between onset and evaluation of an eye, fundus parameters change, and do not provide valid information about the natural history of fundus changes.

Exclusion criteria

We excluded all other retinopathies mimicking BRVO. All patients with inadequate information required for evaluation of fundus changes were excluded. Patients who had any other retinal or optic nerve lesion or any other factor (e.g., cataract), including any treatment for BRVO which could have influenced the fundus findings, were excluded.

STUDIES PERFORMED—The intention was to document the natural history of fundus changes serially during follow-up. The data were collected prospectively and systematically. At the initial visit, all patients were seen by one of us (SSH) in the Ocular Vascular Clinic and had a detailed ocular and medical history as well as a comprehensive bilateral ophthalmic evaluation. This included, (i) careful testing of the best corrected visual acuity using the Snellen visual acuity chart, (ii) visual field plotting with a Goldmann perimeter

(using I-2e, I-4e and V-4e targets regularly), (iii) intraocular pressure recording with a Goldmann applanation tonometer, (iv) relative afferent pupillary defect, (v) a thorough anterior segment examination, including slit lamp examination of the anterior segment, lens and vitreous, (vi) a meticulous fundus evaluation by direct and indirect ophthalmoscopy, and, if required, by contact lens, (vii) stereoscopic color fundus photography, and (viii) stereoscopic fluorescein fundus angiography (only in the involved eye).

In addition, the patients had a full systemic evaluation performed either by an internist at the University of Iowa Hospitals & Clinics, or by their local internist/physician.

At each follow-up visit, the same ophthalmic evaluation and stereoscopic color fundus photography were done, except that fluorescein fundus angiography was performed only when considered essential; also many patients were reluctant to have repeated angiography because of nausea and because it is an invasive procedure.

Follow-up protocol for all patients

All patients were followed (by SSH) according to a protocol practiced in this Clinic for BRVO patients - at about 3 monthly intervals for 3 visits, then 6 monthly intervals for 4 visits, then annually. Both eyes were examined at each visit. Since this was a natural history study of fundus changes, no intervention of any kind whatever was undertaken in this cohort of patients with BRVO. If any eye had any treatment, the information was included only from the onset to the time of intervention.

Evaluation of fundus findings—In each eye the following fundus changes were documented meticulously. Changes were evaluated in a MASKED FASHION, by a single investigator (SSH), by comparing findings in 30° and 60° fundus photographs with the standard fundus photographs for various grades of retinal changes, as was done in our previous studies^{9,11–13} dealing with retinal fundus changes in retinal vein occlusion.

1. *Retinal hemorrhages*

Final evaluation was always done from stereoscopic color fundus photographs (30° and 60° photographs), and also for peripheral hemorrhages based on the indirect and direct ophthalmoscopic evaluation. For each visit, the retinal hemorrhages at various locations in the retina were evaluated (comparing with the standard photos for various grades), using the following criteria:

Subjective grading of retinal hemorrhages: 1 = no hemorrhages; 2 = minimal/small/isolated hemorrhages; 3 = medium amount of hemorrhages; 4 = extensive hemorrhages; 5 = uncertain/questionable hemorrhages; 9 = no data.

Regions of the retina: For descriptive purposes, the entire fundus was divided into the following 5 regions: (1) foveal center, (2) perifoveal region, (3) rest of the macular region, (4) rest of posterior pole (in the region outside the vascular arcades), and (5) peripheral region. This is because different areas of the retina had hemorrhages of different severity of in BRVO. Retinal hemorrhages were evaluated separately in the 5 regions.

Ordinary retinal hemorrhages were intra-retinal; but when the hemorrhages were lying on the surface of the nerve fiber layer and under the internal limiting membrane, those were classified as “pre-retinal hemorrhages”, while those lying in the subhyaloid space in front of the internal limiting membrane were labeled as “subhyaloid hemorrhages”.

2. **Macular edema:** Critical evaluation of the macular edema was done by using: (i) direct ophthalmoscopy, (ii) Hruby contact lens, (iii) stereoscopic fundus photographs of the macular region, and (iv) stereoscopic fluorescein fundus angiography of the macular region. Optical coherence tomography or other modern technologies to evaluate macular edema were not available during the period data collection in this study. The severity of macular edema was graded as minimal, medium, and marked (compared with the standard photos for various grades).
3. **Submacular serous retinal detachment:** This was evaluated in our study from combined information provided by Hruby contact lens and stereoscopic color fundus photographs and stereoscopic fluorescein angiograms.
4. **Retinal venous engorgement:** This was graded as none, mild, moderate and marked, comparing with the standard photos for various grades.
5. **Cotton wool spots:** Their location and presence was documented, and when possible their number was recorded.
6. **Other fundus parameters recorded:** These included the presence of epiretinal membrane, macular retinal pigment epithelial degeneration, macular hole, retinal venous sheathing, retinal arterial abnormality, lipid deposits (“hard exudates”), optic disc pallor, retinal collaterals, and any other finding.
7. **Fluorescein fundus angiography:** In the fovea, perifovea, macula, the rest of the posterior pole (outside the vascular arcades) and peripheral retina, we evaluated the presence or absence of fluorescein staining, perivenous fluorescein staining, microaneurysms, retinal capillary obliteration, retinal capillary foveal arcade intact or broken, and arteriovenous filling time (in seconds). Severity of retinal capillary obliteration was graded as none, small patchy, moderate and extensive, according to a set of slides with different grades. Since fluorescein angiography was mainly evaluated from angiograms covering the central 30° to 60°, findings in the extreme peripheral retina could not be evaluated; there were only a limited number cases where the peripheral retina was scanned. This is a limitation with routine fluorescein fundus angiography.

Resolution of Retinopathy—This was defined as when retinal hemorrhages, macular edema, serous retinal detachment, cotton wool spots and other retinal changes had all resolved.

Statistical Analysis—Initial grades of hemorrhage severity, macular edema, and severity of capillary obliteration were compared between major and macular BRVO using exact Wilcoxon rank-sum test. Kaplan-Meier curves were constructed for resolution of hemorrhage and were compared using log-rank test. Similar analysis was performed of time

to development of cotton wool spots, epiretinal membrane, macular pigmentary degeneration, retinal vein sheathing, lipid deposits, retinal arterial attenuation, and serous detachment.

Results

Demographic Characteristics

Our study comprised 143 patients (144 eyes) with major BRVO and 71 patients (72 eyes) with macular BRVO. This is the same cohort of patients in which we previously reported the natural history of visual outcome in BRVO⁹. Descriptive statistics of the demographic variables are presented in Table 1.

Retinal Hemorrhages

Fundus examination at the initial visit of major BRVO eyes showed moderate to severe retinal hemorrhage in the fovea in 51% and in more than 65% in the perifovea, macula, and posterior pole (see Table 2). For eyes with macular BRVO, moderate to severe retinal hemorrhage was seen in 38% in the fovea, 52% in the perifovea, and 63% in the macula. The distribution of severity of hemorrhage at each location is shown in Table 2.

Kaplan-Meier curves for the resolution of retinal hemorrhage are shown in Figure 3 for major BRVO and Figure 4 for macular BRVO. Retinal hemorrhages in the peripapillary region had the shortest resolution time and peripheral retinal hemorrhages had the longest resolution time in major BRVO. The median times to resolution at each location are presented in Table 2. Resolution time of retinal hemorrhage in the fovea was significantly longer in major BRVO compared to macular BRVO ($p=0.029$). Resolution time of retinal hemorrhages in the perifovea ($p=0.510$), and macula ($p=0.112$) did not differ between major and macular BRVO.

Pre-Retinal and Subhyaloid Hemorrhages

Pre-retinal hemorrhages mostly developed within 3 months of onset for both major and macular BRVO. In major BRVO, the cumulative probability of pre-retinal hemorrhage was $16.4\% \pm 3.1\%$ within 2 months, and $24.7\% \pm 3.7\%$ within 6 months from onset. Compared to major BRVO, pre-retinal hemorrhage developed at a similar rate in macular BRVO ($p=0.510$) with $17.1\% \pm 4.5\%$ within 2 months, and $23.0\% \pm 5.1\%$ within 3 months from onset. The pre-retinal hemorrhages also resolved at a similar rate in major and macular BRVO ($p=0.980$), with hemorrhage resolving in $28.4\% \pm 7.6\%$ of major BRVO and $26.3\% \pm 11.3\%$ of macular BRVO within 9 months.

Subhyaloid hemorrhages developed only in major BRVO not in macular BRVO. Most appeared within 6 months from onset of major BRVO, with cumulative probability of $5.2\% \pm 1.9\%$ at 6 months and $7.7\% \pm 2.3\%$ within 9 months.

Macular Edema

At the initial visit, eyes with major BRVO presented with more marked macular edema than those with macular BRVO ($p=0.007$). Macular edema grade in those with major BRVO was

50% with none-mild, 33% moderate, and 18% severe, compared to 72% none-mild, 23% moderate, and 6% severe in macular BRVO.

Resolution time of macular edema did not significantly differ between major and macular BRVO ($p=0.647$). In major BRVO, resolution of macular edema was $33.1\% \pm 4.6\%$ within 12 months from onset, $42.6\% \pm 4.9\%$ within 18 months, and $50.8\% \pm 5.1\%$ within 24 months. The median time to resolution of macular edema in major BRVO was 20.8 (IQR: 10.3–54.8) months. For macular BRVO, $30.4\% \pm 6.4\%$ resolved within 12 months from onset, $49.4\% \pm 7.4\%$ within 18 months, and $56.7\% \pm 7.4\%$ within 24 months; median time to resolution was 18.2 (IQR: 9.7–58.4) months.

Other Macular Changes

Kaplan-Meier product-limit estimates of the development of epiretinal membrane, macular retinal pigment epithelial degeneration, and serous macular detachment are shown in Table 3. Epiretinal membrane ($p=0.008$) and serous macular detachment ($p=0.002$) developed at a significantly higher rate in major BRVO than in macular BRVO. In eyes with major BRVO, epiretinal membrane had developed in $8.6\% \pm 2.6\%$ of eyes within 12 months from onset, and in $13.7\% \pm 3.5\%$ within 36 months from onset. Only 1 eye with macular BRVO developed epiretinal membrane. Serous macular detachment mostly developed within 3 months from onset of major BRVO, with cumulative probability of $17.7\% \pm 3.2\%$. In macular BRVO, serous macular detachment developed in $3.0\% \pm 2.1\%$ within 6 months from onset.

There was no significant difference in the rate of macular retinal pigment epithelial degeneration between major BRVO and macular BRVO ($p=0.366$), where $26.2\% \pm 4.1\%$ in major BRVO and $22.0\% \pm 5.4\%$ in macular BRVO had developed macular retinal pigment degeneration epithelial within 12 months from onset; by 36 months, it was $43.0\% \pm 5.0\%$ in major BRVO and $33.6\% \pm 6.7\%$ in macular BRVO.

Retinal Vascular Changes

Cotton Wool Spots—More cotton wool spots were seen in the eyes with major BRVO compared to macular BRVO, but this was not significant at the 0.05 significance level ($p=0.099$). In major BRVO, 20% had 8 or more cotton wool spots compared to 11% in macular BRVO. Time to development of cotton wool spots did not significantly differ between major BRVO and macular BRVO ($p=0.626$). Within 3 months from onset, cotton wool spots had developed in $54.2\% \pm 4.2\%$ in major BRVO and $50.6\% \pm 6.1\%$ in macular BRVO; within 12 months it was $64.3\% \pm 4.2\%$ in major BRVO and $61.0\% \pm 6.1\%$ in macular BRVO.

Retinal Venous Engorgement and Sheathing—In major BRVO, retinal vein engorgement was moderate in 20% and marked in 54%; that was significantly ($p<0.0001$) more severe than in macular BRVO with venous engorgement: 18% and 10% respectively. Comparing the rates of resolution of retinal vein engorgement showed a slower rate of resolution in major BRVO than in macular BRVO ($p=0.006$). The cumulative proportion that resolved in major BRVO was $2.6\% \pm 1.5\%$ within 12 months from onset, and $7.2\% \pm 2.6\%$ within 24 months. For macular BRVO, $8.8\% \pm 4.2\%$ had resolved within 12 months,

and $16.3\% \pm 5.7\%$ within 24 months. There was less of a difference in resolution rates between the BRVO types after adjusting for the severity of initial retinal vein engorgement ($p=0.091$).

Major BRVO had a significantly higher rate of retinal perivenous vein sheathing than macular BRVO ($p<0.0001$). Retinal perivenous vein sheathing had appeared in $27.5\% \pm 4.0\%$ within 12 months, $43.9\% \pm 4.7\%$ within 24 months, and $58.4\% \pm 5.1\%$ within 48 months from onset of major BRVO. Only 1 eye with macular BRVO developed retinal perivenous vein sheathing.

Retinal Venous Attenuation of Involved Vein—There was a higher rate of vein attenuation in major BRVO than macular BRVO ($p=0.058$). For major BRVO, retinal venous attenuation was seen in $10.8\% \pm 2.8\%$ within 12 months, $16.8\% \pm 3.6\%$ within 24 months, and $19.4\% \pm 3.8\%$ within 48 months from onset. In contrast, for macular BRVO, retinal venous attenuation presented in $3.5\% \pm 2.5\%$ within 12 months, and $8.1\% \pm 4.0\%$ within 24 months.

Retinal Arterial Attenuation and Sheathing—Two eyes with major BRVO and no eyes with macular BRVO developed retinal arterial attenuation. Retinal arterial sheathing was found in only 5 eyes with major BRVO and none in macular BRVO.

Retinal Collaterals—The rate of development of these collaterals differed significantly between major BRVO and macular BRVO ($p<0.0001$). For major BRVO, $10.6\% \pm 2.7\%$ developed retinal collaterals within 6 months, and $30.2\% \pm 4.2\%$ within 12 months from onset. It was $1.6\% \pm 1.6\%$ within 6 months, and $3.3\% \pm 2.3\%$ within 12 months from onset for macular BRVO.

A fibrous tissue band extending into the vitreous from the retinal surface was seen in 6 eyes with major BRVO and no eyes with macular BRVO. This band appeared in $3.1\% \pm 1.8\%$ within 24 months of onset of major BRVO.

Optic Disc Pallor

Optic disc pallor appeared at a significantly higher rate in major BRVO than in macular BRVO ($p<0.0001$). In major BRVO, optic disc pallor had developed in $14.0\% \pm 3.2\%$ within 12 months from onset, and in $20.6\% \pm 3.9\%$ within 36 months from onset. Only 1 eye with macular BRVO developed optic disc pallor.

Lipid Deposits

There was a significantly higher rate of development of lipid deposits in major BRVO compared to macular BRVO ($p=0.004$). For major BRVO, the cumulative probability at 12 months was $38.5\% \pm 4.4\%$ and $47.4\% \pm 4.6\%$ at 24 months and for macular BRVO, it was $15.4\% \pm 4.5\%$ at 12 months and $21.6\% \pm 5.4\%$ at 24 months.

Fluorescein Fundus Angiographic Findings

The results of fluorescein angiography done within 4 months from onset are presented in Tables 4 and 5. Comparing fluorescein staining between major BRVO and macular BRVO showed a significantly higher proportion with posterior pole and perivenous staining in major BRVO (both $p < 0.0001$) (see Table 4). Similarly, major BRVO had 13% with microaneurysm in the posterior pole compared to 2% in macular BRVO ($p < 0.0001$). There was no significant difference in the prevalence of retinal capillary dilatation between major and macular BRVO ($p = 0.361$).

Capillary obliteration was significantly more common and extensive in eyes with major BRVO compared to macular BRVO (all $p < 0.001$; see Table 5). Capillary obliteration was present in less than 10% of eyes with macular BRVO. In contrast, at least 15% of eyes with major BRVO had moderate to severe capillary obliteration in any of the five regions. Because of overlying retinal hemorrhages it was not possible to evaluate capillary obliteration in all eyes. In major BRVO perifoveal capillary net was complete in 71% and incomplete in 29%; none of the eyes with macular BRVO had incomplete net.

Resolution of Retinopathy

The Kaplan-Meier curves for the resolution of major BRVO and macular BRVO are shown in Figure 5. The time to resolution of BRVO was significantly longer for major BRVO than macular BRVO ($p < 0.0002$). The median time to resolution of major BRVO was 4 years (interquartile range: 2.2–9.8 years) and for macular BRVO was 1.5 years (interquartile range: 1.0–6.0 years) for macular BRVO. The hazard ratio of resolution for major BRVO relative to macular BRVO was 0.47 (95% CI: 0.31, 0.70).

There was no significant effect of diabetes on time to resolution of major BRVO ($p = 0.912$) or macular BRVO ($p = 0.555$).

Arteriovenous Crossing

At the site of occlusion, the retinal arteriole was anterior to the branch retinal vein in 96% and posterior to the vein in 4%. The order of arteriovenous crossing at which the vein was occluded in inferior temporal major BRVO was: at the first crossing in 44%, and at the second crossing in 56%. In superior temporal major BRVO, occlusion was at the first arteriovenous crossing in 54%, at the second in 42%, and at the third crossing in 4%.

The distance of the blockage from the disc margin in inferior temporal major BRVO was at the disc margin in 13%, 0.5–1 disc diameter in 27%, 1.5–2 disc diameters in 24%, and 3–4 disc diameters in 36%, and in superior temporal major BRVO the disc margin in 15%, 0.5–1 disc diameter in 39%, 1.5–2 disc diameters in 27%, and 3–4 disc diameters in 18%.

In macular BRVO, the site of occlusion was at the first arteriovenous crossing in 33%, at the second crossing in 58%, and at the third crossing in 9%. The distance of the blockage from the disc margin was at the disc margin in 6%, 0.5–1 disc diameter in 26%, 1.5–2 disc diameters in 39%, and 3–4 disc diameters in 30%.

Development of Retinal and Optic Disc Neovascularization

This was seen only in major BRVO and not in macular BRVO. In major BRVO retinal neovascularization developed in $9.2\% \pm 8.4\%$ within 12 months from onset, and in $14.8\% \pm 3.5\%$ within 36 months from onset. Optic disc neovascularization was seen in $8.3\% \pm 2.5\%$ within 12 months from onset and in $10.4\% \pm 2.9\%$ within 30 months from onset.

Discussion

Our studies⁷⁻⁹ have shown that BRVO actually consists of two distinct clinical entities: major BRVO and macular BRVO. As indicated earlier, in the literature, available information on fundus changes in BRVO deals mostly with general ophthalmoscopic fundus and fluorescein fundus angiographic findings, without giving any comprehensive scientific data of different lesions and their natural history in a large cohort of BRVO eyes. Moreover, in all those studies major and macular BRVOs have been combined into one group. We investigated various fundus lesions separately in 144 eyes with major BRVO and 72 eyes with macular BRVO eyes, seen within 3 months of onset.

There are several BRVO studies but they primarily deal with the visual outcome with different treatment modalities, as discussed in our previous study dealing with visual outcome in BRVO.⁹ Rogers et al.⁴, based on a review of BRVO articles published in English language up to 2008, reported that in 1608 eyes, over a 1-year period, 5% to 15% of developed macular edema, but of those with macular edema at baseline, 18% to 41% resolved. Recently there have been a few optical coherence tomographic studies¹⁴⁻¹⁸ dealing with evaluation of macular edema or serous retinal detachment in BRVO (without differentiation between major and macular BRVO); their results are conflicting and cannot be compared with our study. The study by Yamaguchi et al.¹⁰ is the only one that describes findings for major and macular BRVO separately, but it deals only with serous macular detachment, without giving information about other fundus findings. They concluded that serous macular detachment occurs more frequently in major BRVO than in macular BRVO, as we also found. Thus, overall there is little comprehensive information giving detailed data about the various ophthalmoscopic and fluorescein angiographic parameters in the two types of BRVO and their natural history, other than dealing with data on neovascularization and crossing of the retinal arteriole over or under the retinal vein at arteriovenous crossing.

The various fundus findings in BRVO in our study are discussed in detail in the Results section above. Following are the salient features. These findings mostly differ in the two types of BRVO, as shown below.

Retinal Hemorrhages

Eyes with BRVO may initially have only engorged retinal veins without any hemorrhages; although later all of them develop hemorrhages. Initially retinal hemorrhages were moderate to severe in more than 65% in major BRVO and in 63% in macular BRVO. As shown in Table 2, the distribution, severity and time to resolution of retinal hemorrhages in different regions of the retina varied in both types of BRVO. The cumulative probability of developing pre-retinal hemorrhage was similar in the two types of BRVO ($p=0.510$); they

also resolved at a similar rate in both ($p=0.980$). Subhyaloid hemorrhages were seen only in major BRVO and those mostly appeared within 6 months from onset, with cumulative probability of $7.7\% \pm 2.3\%$ within 9 months. Resolution time of retinal hemorrhage in the fovea was significantly longer in major BRVO than in macular BRVO ($p=0.029$) but it did not differ in the perifovea and rest of the macula. Peripheral hemorrhages in major BRVO were the last to resolve.

Macular Changes

At the initial visit, eyes with major BRVO presented with more marked macular edema than those with macular BRVO ($p=0.007$); however, resolution time of macular edema did not differ significantly between the two types of BRVO ($p=0.647$) - for macular edema resolution within 24 months was $50.8\% \pm 5.1\%$ in major and $56.7\% \pm 7.4\%$ in macular BRVO. Serous macular detachment developed at a significantly ($p=0.002$) higher rate in major BRVO than in macular BRVO. The cumulative probability of development of serous macular detachment was $17.7\% \pm 3.2\%$ in major BRVO within 3 months from onset, and $3.0\% \pm 2.1\%$ within 6 months in macular BRVO. Serous macular detachment may be located only in the foveal region or involve the entire macular region, and it varied from flat to bullous type. In major BRVO, serous retinal detachment involving the retina in the region of the vascular arcade and adjacent area was observed in only 4 eyes. Serous macular retinal detachment ($p=0.002$) and epiretinal membrane ($p=0.008$) developed at a significantly higher rate in major than in macular BRVO. One eye with major BRVO had retinal pigment epithelial detachment. There was no significant difference in the rate of macular retinal pigment epithelial degeneration between major BRVO and macular BRVO ($p=0.366$).

Retinal Vascular Changes

Within 3 months from the onset, cotton wool spots had developed in $54.2\% \pm 4.2\%$ in major BRVO and $50.6\% \pm 6.1\%$ in macular BRVO; within 12 months it was $64.3\% \pm 4.2\%$ and $61.0\% \pm 6.1\%$ respectively. Major BRVO had a significantly higher rate of retinal perivenous sheathing than macular BRVO ($p<0.0001$). There was a higher rate of venous attenuation in major BRVO than in macular BRVO ($p=0.058$). The rate of development of retinal collaterals differed significantly between major BRVO and macular BRVO ($p<0.0001$) - within 12 months they developed in $30.2\% \pm 4.2\%$ in major BRVO and only $3.3\% \pm 2.3\%$ in macular BRVO. Optic disc pallor appeared at a significantly higher rate in major BRVO than in macular BRVO ($p<0.0001$). There was a significantly higher rate of development of lipid deposit in major BRVO than in macular BRVO ($p=0.004$).

Fluorescein Fundus Angiographic Findings

Fluorescein fundus angiography showed that posterior pole and perivenous staining was significantly more common in major BRVO than in macular BRVO (both $p<0.0001$). Similarly, microaneurysm in the posterior pole developed in 13% in major BRVO and only 2% in macular BRVO ($p<0.0001$). Retinal capillary obliteration was significantly more common and more extensive in major BRVO compared to macular BRVO ($p<0.001$).

Clemett et al.¹⁹ described the importance of an intact perifoveal capillary net in determining the visual outcome in major BRVO. They concluded that eyes with an intact perifoveal

capillary arcade have a better visual prognosis than eyes with an incomplete arcade. We have previously reported⁹ that visual acuity improved in 81% of those with an intact perifoveal capillary arcade and 58% with a broken arcade ($p=0.082$).

Resolution of Retinopathy

The time to resolution of BRVO was significantly longer for major BRVO than for macular BRVO ($p<0.0001$) – median time was 4 years (interquartile range: 2.2–9.8 years) in major and 1.5 years (interquartile range: 1.0–6.0 years) in macular BRVO (Fig. 5).

Neovascularization

It is well known that some eyes with BRVO develop retinal and/or optic disc neovascularization. Hayreh et al.⁷ in 1983 summarized the incidence of ocular neovascularization in BRVO reported in papers published from 1925 to 1981, and that showed development of optic disc neovascularization in 7% to 29% and retinal neovascularization in 16% to 30%. In 1983 they reported in their own series of 191 major BRVO eyes with disc and retinal neovascularization in 11.5% and 24.1% respectively, and none in 73 macular BRVO. The Branch Vein Occlusion Study Group²⁰, in 159 BRVO control eyes, reported retinal neovascularization in 22%. In our current study, neovascularization occurred in major BRVO but not in macular BRVO. Optic disc neovascularization was seen in $10.4\pm2.9\%$ within 30 months from onset. Retinal neovascularization developed in $14.8\pm3.5\%$ within 36 months after onset.

Arteriovenous Crossing

It is well-known that BRVO almost invariably develops at the retinal arteriovenous crossing. Therefore, there have been many studies dealing with the positional relationship between the retinal arteriole and vein at the arteriovenous crossing. All of them have shown that the arteriole most commonly lies anterior to the vein. Both types of crossings have a common adventitial sheath when each vessel is of large calibre.²¹ Weinberg et al.²² in 103 BRVO eyes, 90 fellow eyes, and 99 control eyes without BRVO, found a greater proportion of arteriolar overcrossings in eyes with BRVO (77.7%) compared to fellow eyes (70.6%) or control eyes (67.0%). Zhao et al.²³ evaluated the relationship between the retinal arteriole and retinal branch vein in 106 eyes, by dividing their cases into the following three groups: (1) the ipsilateral but opposite vessel arcade within eyes affected by BRVO, (2) the same quadrant in unaffected eyes of BRVO patients, and (3) the same quadrant in eyes of patients without BRVO. The artery was anterior to the vein in 62%, 61%, and 54% of the crossings, respectively, yielding statistically significant differences for each group of control crossings compared with BRVO crossings ($p<0.001$). Similarly, Staurenghi et al.²⁴, in 65 BRVO eyes, found that when comparing the crossing of the arteriole anterior to the vein in the involved segment and the corresponding opposite arcade in the same eye, the arterioles were anterior to the veins in second-order branches in a statistically significant ($p=0.0004$) percentage of crossings. Weinberg et al.²⁵, in 51 normal eyes, found that in the superotemporal quadrant a greater proportion of the veins crossed posteriorly than in the inferotemporal quadrant ($p=0.01$). Zhang²⁶ found at arteriovenous crossing the arteriole anterior to the vein in 95.0% in major and 93.0% in macular BRVO. Muraoka et al.²⁷, in an optical coherence tomographic study in BRVO, found that the affected veins were

compressed and choked between the internal limiting membrane and the arterial wall at the venous overcrossing. Frangieh et al.²⁸, in histopathology of 8 eyes, found varying degrees of sclerosis, and no definite thrombus in any of them; however, the eyes were examined 8 months to 12 years after the onset of BRVO, giving misleading information about the thrombus. Bowers et al.²⁹, in a histopathological study of one eye with two BRVOs in a 72-year-old woman, found both venous occlusions at arteriovenous crossings and associated with moderately sclerotic retinal arterioles.

In our current study, at the site of occlusion, the retinal arteriole was anterior to the branch retinal vein in 96% of eyes and posterior to the vein in 4%. We have discussed above the distance of the site of occlusion from the optic disc margin, and different arteriovenous crossings at which the occlusion developed, in both types of BRVO.

Sceptics may question the validity of the data collected by us by using the combined methods of contact lens, stereoscopic color fundus photography and stereoscopic fluorescein angiography to evaluate macular edema and submacular serous retinal detachment, compared to the data provided by optical coherence tomography. As mentioned above, during the period of this study, optical coherence tomography was not available to evaluate macular edema and submacular serous retinal detachment. No doubt optical coherence tomography provides more subtle information than the conventional methods used by us. However, the amount of additional information provided by optical coherence tomography, compared to the conventional methods used over the years and by us, does not invalidate most of the information provided by the methods used till earlier. This is also supported by the following fact: in our similar study of fundus changes in central retinal vein occlusion³⁰, the data on submacular serous retinal detachment provided by our same conventional methods was no different from that provided by the optical coherence tomography study³¹.

The natural history of a disease always acts as the gold standard against which the effectiveness of various therapies can be judged. We hope that our natural history findings on fundus changes in BRVO will serve as a reference for future therapeutic trials.

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Fig. 1.
Fundus photograph of right eye with superior temporal major BRVO.

Fig. 2.
Fundus photograph of right eye with macular BRVO.

Fig. 3.
Kaplan-Meier curves for the resolution of retinal hemorrhage in different part of the retina in major BRVO.

Fig. 4.
Kaplan-Meier curves for the resolution of retinal hemorrhage in different part of the retina in macular BRVO.

Fig. 5.
Kaplan-Meier curves for the resolution of major and macular BRVO.

Table 1Demographic and Clinical characteristics of BRVO patients (Reproduced from Hayreh and Zimmerman¹⁰.)

Demographic/Clinical Variable	Major BRVO (n=143 patients, 144 eyes)	Macular BRVO (n=71 patients, 72 eyes)
Gender (Male)	70 (49%)	38 (54%)
<u>Age at initial visit</u>		
Mean±SD	63.6±11.3	63.0±12.0
Range	20–92	28–90
<u>Distribution by age</u> (count, %)		
<45	6 (4%)	3 (4%)
45–<65	66 (46%)	36 (51%)
65 and older	71 (50%)	32 (45%)
<u>Eye involvement</u>		
OD	74 (52%)	34 (48%)
OS	68 (48%)	36 (51%)
OU	1 (1%)	1 (1%)
<u>Follow-up</u>		
Median (25 th –75 th percentile)	2.8 yrs (0.9 – 6.2 yrs)	2.5 yrs (1.0 – 4.9 yrs)
Minimum-Maximum	0.2 mos – 29.6 yrs	0.5 mos – 16.4 yrs
<u>Systemic Conditions</u>		
Arterial hypertension	95 (66%)	33 (46%)
Ischemic heart disease	17 (12%)	4 (6%)
Diabetes mellitus	12 (8%)	7 (10%)
	(n=131, 12 missing)	(n=65, 6 missing)
Smoked current/past	68 (52%)	31 (48%)
<u>Sector involved</u>		
Superior temporal involvement *	94 (65%)	21 (30%)
Inferior temporal involvement **	45 (31%)	6 (8%)
Superior nasal only	4 (3%)	37 (51%)
Inferior nasal only	1 (1%)	8 (11%)
<u>Sector size</u>		
<u>In superior half</u>		
45	13 (13%)	44 (76%)
>45–90	74 (76%)	14 (24%)
>90	11 (11%)	0 (0%)
<u>In inferior half</u>		
45	3 (7%)	9 (64%)
>45–90	37 (80%)	5 (36%)

Demographic/Clinical Variable	Major BRVO (n=143 patients, 144 eyes)	Macular BRVO (n=71 patients, 72 eyes)
>90	6 (13%)	0 (0%)
<u>Visual acuity at initial visit</u>		
20–15–20/20	23 (16%)	12 (17%)
20/25–20/30	16 (11%)	22 (31%)
20/40–20/60	37 (26%)	19 (26%)
20/70–20/100	21 (15%)	9 (12%)
20/200–20/400	36 (25%)	9 (12%)
CF or worse	11 (8%)	1 (1%)

SD=Standard deviation

* Includes those with entire superior half involved, 5 major and 17 macular

** Includes those with entire inferior half involved, 6 major and 6 macular

Table 2

Retinal Hemorrhage at Initial Visit and Median Time to Resolution

Location of Hemorrhage	Grade				Time to Resolution, months Median (25 th –75 th percentile)
	None	Mild	Moderate	Severe	
Major BRVO (n=143, 1 missing) (except peripheral 7 missing, peripapillary 4 missing)					
Fovea (center)	31 (22%)	39 (27%)	25 (17%)	48 (34%)	10.9 (8.3–18.3)
Perifovea	22 (15%)	28 (20%)	44 (31%)	49 (34%)	12.3 (9.6–19.2)
Macular	14 (10%)	26 (18%)	52 (36%)	51 (36%)	16.8 (10.8–32.1)
Posterior Pole	2 (1%)	35 (24%)	59 (41%)	47 (33%)	20.3 (14.2–56.1)
Peripheral	1 (1%)	61 (45%)	60 (44%)	15 (11%)	31.3 (16.0–82.3)
Peripapillary	109 (78%)	8 (6%)	5 (4%)	18 (13%)	9.7 (5.8–13.9)
Macular BRVO (n=72) (except posterior pole and peripapillary with 1 missing)					
Fovea (center)	15 (21%)	29 (40%)	14 (19%)	14 (19%)	9.1 (6.2–13.0)
Perifovea	9 (12%)	26 (36%)	22 (31%)	15 (21%)	10.7 (8.0–17.8)
Macular	6 (8%)	21 (29%)	18 (25%)	27 (38%)	15.1 (9.4–19.4)

Table 3

Kaplan-Meier Product-Limit Estimates for Development of Macular Changes

Macular change	Major BRVO (n=144)	Macular BRVO (n=72)
Epiretinal membrane		
Total Developed	19	Only 1 developed
Cumulative % (SE):		
9 months	6.7% (2.3%)	
12 months	8.6% (2.6%)	
24 months	8.6% (2.6%)	
36 months	13.7% (3.5%)	
72 months	18.1% (4.6%)	
96 months	24.6% (6.1%)	
Macular pigmentary degeneration		
Total Developed	51	21
Cumulative % (SE):		
6 months	6.2% (2.1%)	3.1% (2.1%)
9 months	17.9% (3.5%)	13.0% (4.3%)
12 months	26.2% (4.1%)	22.0% (5.4%)
18 months	32.1% (4.4%)	25.9% (5.8%)
24 months	37.7% (4.7%)	25.9% (5.8%)
36 months	43.0% (5.0%)	33.6% (6.7%)
60 months	46.4% (5.2%)	37.7% (7.5%)
Serous macular detachment		
Total Developed	30	3
Cumulative % (SE):		
1 month	6.2% (2.0%)	0%
2 months	14.0% (2.9%)	1.5% (1.5%)
3 months	17.7% (3.2%)	3.0% (2.1%)
6 months	20.0% (3.4%)	3.0% (2.1%)

Table 4

Fluorescein Leak, Microaneurysm, and Capillary Dilatation within 4 Months from Onset

Location	Major BRVO (n=124)		Macular BRVO (n=61)	
	Present	Not determined due to hemorrhage	Present	Not determined due to hemorrhage
Fovea/Perifovea/Macular leak	108 (87%)	1 (1%)	52 (85%)	2 (3%)
Posterior pole leak	94 (76%)	5 (4%)	2 (3%)	1 (2%)
Perivenous staining	105 (85%)	3 (2%)	22 (36%)	10 (16%)
Fovea/Perifovea/Macula microaneurysm	30 (24%)	34 (27%)	19 (31%)	18 (30%)
Posterior pole microaneurysm	16 (13%)	37 (30%)	1 (2%)	6 (10%)
Capillary dilatation	113 (92%)	7 (6%)	52 (85%)	6 (10%)

Table 5

Capillary Obliteration within 4 Months from Onset

Location	Grade				Not able to grade photo**
	None	Patchy or Small	Moderate	Extensive	
Major BRVO (n=124)					
Fovea (center)	51 (41%)	6 (4%)	6 (5%)	12 (10%)	49 (40%)
Perifovea	42 (34%)	2 (2%)	4 (3%)	20 (16%)	56 (45%)
Macular	37 (30%)	4 (3%)	3 (2%)	23 (19%)	57 (46%)
Post. Pole	32 (26%)	6 (5%)	3 (2%)	26 (21%)	57 (46%)
Peripheral	34 (27%)	4 (3%)	3 (2%)	25 (20%)	58 (47%)
Macular BRVO (n=61)					
Fovea (center)	38 (62%)	0 (0%)	1 (2%)	0 (0%)	22 (36%)
Perifovea	34 (56%)	1 (2%)	1 (2%)	2 (3%)	23 (38%)
Macular	32 (52%)	0 (0%)	1 (2%)	3 (5%)	25 (41%)
Post. Pole	55 (90%)	0 (0%)	2 (3%)	1 (2%)	3 (5%)
Peripheral	55 (90%)	0 (0%)	2 (3%)	1 (2%)	3 (5%)

* Not able to grade severity of capillary obliteration because of extensive hemorrhage