Imaging for BRVO and CRVO

OCT images layers of the retina that are relevant to the evaluation of RVO.

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Retinal blood supply is provided by two vascular systems that consist of retinal and choroidal vessels. Retinal vessels supply the inner two-thirds of the retina, whereas choroidal and retinal vessels are supplied by both systems. The central retinal artery enters the eye at the optic disc and branches along the surface of the retina toward its far periphery to form the superficial, intermediate, and deep capillary beds. Blood is then drained into a venous network, merging into the central retinal vein, which exits together with the optic nerve. Retinal arteries and veins often run in close proximity, rarely overlapping in their distribution pattern. 1 The pathogenesis of retinal vein occlusion (RVO) is believed to be based on the principles of Virchow’s triad for thrombogenesis, involving stasis, vessel damage, and hypercoagulability. 2 As a result of destruction caused by atherosclerotic alterations, rheologic properties in the adjacent vein are impaired, contributing to stasis, thrombosis, and thus occlusion. RVO may also be caused by inflammatory disease following these mechanisms. Subsequently, ischemia occurs as retinal vessels are obstructed, not least due to the lack of compensating collaterals. 2

According to the site of occlusion, RVO is classified into two distinct types. 1 In central retinal vein occlusion (CRVO), the region proximal to the lamina cribrosa of the optic nerve is typically affected, where the central retinal vein exits the eye. In branch retinal vein occlusion (BRVO), the occlusion is characteristically located at an arteriovenous intersection. Depending on the location of occlusion, the severity of BRVO may vary significantly. The more proximal the vessel closure occurs, the more retinal edema and subsequent visual deterioration occur. Although inhibited perfusion of perifoveal capillaries is a partial source of vision loss, retinal edema is the predominant cause of decline in visual function. 1 Dilated tortuous retinal veins, hyperemia of the optic disc accompanied by edema, severe

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intraretinal hemorrhages, and severe central edema often lead to a rapid decrease in visual acuity. 

**PREVALENCE AND RISK FACTORS**

The prevalence of RVO is 1% to 2% in persons older than 40 years of age. Pooled data from population studies from the United States, Europe, Asia, and Australia have shown a lower prevalence for CRVO than BRVO. On the basis of these data, an estimated 16.4 million adults are affected by RVO, with 2.5 million affected by CRVO and 13.9 million affected by BRVO. Documented risk factors include diabetes mellitus, arterial hypertension, smoking, high body mass index, male sex, higher activated factor VII, hypermetropia, and open-angle glaucoma. In patients affected by RVO, the assessment of cardiovascular risk factors, including hypertension, dyslipidemia and others, appropriate treatment planning is necessary to prevent organ damage. However, there is no consistent evidence that an appropriate management of cardiovascular risk factors has an influence on the visual prognosis of patients with RVO. Coagulation abnormalities are to be excluded in selected patients, such as patients younger than 50 years of age, or those affected by bilateral RVO. Despite a large number of natural history studies and numerous advances regarding treatment options in other retinal pathologies, ophthalmologists have had few options to offer to patients affected by BRVO or CRVO except for watchful waiting for spontaneous improvement or the formation of ocular neovascularization. Optical coherence tomography (OCT), which is successfully used in the evaluation of age-related macular degeneration (AMD) and diabetic macular edema, is a unique imaging tool that provides 3-D, cross-sectional imaging of retinal layers relevant to the evaluation of RVO. With OCT, conclusions regarding disease development and progression can easily be drawn, leading to a more targeted treatment approach.

**VISUAL ACUITY**

In CRVO, the prognosis for visual acuity is largely dependent on the initial visual performance and the level of ischemia. The correlation of initial and final visual acuity was examined in the Central Retinal Vein Occlusion Study. Patients with an initial visual acuity of 0.5 (Snellen decimal) or greater remained stable after 3 years. If the initial visual acuity was between 0.1 and 0.4, 44% of patients remained stable within this interval, whereas 19% of patients improved to 0.5 or greater and 37% worsened to less than 0.1. Eighty percent of patients with an initial visual acuity of greater than 0.1 remained stable after 3 years. A decrease in visual acuity of 0 to 1 line is to be expected within 1 year, whereas a spontaneous improvement of 3 lines or more is found in 13% to 17% of patients.

McIntosh et al found that untreated eyes with CRVO have generally poor visual acuity, declining in the natural history of the disease. McIntosh and colleagues reviewed 53 studies, providing 3,271 eyes with a diagnosis...
of CRVO, to analyze natural disease development. In general, visual acuity was poor at baseline (mean, less than 20/40) and decreased further over time. Six studies reported an improvement in visual acuity, although none of these revealed a better outcome in final visual acuity than 20/40. Additionally, one-fourth of eyes with primarily nonischemic CRVO converted to ischemic CRVO within a 3-year period, and neovascular glaucoma developed in at least 23% of eyes within 15 months.

In BRVO, Rogers et al21 have shown that visual acuity usually improves without intervention, even though an increase in visual acuity to more than 20/40 was uncommon. Rogers and colleagues24 assessed studies, providing 1,608 eyes with BRVO for natural course development analysis.21 Five percent to 15% of eyes with BRVO developed macular edema over a 1-year period, although 18% to 41% of eyes presenting with macular edema at baseline resolved over time. Five percent to 6% of patients had bilateral BRVO, whereas 10% developed bilateral CRVO.21 Visual field constriction may be found in RVO; however it is not a characteristic appearance of the disease. Common causes of visual acuity loss are macular edema, nonperfusion of the macular region, and complications such as intraretinal bleeding,17 intravitreal hemorrhage, neovascularization, glaucoma, epiretinal membrane formation, and tractional retinal detachment.22-25 Verification of visual acuity should be carried out at the time of diagnosis as well as every 4 weeks during the first 6 months of follow-up. Additional visual acuity assessment becomes necessary in cases with aggravated symptoms26,27 and is important because macular thickness determined by OCT does not necessarily correlate with visual performance.28

**DIAGNOSTIC AND IMAGING PROCEDURES**

Patients with RVO typically present with rapid and painless loss of vision. The degree of symptoms may vary according to the degree of retinal involvement and macular perfusion status.2 Biomicroscopy is essential for primary diagnosis as well as for follow-up examinations. Characteristic findings in BRVO are the presence of hemorrhages, edema, cotton-wool spots and venous dilatation and tortuosity.2 In CRVO, more extensive retinal signs are evident, with dilated and tortuous veins in all quadrants, often along with optic-disk edema.2 RVO is usually diagnosed on the basis of the clinical examination alone.2 If visual acuity is less than 20/200, nonperfused RVO may be suggested. A relative afferent pupillary defect as well as extensive hemorrhages are commonly observed.
found in these cases. To evaluate the severity of macular edema and perfusion status, fluorescein angiography should be routinely performed.

For evaluation of treatment success and the monitoring of macular edema, OCT is perfectly qualified. This imaging technique has become a useful diagnostic tool for the evaluation of posterior segment morphology in a variety of retinal diseases since its implementation in 1995. Modern OCT technology provides an excellent assessment of retinal morphology. The recent introduction of spectral-domain (SD) OCT enables in vivo imaging of intra- and subretinal structures, offering a realistic, histology-like image quality. These fourth-generation, high-resolution OCT systems acquire scans in a raster pattern throughout the entire macular area, achieving a maximum resolution of 5 µm in axial and 20 µm in transverse directions. As a result, retinal morphology features can be imaged transversally at all locations and may be located to all retinal layers axially. These advances in OCT technology offer novel diagnostic insights and the ability to conduct follow-up treatment evaluation.

OCT has been successfully used to assess the outcomes of various treatments for macular edema associated with CRVO and BRVO in previous investigations. Images reveal that the increase in retinal thickness is mainly caused by the formation of large cystoid structures primarily localized at the level of the inner nerve layer of the foveal region and diffuse intraretinal edema of the foveal and perifoveal areas.

### EFFECT OF VEGF INHIBITION ON RETINAL MORPHOLOGY

Vascular endothelial growth factor (VEGF) is a key factor in the development of macular edema and angiogenesis, and increased vascular permeability. Upregulation of VEGF mRNA has been observed in the human retina in patients with CRVO, as has a correlation of the severity of macular edema with aqueous and vitreous levels of VEGF. Funk et al investigated concentrations of growth factors and inflammatory cytokines in aqueous humor of eyes with CRVO and BRVO prior to and during treatment with bevacizumab (Avastin, Genentech) in a prospective clinical trial in 13 consecutive eyes (CRVO [n=5], BRVO [n=8]) during a follow-up period of 15 months. Intravitreal bevacizumab was administered at baseline and months 1 and 2. Retreatment was given if OCT showed edema or in case of decreased visual performance. This study showed a significant elevation of VEGF levels in patients with CRVO when compared with control eyes and a correlation of VEGF levels and macular edema. Intravitreal injections of bevacizumab resulted in a significant decrease of VEGF below physiologic levels remaining low under the loading dose of three consecutive monthly retreatments, further emphasizing the role of VEGF in the pathogenesis of RVO (Figure 1).

### FUNCTIONAL AND ANATOMIC RELATIONSHIP

Several studies have evaluated functional and morphologic associations in patients with RVO. Prager et al investigated functional and anatomic changes after intravitreal bevacizumab in eyes with persistent macular edema secondary to BRVO or CRVO. Twenty-nine eyes with macular edema secondary to BRVO (n=21 eyes) or CRVO (n=8 eyes) were treated with three initial intravitreal injections of 1 mg bevacizumab on a monthly basis. Patients
were retreated if there was evidence of intraretinal or subretinal fluid observed on OCT. If continuous injections were necessary up to month 6, the dose was increased to 2.5 mg. Mean visual acuity increased from 50 letters on the ETDRS eye chart (20/100) at baseline to 66 letters (20/50+1; an increase of 16 letters; \( P = .001 \) at month 12. Central retinal thickness (CRT) decreased from 558 μm at baseline to 309 μm at month 12 (249 mm; \( P = .001 \)), underlining the efficacy of anti-VEGF treatment in patients with macular edema secondary to RVO, despite short-term effectiveness and high recurrence rates (Figure 2) as primarily observed on OCT.

Kriechbaum et al. evaluated the association between functional and anatomic retinal changes during anti-VEGF therapy with bevacizumab in patients with cystoid macular edema secondary to RVO using microperimetry and SD-OCT. In this study, 28 patients with cystoid macular edema secondary to RVO were included. Patients initially received three consecutive intravitreal injections of 1.25 mg bevacizumab at 4-week intervals. Further treatment was based on morphologic (OCT) and functional visual acuity findings during a 1-year follow-up period. Within 6 months, the mean area of absolute scotoma as assessed by micoperimetry was reduced from 21.4% of the central visual field to 6.4% and remained at this level until month 12 (7.4%). Mean visual acuity improved from 51 to 66 letters on ETDRS charts. CRT, central subfield thickness (CST), and mean retinal thickness decreased significantly \( (P < .002) \) and remained stable during follow-up. Significant associations between functional and morphologic outcomes were evident. An exemplary case emphasizing the association between function and morphology at each interval is shown in Figure 3. Central retinal morphology, especially CRT and CST measured by conventional and SD-OCT as well as retinal function, improved significantly during treatment and follow-up (Table 2).

Visual acuity correlated with OCT parameters at different levels: CST \( (P < .001) \), mean retinal thickness \( (P < .001) \), mean retinal sensitivity, CRT \( (P < .0001) \), and retinal volume \( (P < .05) \). This once more highlights the value of OCT imaging, and it may be recommended that SD-OCT and related parameters should be introduced as regular tools for routine clinical examinations for this disease.

**MANAGEMENT OF CRVO AND BRVO**

Laser treatment is primarily used for managing patients with RVO. In BRVO, grid laser photocoagulation are primarily used for treatment of macular edema; scatter laser photocoagulation may be implemented in order to prevent neovascularization. Laser photocoagulation decreases the risk of neovascular glaucoma development in patients with iris neovascularization. However, data are now also available assessing the effectiveness of substances inhibiting VEGF. The BRAVO and CRUISE trials demonstrated positive functional results in patients with RVO following treatment with anti-VEGF agents.

**CONCLUSION**

In addition to a general medical systemic assessment by the patient’s physician to rule out potential cardiovascular risk factors, a complete examination of patients with RVO should comprise fluorescein angiography for perfusion status and leakage evaluation as well as OCT imaging. Due to the unique, specific imaging characteristics of OCT, and because this imaging device is successfully used in the evaluation of common retinal pathologies such as age-related macular degeneration and diabetic macular edema, it would be reasonable to frequently implicate this novel imaging modality in the diagnostic and treatment follow-up process of RVO. Moreover, OCT provides 3-D, cross-sectional imaging of retinal layers most relevant in the detailed evaluation process of an exudative disease such as RVO. Not least, quantitative conclusions regarding disease development and progression can easily be drawn.

Regarding treatment, grid laser photocoagulation should be applied, and the application of intravitreal injections of anti-VEGF agents should be discussed. Regarding BRVO, advantages of grid laser photocoagulation are the availability of long-term clinical data and cost effectiveness as well as lower rates of adverse events. Selected patients (eg, those with dense macular hemorrhage that restrains the use of laser treatment) may benefit from an initial injection of anti-VEGF as a first line treatment; however, this may be associated with increased risk of thromboembolic events. Close monitoring of patients is indispensable to be sure to rule out neovascularization.

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