Practical Retina
Incorporating current trials and technology into clinical practice

Current concepts in managing retinal vein occlusion in young patients

by Luke B. Lindsell, OD, MD, and Michael M. Lai, MD, PhD

Our management of retinal vein occlusion (RVO) has changed dramatically over the last 3 decades since the results of the Branch Vein Occlusion Study (BVOS) and Central Vein Occlusion Study (CVOS) were published in the 1980s and 1990s.

While most patients who present with RVO are 60 years of age or older, young patients can pose particular diagnostic and treatment challenges.

In this installment of Practical Retina, Drs. Luke Lindsell and Michael Lai from Washington, D.C., address what should be included in an appropriate diagnostic work-up for younger patients who present with RVO, provide pearls for detecting uncommon underlying systemic etiologies, and review their treatment paradigm.

Retinal vein occlusions (central, hemicentral, and branch retinal veins) are among the most common retinal vascular disorders and account for a significant amount of ocular morbidity. These conditions typically affect older individuals, with most studies reporting the majority of retinal vein occlusions in adults over 60 years of age. A minority of patients, around 10% to 15%, are typically younger than 50 years of age, representing a significant number of working-aged adults. Up to 16% of all instances of central retinal vein occlusion (CRVO), 10% of all hemicentral retinal vein occlusion (HRVO), and 1% to 5% of all branch retinal vein occlusion (BRVO) occur in younger patients.

Vision loss in BRVO (Figure 1) is generally secondary to macular edema and in CRVO (Figure 3) may be from a combination of macular edema, macular ischemia, vitreous hemorrhage, and neovascular glaucoma. Younger patients with retinal venous occlusive disease generally fair better visually than their older counterparts. This is particularly true among young CRVO patients, where the majority have less ischemia compared to older CRVO patients.
**Pathogenesis**

Retinal vein occlusions are the result of thrombus formation at an anatomically vulnerable location. In the case of CRVO, the central retinal artery and vein are in close relationship, sharing a common fibrous sheath as they course through the optic nerve.\(^\text{10,14}\)

Normal laminar flow in the central retinal vein is compromised, whether from anatomic variations in the relationship between the artery and vein or atherosclerotic disease in the artery compressing the vein, and a thrombus can potentially form. Certainly other factors, such as inflammation within the blood vessel wall or blood dyscrasias, can compound the issue. The location of the thrombus is critical as locations more posterior to the lamina cribosa are typically less ischemic than a thrombus nearer the lamina cribosa due to the availability of venous tributaries, which are nearly nonexistent at the lamina cribosa.\(^\text{10}\)

In BRVO, nearly all occlusive events occur at the intersection of a retinal artery and vein. In these locations, the venule and artery share a common, adventitia and the artery, especially if damaged by atherosclerosis, compresses the more compliant vein, disrupting laminar flow. Similar to CRVO, this increases the chances of thrombus formation at this site and eventually occlusion of the vein.\(^\text{14}\)

Historically, CRVO in younger patients (typically less than 45 years old) was coined papillophlebitis, and the condition was thought to arise from a localized vasculitis.\(^\text{11}\)

However, histopathological studies of eyes from younger patients in which a CRVO was diagnosed showed no evidence of vasculitis but instead chronic inflammatory changes in the vessel wall similar to older patients.\(^\text{11,15}\)

Therefore, other than vein occlusion secondary to retinal vasculitides associated with systemic disorders (eg, sarcoidosis, Behcet’s disease, and syphilis), the majority of CRVOs in younger patients are not believed to be the result of a vasculitic process.

---

**Figure 1.** Branch retinal vein occlusion in a 41-year-old man. Note delayed venous filling in superior arcade (top right). Yellow arrow (bottom left) pointing to site of occlusion at an arterial-venous intersection. Late leakage within macula (bottom right).
Diagnosis, Work-up

The ophthalmic work-up for patients with retinal vein occlusion regardless of age should include a thorough history of any previous thrombotic events (such as deep vein thrombosis, pulmonary embolism, or miscarriage). Vision, intraocular pressure, and attention to the absence or presence of an afferent pupillary defect are routine portions of an eye examination but help to provide clues regarding the retinal perfusion status, particularly in a central retinal vein occlusion.10,12 A dilated examination is supplemented with appropriate ancillary testing, including spectral-domain optical coherence tomography (SD-OCT) and intravenous fluorescein angiography (IVFA). Other tests, such as electoretinography and wide-field angiography, can help differentiate between an ischemic and nonischemic CRVO. Care should be taken when diagnosing a CRVO as ischemic versus nonischemic based on the traditional “10-disc area of retinal capillary obliteration”2,10 because a significant number of patients with up to 30 disc areas of nonperfusion were found to not develop anterior segment neovascularization.10 Additionally, significant intraretinal hemorrhage can make assessment of capillary perfusion difficult.

A fair amount of controversy surrounds the systemic work-up of vein occlusions in younger patients. Systemic diseases such as hypertension and hyperlipidemia, while commonly identified as risk factors of retinal vein occlusions among older patients, are less prevalent in younger patients; therefore, it has been assumed that another disease process is responsible for the vein occlusion. Some of this was borne out of case reports demonstrating an abnormal thrombophilia work-up, such as activated protein C resistance, in younger patients with RVO.16 The genetic defect leading to activated protein C resistance is factor V Leiden, and multiple studies have found no difference in incidence of RVO between patients possessing this abnormality versus controls.17-20 The activated protein C resistance test is a functional test and can return abnormal results due to other causes such as pregnancy, oral contraceptive use, and lupus.19

Other thrombophilic disorders have been reported to occur in younger patients with retinal vein occlusion and include protein C and S deficiencies, antithrombin III deficiency, and prothrombin 20210 A mutations.21,22 However, in Tekeli et al’s study, six of the nine patients with a deficiency in protein C also had hypertension, which is a well-known risk factor for RVO. Additionally, in a larger series by Lahey et al in patients under 56 years of age with RVO, none had deficiencies in protein C activity.23 Hyperhomocystinemia and a mutation in the MTHFR gene is another cited lab abnormality linked with RVO in young adults. Elevated homocysteine levels are found in patients with vascular diseases24,25 and can be found in patients with genetic mutations in the MTHFR gene. However, two larger studies investigating the role of these two factors found that a mutated MTHFR gene was not associated with RVO.24,25 Homocysteine levels have been found in higher numbers amongst RVO patients, although this is likely an indicator of an underlying vascular disease process (namely arteriosclerosis) rather than a separately occurring risk factor.24 Other factors such as diet and medications can alter homocysteine levels adding to the difficulty in using this as the causal factor in RVO.24 Certainly patients with elevated homocysteine levels should clue the physician in to likely coexisting systemic abnormalities.

Standard work-up for younger patients with RVO should consist of the normal battery of ophthalmic testing as described above. Systemic testing should focus on identifying those patients who present with a negative medical history, namely assessing for hypertension, hypercholesterolemia, diabetes mellitus, body mass index (BMI), and smoking status. Several studies in younger patients with CRVO or BRVO have shown that systemic risk factors such as hypertension, hyperlipidemia, elevated BMI, and diabetes are found less frequently than in older patients but still occur in significant numbers.9,11,25 Screening for the aforementioned diseases is probably a more useful exercise than chasing down a patient with elevated homocysteine levels should clue the physician in to likely coexisting systemic abnormalities.

Figure 2. OCT of patient in Figure 1 before (top) and 6 weeks after (bottom) dexamethasone intravitreal implant injection. Visual acuity improved but is limited by significant ellipsoid zone damage.
hypercoaguable defect, which may or may not have any clinical relevance. Naturally, in patients with a previous thrombotic history or strong family history of thrombophilia, laboratory work-up is appropriate.

Treatment

CRVO, HRVO

These two manifestations of RVO are addressed together because both share similar pathophysiology and are subclassified as ischemic or nonischemic. The majority of vision loss in nonischemic disease is due to macular edema, while retinal and macular ischemia are the main causes of vision loss in ischemic disease. Treatment of CRVO in young patients is analogous to modalities used in older individuals.

For patients presenting as nonischemic with good visual acuity and no macular edema, observation is an appropriate strategy. Close follow-up is critical because a portion of these patients can develop subsequent macular edema or progress to an ischemic CRVO.

Until recently, the only treatment option for patients with macular edema was focal/grid laser photocoagulation. The Central Vein Occlusion Study demonstrated that while macular edema improved, this did not translate into visual gain. Modern treatment revolves around suppressing intraocular VEGF and reducing retinal capillary permeability via corticosteroids or anti-VEGF medications. Corticosteroids have been shown in both the GENEVA and SCORE studies to be of benefit at reducing macular edema (Figure 2) and improving vision. In the GENEVA study, a dexamethasone implant (Ozurdex; Allergan, Irvine, CA) was used and demonstrated peak effect at 2 months with progressive

Figure 3. Central retinal vein occlusion in a 31-year-old man with 20/60 visual acuity in the right eye. There is tortuosity and significant disc edema but only moderate intraretinal hemorrhaging. Significant venous delay at 43 seconds into fluorescein angiography (top right). Late image (bottom left) showing staining of the disc and veins. There is also some mild leakage within the macula. The same eye 17 months later (bottom right) with resolution of hemorrhaging but the disc still appears mildly edematous. Visual acuity was 20/25.
decline back to baseline by month 6, which coincides with the predicted life span of the implant. Patients who were treated earlier in the course (less than 90 days) of their macular edema showed better visual acuities than those treated later (more than 90 days). Corticosteroids were also shown to be beneficial in the SCORE-CRVO study with a 5-times greater likelihood of achieving a gain of 15 letters for both the 1-mg (average 2.2 injections in 12 months) and 4-mg (average two injections in 12 months) triamcinolone acetonide groups versus sham injection. A better safety profile, mainly a lower incidence of cataract and elevated intraocular pressure, was observed in the 1-mg group. The CRUISE study examined the role of ranibizumab (Lucentis; Genentech, South San Francisco, CA) for macular edema due to CRVO and found significant gains in vision (average 14.9 letters) in the 0.5-mg group dosed monthly for the first 6 months and then as needed for the subsequent 6 months. Visual acuity gains were maintained after the treatment strategy was switched to as-needed dosing. No large clinical studies similar to the CRUISE study exist for bevacizumab (Avastin; Genentech, South San Francisco, CA), but smaller prospective studies have illustrated similar findings as the CRUISE study (Figure 4). Recently, aflibercept (Eylea; Regeneron, Tarrytown, NY), which also binds placental growth factor (PGF) in addition to VEGF, was shown to have significant visual gains (more than 15 letters) versus sham when injected monthly for 6 months and then as needed thereafter in both the COPERNICUS and GALILEO studies through 1 year.

One treatment strategy, which has been shown to be potentially harmful, is aspirin or other antiplatelet therapy. On the surface, it seems to make sense, but antiplatelet therapy does not reduce the incidence of CRVO, can potentially make retinal hemorrhaging worse, and has been associated with an increased likelihood of visual deterioration.

The incidence of neovascular glaucoma (NVG) is about 10% for all CRVO types but occurs in up to 45% of ischemic CRVOs. In the CVOS, the true incidence of NVG was not determined because all patients with more than 2 clock hours of iris neovascularization underwent panretinal photocoagulation (PRP). Any evidence of NVG certainly warrants prompt PRP, but whether all patients with iris and/or angle neovascularization require PRP is not entirely clear. Anti-VEGF medications in NVG have been shown to be a useful adjunct to PRP and can be used simultaneously to effect regression of anterior segment neovascularization.

BRVO

Two subtypes exist for this form of RVO and are classified based on location, either along a major retinal vein or along a smaller second order vessel typically within the macula. The primary source of vision loss in BRVO pa-
tients is macular edema. Patients often have better presenting visual acuity and significant number will improve without intervention but few will obtain significant improvement beyond 20/40. Treatment is akin to that in CRVO with some key differences. One notable difference is the BVOS study which showed that focal/grid photocoagulation both reduced macular edema and improved visual acuity in patients meeting criteria for intervention. Another surprising difference from CRVO treatment was shown in the SCORE-BRVO study. They found no difference between focal/grid photocoagulation versus 1-mg and 4-mg triamcinolone acetate. Consequently, when balanced against the increased adverse event rate with triamcinolone, they recommended focal/grid photocoagulation as the gold-standard (SCORE-BRVO) for treating macular edema. However, subanalysis of patients with macular edema greater than 3 months showed a greater but not statistically significant improvement in vision in the 4-mg triamcinolone group versus laser. In contrast to the SCORE-BRVO study, corticosteroids were beneficial in the GENEVA study. Specifically, the subgroup analysis of BRVO in the GENEVA study (Ozurdex dexamethasone implant) showed a statistically significant improvement in vision from baseline compared to sham treatment. Earlier treatment of macular edema was associated with a higher likelihood of improving more than 15 letters, and peak effect was noted at day 60. The role of ranibizumab was studied in the BRAVO study, and patients receiving the medication demonstrated improvement of more than 15 letters versus sham injections and rescue grid laser treatment. Similarly, bevacizumab has also been shown to provide improvement in vision. The most recent study regarding treatment of macular edema secondary to BRVO is the VIBRANT study (aflibercept) versus focal laser. Unsurprisingly, patients treated with aflibercept were statistically more likely to gain more than 15 letters compared to those treated with laser.

In summary, young patients with both CRVO and BRVO have lower but still significant incidences of systemic risk factors — namely, hypertension, hyperlipidemia, diabetes, increased BMI, and smoking history. Thrombophilias are typically rare and sporadic in younger patients, but in those at increased risk, laboratory work-up is warranted. Involvement of the patient’s primary care provider is critical in optimizing systemic therapy. Ophthalmic treatment is primarily targeted at macular edema in both CRVO and BRVO, and current therapeutic strategies include both corticosteroids and anti-VEGF agents. Other sequelae, such as neovascular glaucoma (primarily in CRVO), can be treated with prompt PRP and adjunctive anti-VEGF agents.

REFERENCES


__Michael M. Lai, MD, PhD__, Retina Group of Washington, 5454 Wisconsin Avenue, Suite 650, Chevy Chase, MD 20815; 301-656-8100; fax: 301-652-2957; email: mlai@rgw.com.

__Luke B. Lindsell, OD, MD__, can be reached at 5454 Wisconsin Avenue, Suite 650, Chevy Chase, MD 20815; 301-656-8100; fax: 301-652-2957; email: luke.lindsell@gmail.com.

__Howard F. Fine, MD, MHSc__, can be reached at NJ Retina, 10 Plum Street, Suite 600, New Brunswick, NJ 08901; 732-220-1600; fax: 732-220-1603; email: hffne@gmail.com.

Disclosures: Drs. Lai and Lindsell report no relevant financial disclosures. Dr. Fine has received research grants, consulting fees, and/or is on the speakers bureau for Allergan/Actavis, Genentech, and Regeneron. He has equity, patent, and consulting interests in Auris Surgical Robotics.