Treatment of Central Retinal Vein Occlusion

Caroline R. Bauman, MD, FRCSC; Gary C. Brown, MD

Oclusion of the central retinal vein is a significant cause of ocular and visual morbidity, particularly in the elderly population. Large, multicenter clinical trials have recently evaluated the risk factors for central retinal vein occlusion (CRVO) and the efficacy of laser photocoagulation therapy. In this article, the diagnostic features of CRVO and the therapeutic alternatives are reviewed.

CLINICAL FEATURES OF CRVO

The mean age of patients at the onset of CRVO is in the early- to mid-60s; however, CRVO has been reported in patients ranging from 9 months to 90 years of age. Ninety percent of patients are older than age 50 at the time of onset. Approximately 60% of the patients are male and 40% are female. Involvement of the left eye is as common as involvement of the right eye, and the incidence of bilateral involvement ranges from 6% to 14%. Patients usually present with blurred vision or metamorphopsia in the involved eye, although a change in vision may not be noted if the fellow eye has normal acuity. The onset may be either abrupt or gradual, occurring in a span of days or even weeks. The initial visual acuity is variable, ranging from 20/20 to light perception.

Funduscopic examination of an acute CRVO demonstrates a variable degree of intraretinal hem-

---

From the Retina Service, Wills Eye Hospital, Philadelphia, PA.
Accepted for publication May 2, 1997.
Request reprints from Gary C. Brown, MD, Retina Service, Wills Eye Hospital, 900 Walnut Street, Philadelphia, PA 19107.

Figure 1. (A) Acute nonischemic central retinal vein occlusion in the left eye. Note the optic nerve swelling, dilated and tortuous retinal veins, and intraretinal hemorrhages in all quadrants. Visual acuity was 20/70. (B) Fluorescein angiography does not reveal retinal capillary nonperfusion in the posterior pole.
Figure 2. (A) Acute central retinal vein occlusion with an extensive hemorrhage in the posterior pole. Panretinal photocoagulation was performed for iris neovascularization (arrowheads). An intraretinal hemorrhage is present in the fovea (arrow). Visual acuity was hand motions. (B) Macular pigmentary changes (arrow) are noted after resolution of the foveal hemorrhage. Visual acuity was 20/400.

Figure 3. Chronic changes noted after central retinal vein occlusion include sclerotic vessels, opticociliary collaterals at the optic nerve, and macular pigmentary changes (arrow). Panretinal photocoagulation was performed for iris neovascularization (arrowheads).

Hemorrhages in all four quadrants of the retina and dilation and tortuosity of the retinal veins (Figs. 1A and 2). The retinal hemorrhages are more concentrated in the posterior pole than in the peripheral fundus. Retinal hemorrhages are typically intraretinal dot and blot or superficial in the nerve fiber layer, although hemorrhage in the subretinal space or breakthrough into the vitreous can occur. Acute CRVO should be distinguished from other causes of intraretinal blot hemorrhages, such as diabetic and hypertensive retinopathy or ocular ischemic syndrome secondary to carotid artery disease, in which the hemorrhages occur primarily in the midperipheral fundus and the retinal veins are dilated but not tortuous. Other findings that may be observed in CRVO include cotton-wool spots, optic disc hyper-

chromia or edema, retinal edema (particularly notable in the macula), areas of white ischemic retina due to capillary nonperfusion, and focal areas of exudative retinal detachment. The causes of decreased vision in an acute CRVO include macular pathology, such as edema, hemorrhage, or capillary nonperfusion, vitreous hemorrhage, or, more rarely, an associated retinal arteriolar obstruction.

Fluorescein angiography demonstrates relatively normal retinal arterial and choroidal filling and delayed venous filling. Other features include irregular caliber and staining of retinal venous walls, retinal vascular leakage that produces retinal and macular edema, and areas of capillary nonperfusion. Extensive intraretinal hemorrhage may prevent angiographic evaluation of retinal perfusion.

The clinical course following CRVO is variable. The long-term visual prognosis ranges from full recovery to loss of light perception. The signs of occlusion may resolve in mild cases with minimal retinal injury or retinal hemorrhage, macular edema, and microvascular abnormalities can persist. Sclerotic vessels and optociliary collateral vessels at the optic nerve may develop (Fig. 3). Long-term ocular sequelae of CRVO that may decrease visual acuity include chronic cystoid macular edema, macular ischemia, exudate or pigment in the macula (Fig. 2), retinal artery occlusion, formation of a macular hole, retinal or disc neovascularization, vitreous hemorrhage, tractional or exudative retinal detachment, iris neovascularization, and neovascular glaucoma.
CRVO do not reperfuse with time; they either remain stable or increase in size.

The combined information from four functional tests (visual acuity, visual fields, pupillary light response, and electroretinography) and two morphologic tests (ophthalmoscopy and fundus fluorescein angiography) may be useful during the acute phase of CRVO to distinguish the ischemic from the nonischemic forms. \(^{11}\) The features that are indicative of an ischemic CRVO include an initial visual acuity of 20/200 or worse, the presence of multiple cotton-wool spots, an afferent pupillary defect, and fluorescein angiographic evidence of retinal capillary nonperfusion. In a series of eyes with ischemic CRVO, one third of the eyes had no change in visual acuity, one third improved by at least two lines, and one third lost two or more lines at final evaluation. \(^{12}\) Signs of ischemia on electroretinography (ERG) include reduced b-wave amplitude, reduced ratio of b-waves to a-waves, and prolonged b-wave implicit time. \(^{13-17}\)

Central and peripheral visual field abnormalities are more common in ischemic CRVO. \(^{10}\) Different angiographic guidelines have been used to classify CRVO as ischemic or nonischemic. Magargal et al. classified CRVO based on the ischemic index, which was related to the proportion of retinal ischemia determined with fluorescein angiography. \(^{18}\) An ischemic index of 50% was considered the threshold for a significant risk of neovascular complications and corresponded to approximately 10 disc areas of retinal capillary nonperfusion. In the study conducted by the Central Vein Occlusion Study Group, CRVO was categorized as ischemic when 10 or more disc areas of capillary nonperfusion were present on fluorescein angiography, nonischemic when there were fewer than 10 disc areas of capillary nonperfusion, and indeterminate when there was too much hemorrhage to permit angiographic classification of perfusion. \(^{2}\) Other angiographic signs suggestive of ischemia include severe large-vessel leakage, marked macular edema, and a prolonged arteriovenous transit time of greater than 20 seconds.

Of eyes presenting with CRVO, approximately 70% are nonischemic and 30% are ischemic. \(^{10,19,20}\) Identification of ischemic forms of CRVO is important because complications such as neovascularization (of the iris, retina, or optic nerve), neovascular glaucoma, and vitreous hemorrhage may develop. Factors influencing the incidence of ocular neovascularization include the severity, extent, and duration of retinal ischemia. \(^{19}\) Neovascularization of the iris is typically

---

**CLASSIFICATION OF CRVO**

A distinction is made between different types of CRVO based on clinical and fluorescein angiographic features of severity, which may provide prognostic information. The milder form is known as nonischemic CRVO and has been referred to as partial, hyperpermeable, perfused, or venous stasis retinopathy in the literature. A nonischemic CRVO has minimal or absent retinal capillary nonperfusion and is generally associated with a better visual prognosis (Fig. 1). \(^{9}\) Visual loss is variable, due to macular edema or retinal hemorrhage. The more severe form is called ischemic CRVO; its synonyms include complete, nonperfused, or hemorrhagic retinopathy. In ischemic CRVO, there is widespread retinal capillary nonperfusion and cell death, resulting in severe visual loss and a poorer prospect of visual recovery (Fig. 4). \(^{10}\) Areas of retinal nonperfusion in

---

**Figure 4.** (A) Acute ischemic central retinal vein occlusion in the left eye. Note the peripapillary cotton-wool spot (arrowhead). (B) Fluorescein angiography reveals areas of retinal capillary nonperfusion and microvascular abnormalities.
noted within the first 3 months after ischemic CRVO, although it can occur at any time. Studies have reported neovascularization of the iris developing in 45% to 80% of eyes with ischemic CRVO. Anterior segment neovascularization typically progresses rapidly to a painful neovascular glaucoma, and has been noted in up to 60% of eyes with ischemic CRVO. Retinal neovascularization tends to occur later in follow-up and has been reported in up to 24% of eyes with CRVO.

Ocular neovascularization is rare in nonischemic CRVO, although eyes presenting with nonischemic CRVO may develop progressive retinal ischemia. In the study conducted by the Central Vein Occlusion Study Group, 16% of the eyes that were initially classified as nonischemic and 83% of the eyes considered to be indeterminate progressed to ischemic CRVO after 4 months of follow-up. During a period of 3 years, 34% of perfused eyes progressed to ischemia. Patients with poor visual acuity (6/30 or less), severe macular edema, and progressive intraretinal hemorrhage with nonischemic CRVO at presentation may be at increased risk of advancing to ischemic CRVO. The pathogenesis of increased retinal ischemia is speculative, but may be related to progressive thrombosis in the central retinal vein.

**PATHOGENESIS**

Clinically, CRVO is caused by obstruction of retinal venous outflow, which may result from thrombus formation, a primary venous disease such as vasculitis, or external vascular compression. Histopathologic studies of CRVO in human eyes have demonstrated thrombus formation in the lumen of the central retinal vein in the region of the lamina cribrosa. The central retinal artery and vein are anatomically associated in this region and share a common fibrous tissue sheath. The connective tissue of the lamina cribrosa limits expansion of the traversing central retinal vessels and may contribute to hemodynamic turbulence. Thickening of a sclerotic central retinal artery, which can occur in hypertension, may compress the lumen of the central retinal vein and predispose a patient to thrombus formation. Factors such as endothelial damage, increased blood viscosity, and altered blood flow may play a role in thrombus formation. Hayreh has hypothesized that nonischemic CRVO is a result of occlusion of the central retinal vein and that ischemic CRVO results from temporary occlusion of the central retinal arterial in addition to occlusion of the vein; however, this has not been supported by other studies.

**ASSOCIATED FEATURES**

A variety of systemic and ocular conditions have been associated with CRVO (see the table). Medical
conditions linked with CRVO are often characterized by vascular disease, hyperviscosity, and hypercoagulability. Up to 70% of elderly CRVO patients have a concomitant systemic disease, such as hypertension, diabetes, or cardiac disease. An associated systemic disease is less frequent in CRVO patients who are younger than age 50.20,22

CRVO has been consistently linked with hypertension, and up to 61% of CRVO patients have hypertension or are using antihypertensive medications.20,32,33 The Eye Disease Case-Control Study compared 258 CRVO patients with 1142 controls and noted an increased risk of CRVO in persons with systemic hypertension, diabetes mellitus, and open-angle glaucoma.34 The risk of CRVO decreased with increasing levels of physical activity, higher levels of alcohol intake, and postmenopausal estrogen use. Cardiovascular disease was associated with an increased risk of ischemic CRVO.35 The mortality and prevalence rates of cardiovascular and cerebrovascular disease were not increased in white CRVO patients when compared with control groups of cataract patients and national health survey patients.36

Hematologic factors, such as elevated lipid and cholesterol, may predispose a patient to CRVO development.36 Some series have demonstrated elevated blood viscosity in CRVO patients, whereas others have not supported these findings. In one series, it was determined that there was no difference in hematocrit, plasma viscosity, red cell aggregation, and red cell filterability between patients with retinal vein occlusion and control subjects who had been matched for age, sex, and cardiovascular risk factors.37 The lupus anticoagulant predisposes a patient to have systemic thrombosis and may be associated with occlusions in the retinal and choroidal circulations.38 A hereditary defect in the anticoagulation system that is characterized by resistance to activated protein C has been associated with CRVO.39 In one series, 26% of all CRVO patients and 36% of CRVO patients 45 years old or younger had activated protein C resistance, compared with the rate of 5% that is present in the general population.40

Ocular conditions associated with CRVO include open-angle glaucoma, optic nerve disease, retinal artery occlusion, and hyperopia.1 Up to 40% of CRVO patients had preexisting ocular hypertension or open-angle glaucoma or experienced this condition during follow-up.19,41-43

**THERAPY FOR CRVO**

Treatment of CRVO should consider the primary process of CRVO, which stems from obstruction of the central retinal vein at the lamina cribrosa, as well as therapy for complications resulting from CRVO, such as macular edema and ocular neovascularization. Fluorescein angiography is often used as an adjunct to assess the level of ocular ischemia and to identify complications of CRVO.

**MEDICAL TREATMENT**

Currently, there is no effective medical management for most forms of acute CRVO. Although the therapies for associated medical or ocular conditions (such as hypertension or glaucoma) do not reverse the visual effects of CRVO, they may inhibit its progression from a nonischemic to an ischemic form, and they may prevent the occurrence of CRVO in the contralateral eye. The therapy for hyperviscosity syndromes such as polycythemia vera and Waldenström's macroglobulinemia is the exception to the rule, as treatment of the systemic condition and normalization of the blood viscosity may improve the CRVO.44,45

Medical therapies for CRVO have focused on pharmacologic agents to lyse the thrombus, or on methods to alter the hemorheologic characteristics of blood and improve the passage of venous blood past the obstruction. Anticoagulant therapy with systemic heparin, Coumadin and streptokinase has been evaluated.42,46-48 These agents have not been proven to have long-term visual benefit, and they predispose the patient to the systemic and ocular risk of hemorrhage.

Other potentially therapeutic agents include aspirin, Persantine, and tissue plasminogen activator, but further evaluation of their efficacy is necessary.49 Isosolaelic hemodilution has been proposed as a method to decrease blood viscosity while increasing it in areas of compromised retinal microcirculation to improve the visual prognosis in CRVO patients.47,50 The rationale for this therapy is based on an increased blood viscosity and packed cell volume demonstrated in some series of CRVO patients.49,51,52 Acetazolamide has been recommended for treatment of macular edema due to other causes, but has not been specifically evaluated for macular edema secondary to central vein occlusion. Therapy with hyperbaric oxygen and irradiation has been attempted with little success.53,54

The pathogenesis of CRVO in younger patients may not be related to thrombus formation, but, rather, to venous inflammation producing outflow obstruc-
tion. The presence of signs of ocular inflammation, such as vitreous cells and phlebitis, may support this theory. Although there have been no controlled studies to test the effectiveness of steroid therapy, systemic and periocular steroids have been advocated to treat CRVO and associated macular edema in young patients. Hayreh found that steroids had a beneficial effect on vision; however, poor vision recurred after discontinuation of steroid therapy. Although steroids may be useful in selected cases of CRVO in young adults, patients must be monitored carefully for side effects of steroid therapy, such as increased intraocular pressure, which may play a role in the pathogenesis or progression of CRVO.

**LASER TREATMENT**

Several studies have evaluated whether prophylactic laser panretinal photocoagulation (PRP) in eyes with ischemic CRVO can reduce the long-term risk of iris neovascularization and neovascular glaucoma. The rationale of PRP is similar to that of diabetic retinopathy in that it reduces the stimulus for neovascularization. This follows from destruction of hypoxic retina, especially photoreceptors with their high oxygen requirement, which may improve oxygen perfusion to the remaining viable retina.

It was initially suggested that early prophylactic PRP was beneficial in the prevention of ocular neovascularization and neovascular glaucoma in eyes with ischemic CRVO. However, in a 10-year, prospective evaluation of argon laser PRP in 123 eyes with ischemic CRVO, there was no significant difference in the incidence of angle neovascularization, neovascular glaucoma, retinal neovascularization, vitreous hemorrhage, or visual acuity between the eyes treated with the laser and the observed eyes; moreover, the eyes treated with the laser demonstrated a greater loss of peripheral visual field than did the observed eyes.

Due to these differing results, a large, randomized clinical trial was performed to evaluate laser treatment for the complications of CRVO. The Central Vein Occlusion Study was a multicenter, randomized, controlled clinical trial supported by the National Eye Institute to assess the natural history of CRVO, the efficacy of prophylactic PRP in preventing anterior segment neovascularization in ischemic eyes, and the effect of grid photocoagulation for macular edema due to CRVO. To assess the effect of PRP, 90 eyes with ischemic CRVO were randomly treated with early prophylactic PRP, and another 91 eyes were observed. If 2 clock hours of iris neovascularization or any angle neovascularization developed, untreated eyes received PRP and previously treated eyes received supplemental PRP. Laser PRP was performed with a technique similar to that which was used in the Diabetic Retinopathy Research Study. PRP treatment consisted of 1000 to 2000 burns of medium white intensity, spaced a half to a full burn width apart and placed in all four quadrants from the vascular arcades to the equator or beyond (Figs. 2A and 3). Laser parameters included a 200- to 500-μm diameter spot size and a 0.2-second duration.

The results demonstrated that prophylactic PRP tends to decrease the risk, but does not totally prevent iris or angle neovascularization, and that prompt regression of iris-angle neovascularization is more likely to occur in eyes that have not received early prophylactic treatment. Factors associated with the development of anterior segment neovascularization included extensive retinal capillary nonperfusion, large amounts of retinal hemorrhage, duration of CRVO of less than 1 month, and male sex. The study recommended observation of eyes with ischemic CRVO with monthly ocular examinations for the first 6 months, including slit-lamp evaluation and gonioscopy, as well as prompt performance of PRP in eyes that develop iris or angle neovascularization. If close follow-up is not possible, prophylactic PRP may be considered for patients at high risk for anterior segment neovascularization.

For patients with ischemic CRVO who are examined after the development of neovascular glaucoma, therapy includes topical steroids, cycloplegics, and intraocular pressure-lowering medications. Laser PRP is recommended to decrease ocular neovascularization even if the angle is closed, as this may increase the success of future glaucoma surgery if it is indicated for preservation of some vision and ocular comfort. Alternatively, retinal cryotherapy may be performed if visualization is inadequate for PRP, although this is less favorable due to increased patient discomfort.

Macular edema in CRVO may be associated with macular capillary leakage or nonperfusion as determined with fluorescein angiography. If macular capillary nonperfusion is present, there is no therapy available. Initial reports suggested that the grid pattern of photocoagulation may improve macular edema due to capillary leakage in CRVO. Laser photocoagulation has proven beneficial for improving visual acuity in selected eyes with branch retinal vein occlusion of 3
to 18 months' duration and associated macular edema that reduced vision to 20/40 or worse. The mechanism of grid laser photocoagulation is unclear, but possibilities include reduction in blood flow, increase in inner retinal oxygen, replacement of coagulated retinal pigment epithelial cells, and proliferation of endothelial cells in capillaries and venules overlying the laser lesions that are capable of reinforcing the outer and inner blood–retinal barriers, respectively. The inner retinal effects are believed to result indirectly from targeting of the outer retina.

In the Central Vein Occlusion Study, eyes with CRVO of at least 3 months' duration were randomized for macular grid laser photocoagulation if visual acuity was decreased to 20/50 or worse due to macular edema involving the foveal center with angiographically documented capillary leakage. Seventy-seven eyes were randomly assigned to macular grid photocoagulation, and 78 eyes were observed with up to 3 years of follow-up.

Treatment was performed in one session with argon green laser burns in a grid pattern placed a half to a full burn width apart in the area of leaking capillaries. The area of treatment did not extend within the foveal avascular zone or beyond two disc diameters from the fovea. The laser settings included a 100-μm spot size and a 0.1-second duration with power adjusted for a moderately intense white burn (Fig. 5). If treatable angiographic macular edema was still present 4 months after the initial laser treatment and visual acuity had improved by nine letters or less, a repeat treatment was performed. The laser parameters for re-treatment were identical to those initially used except that the grid laser was directed at areas of

---

**Figure 6.** (A) Laser photocoagulation directed at an inferior retinal vein tributary (arrow) to create a chorioretinal anastomosis in an eye with nonischemic central retinal vein occlusion. Snellen visual acuity measured 20/200 in this 37-year-old woman. (B) Fifteen months after the laser procedure, a chorioretinal anastomosis is present (larrow). A large retinal vein is noted flowing into the chorioretinal anastomosis (small arrow). (C) Fibrovascular proliferation (arrows), causing tractional retinal detachment, was noted to extend inferiorly from the chorioretinal anastomosis at this time. Panretinal photocoagulation was performed. Visual acuity measured 20/30. (Courtesy of Dr. Jay Duker.)
persistent leakage and at previously untreated leaking capillaries. Long-term results showed that angiographic leakage was reduced by the grid laser, but there was no visual benefit demonstrated by treatment at any point in time during the study, and macular grid laser photocoagulation was not recommended.

Creation of a venous anastomosis between the retinal and choroidal circulations with a high-energy laser has been advocated as a means of bypassing the occlusion in the central retinal vein.68,69 In the technique originally described by McAllister and Constable, a high-energy focal laser spot is placed over the edge of the tributary retinal vein to disrupt its wall and rupture the underlying Bruch's membrane (Fig. 6A).70 The laser parameters included a 50-µm spot size at a 0.1-second duration and a power ranging from 1.5 to 2.5 W with the argon blue-green or green laser. The site for the attempted anastomosis was along the inferior temporal or inferior nasal retinal vein branch, approximately three disc diameters away from the optic nerve, to minimize the risk of disrupting a branch of the posterior ciliary artery. Multiple laser attempts at the same or an alternative site may be required. Success of the procedure is determined by rapid sequence fluorescein angiography and by the fundus appearance of a large vein that is flowing into the scar created by the laser photocoagulation (Fig. 6B). The time from laser treatment to creation of a successful anastomosis ranges from 3 to 7 weeks. This technique potentially allows obstructed venous blood to exit the retinal circulation via the choroid to bypass the occlusion site.

Laser-induced chorioretinal venous anastomosis was attempted in 24 human eyes with nonischemic CRVO and progressive visual loss.70 In this series, a successful chorioretinal anastomosis was created in 8 eyes (33%), with subsequent improvement in visual acuity and resolution of the funduscopic appearance of CRVO in all 8 cases. Complications described after this procedure included fibrovascular proliferation (Fig. 6C), retinal and vitreous hemorrhage, closure of the retinal vein distal to the anastomosis site, and choroidal neovascularization.71

This technique may have some value in treating selected patients with CRVO, but further clinical evaluation of its efficacy is necessary. Modification of this technique by increasing the argon laser power level and following with YAG laser (set at 3 to 5 mJ) directed at the retinal vein wall may improve its ability to form a chorioretinal anastomosis (McAllister IL, unpublished data, 1996).

SURGICAL TREATMENT

Vitrectomy may be required for management of vitreous hemorrhage accompanying acute CRVO or secondary to retinal neovascularization. This may be combined with PRP at the time of surgery when neovascularization is present.

DISCUSSION

Currently, there is no effective treatment to prevent visual loss or retrieve lost vision after acute CRVO. The association of treatable conditions such as hypertension, cardiovascular disease, and glaucoma with CRVO suggests that these conditions should be evaluated for and treated appropriately in an effort to prevent the progression of CRVO from nonischemic to ischemic and to decrease the risk of CRVO in the contralateral eye. Recommendations from the recent Central Vein Occlusion Study include close observation for all eyes with CRVO. Eyes initially classified as having nonischemic or indeterminate CRVO may progress to ischemic CRVO and be at risk for ocular neovascularization. Prompt PRP should be performed in ischemic eyes only after the development of iris or angle neovascularization. Macular grid laser photocoagulation for eyes with angiographic macular edema is not recommended, as a visual benefit was not demonstrated.

REFERENCES


49. Lahey JM, Valley C, Kearney JJ. Treatment of acute CRVO with intravitreal tissue plasminogen activator. Ophthalmology. 1996(suppl.).


65. The Branch Vein Occlusion Study Group. Argon laser scatter photocoagulation for macular edema in branch