CHAPTER 6

Retinal Vascular Diseases Associated With Cardiovascular Disease

This chapter includes related activities. Go to www.aao.org/bcscactivity_section12 or scan the QR codes in the text to access this content.

Highlights

- Retinal venous and arterial occlusions are frequently associated with systemic disease and represent a unique opportunity for the ophthalmologist to contribute to a patient's general medical care. The most common associations are hypertension, diabetes, and atherosclerosis; but inflammatory, infectious, or hematologic disorders can also be identified.
- Retinal artery occlusion is a medical emergency that must be regarded as a "stroke equivalent," requiring immediate evaluation for carotid and cardiac disease.
- Pharmacologic therapy is presently the standard of care for macular edema associated with retinal vein occlusion. Intravitreal injection of anti–vascular endothelial growth factor (anti-VEGF) agents is the first-line treatment, and intravitreal corticosteroid may be helpful as a second-line or adjunctive treatment in recalcitrant cases.
- Cases of artery occlusion without obvious emboli must be evaluated for giant cell arteritis, which can result in bilateral blindness if not treated promptly and correctly.

Systemic Arterial Hypertension and Associated Ocular Diseases

Elevated blood pressure (BP) is defined as systolic BP of 120–129 mm Hg *and* diastolic BP less than 80 mm Hg. Stage 1 hypertension is defined as 130–139 mm Hg systolic *or* 80–89 mm Hg diastolic. Ocular effects of hypertension can be observed in the retina, choroid, and optic nerve. Retinal changes can be described and classified with the use of ophthalmoscopy and angiography. An ophthalmologist's recognition of posterior segment vascular changes may prompt the initial diagnosis of hypertension. BCSC Section 1, *Update on General Medicine,* discusses hypertension in more detail.

Hypertensive Retinopathy

Hypertension affects arterioles and capillaries, the anatomical loci of both autoregulation and nonperfusion. An acute hypertensive episode may produce focal intraretinal periarteriolar transudates (FIPTs) at the precapillary level. The presence of infarctions of the nerve fiber layer (NFL), or *cotton-wool spots* (also called *soft exudates*), indicates ischemia of the retinal NFL (Fig 6-1). Uncontrolled systemic hypertension leads to nonperfusion at various retinal levels as well as neuronal loss and associated scotomata (Fig 6-2). Other, more chronic, hypertensive retinal lesions include microaneurysms, intraretinal microvascular abnormalities (IRMAs), blot hemorrhages, lipid exudates (also called *hard exudates*), venous beading, and neovascularization.

The relationship between hypertensive vascular changes and arteriosclerotic vascular disease is complex, with wide variation related to the duration and severity of the hypertension, the presence of diabetic retinopathy, the severity of any dyslipidemia, the patient's age, and a history of smoking. Hence, it is difficult to classify which retinal vascular changes were caused strictly by hypertension; the often-cited features of focal arteriolar narrowing and arteriovenous nicking have been shown to have little predictive value for severity of hypertension. Nonetheless, 1 well-known historical classification of mostly arteriosclerotic retinopathy is the Modified Scheie Classification of Hypertensive Retinopathy:

- Grade 0: No changes
- Grade 1: Barely detectable arterial narrowing
- Grade 2: Obvious arterial narrowing with focal irregularities
- Grade 3: Grade 2 plus retinal hemorrhages and/or exudates
- Grade 4: Grade 3 plus optic nerve head swelling

Hypertension may be complicated by branch retinal artery occlusion, branch retinal vein occlusion, central retinal vein occlusion, or retinal arterial macroaneurysms (all

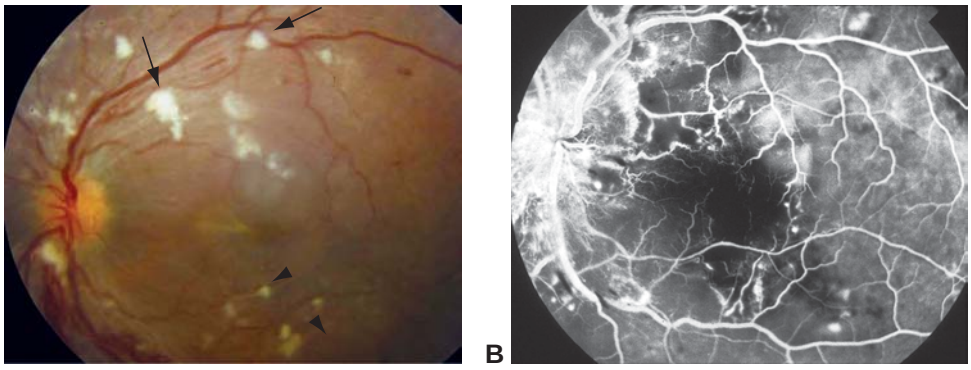

Figure 6-1 Severe hypertensive retinopathy. **A,** Fundus photograph from a 25-year-old man with renal hypertension shows large, superficial, white cotton-wool spots *(arrows)* contrasting with small, deep, tan focal intraretinal periarteriolar transudates (FIPTs, *arrowheads*). **B,** Angiography image shows areas of nonperfusion corresponding to the cotton-wool spots and punctate hyperfluorescence corresponding to the FIPTs. *(Courtesy of Hermann D. Schubert, MD.)*

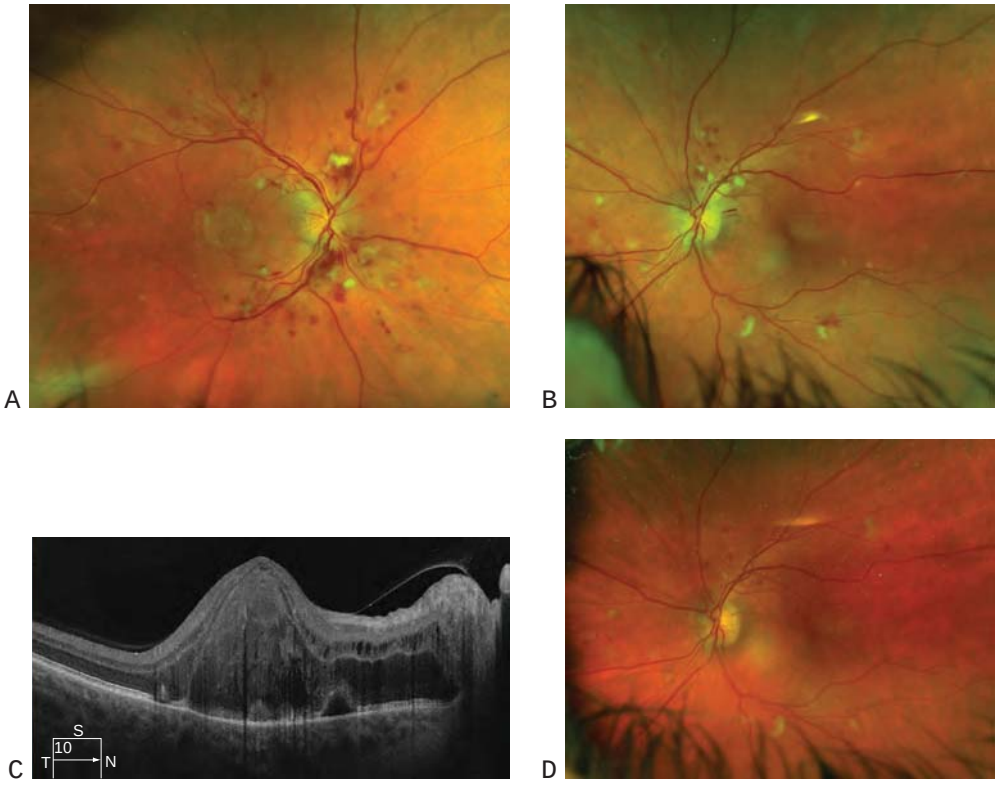

Figure 6-2 Acute hypertensive episode. This 40-year-old patient presented with several weeks of blurred vision and headache. Blood pressure at presentation was 245/150 mm Hg. **A, B,** Fundus photographs of the right and left eyes, respectively, show elements of both retinopathy and optic neuropathy: optic nerve head edema, dilated capillaries on the nerve head, flame-shaped nerve fiber layer (NFL) hemorrhages, cotton-wool spots, macular exudates, and subretinal fluid. **C,** Optical coherence tomography (OCT) of the right macula shows fluid in the NFL, retina, and subretinal space. **D,** Photograph of the left fundus 3 months later, after initiation of systemic antihypertensive medications, shows resolution of optic nerve head edema and reduction in retinal exudation and hemorrhage. Blood pressure at this visit was 197/99 mm Hg. *(Parts A and B courtesy of Jeremy Anderson, OD, and parts C and D courtesy of Franco M. Recchia, MD.)*

discussed later in this chapter). In addition, the coexistence of hypertension and diabetes results in more severe retinopathy.

Cheung CYL, Wong TY. Hypertension. In: Schachat AP, Wilkinson CP, Hinton DR, Sadda SR, Wiedemann P, eds. *Ryan's Retina.* 6th ed. Elsevier/Saunders; 2018:chap 52.

Wong TY, Mitchell P. The eye in hypertension. *Lancet*. 2007;369(9559):425–435.

Hypertensive Choroidopathy

Hypertensive choroidopathy typically occurs in young patients who have experienced an episode of acute, severe hypertension, often associated with preeclampsia, eclampsia, pheochromocytoma, or renal hypertension (see Chapter 9 for more on choroidal disease). Lobular nonperfusion of the choriocapillaris may occur, initially resulting in tan,

lobule-shaped patches that, in time, become hyperpigmented and surrounded by margins of hypopigmentation; these lesions are known as *Elschnig spots*). Linear configurations of similar-appearing hyperpigmentation, known as *Siegrist streaks,* follow the meridional course of choroidal arteries. Fluorescein angiography shows focal choroidal hypoperfusion in the early phases and multiple subretinal areas of leakage in the late phases. Focal retinal pigment epithelium detachments may occur, and in severe cases, extensive bilateral exudative retinal detachments may develop.

Hypertensive Optic Neuropathy

Patients with optic neuropathy secondary to severe hypertension may exhibit linear peripapillary flame-shaped hemorrhages, blurring of the optic nerve head (ONH) margins, florid ONH edema with secondary retinal venous stasis, and macular exudates (see Fig 6-2). The differential diagnosis for patients with this clinical appearance includes central retinal vein occlusion, anterior ischemic optic neuropathy, diabetic papillopathy, radiation papillopathy, neuroretinitis, and retrobulbar tumor.

Retinal Venous Occlusion

Overview of Retinal Venous Occlusion

Retinal venous occlusion (RVO) is the second most common retinal vascular disorder, following diabetic retinopathy. It is caused by a thrombus located at any point along the venous circulation and is named according to the site of the occlusion. A *branch retinal vein occlusion (BRVO)* produces a sectorial (typically quadrantic) area of damage due to thrombosis in 1 of the branches of the intraretinal portion of the venous tree. A *central retinal vein occlusion (CRVO)* arises from thrombosis in the retrolaminar portion and, thus, affects the entire retina. *Hemicentral retinal vein occlusion (HRVO)* occurs in eyes with a persistent vestigial bifurcation in the retrolaminar portion of the central retinal vein, affecting either the superior or the inferior half of the retina.

Clinical presentation and pathogenesis of RVO

Patients typically present with acute decline in central vision and/or a paracentral or peripheral scotoma. The classic ophthalmoscopic findings are dilated, tortuous retinal veins and intraretinal hemorrhages in the areas affected by the occlusion. In BRVO, this is most commonly seen in the superotemporal quadrant (Fig 6-3); the occlusion may also be restricted to the macula, termed a *macular BRVO* (Fig 6-4). In CRVO, all 4 retinal quadrants are involved (Fig 6-5). HRVO may involve either the superior or the inferior half of the retina (Fig 6-6). Cotton-wool spots and ONH edema occur in more severe cases of RVO. Varying degrees of macular edema, macular ischemia, and foveal hemorrhage may be seen. Macular edema is best assessed and quantified with spectral-domain optical coherence tomography (SD-OCT), whereas ischemia is best detected using fluorescein angiography or OCT angiography.

The pathogenesis of RVO mirrors Virchow's triad for thrombosis: endothelial injury, venous stasis, and hypercoagulability. Normally, retinal arteries and veins share a common adventitial sheath. Progressive arteriolosclerosis (as occurs in normal aging

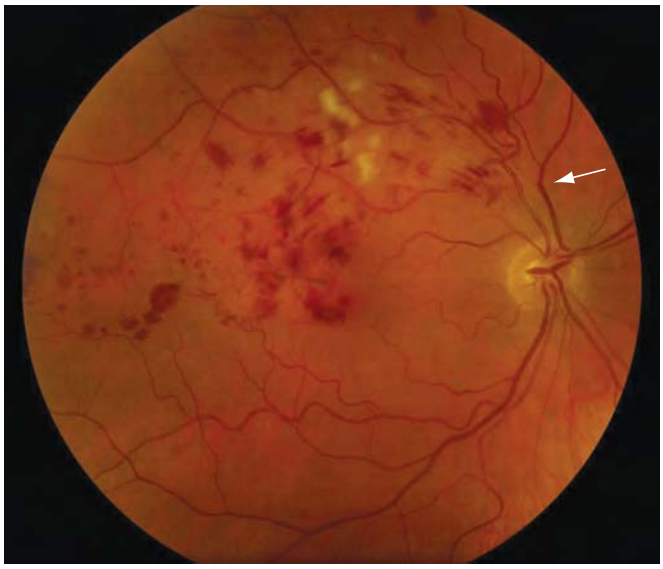

Figure 6-3 Typical findings of a major branch retinal vein occlusion (BRVO): moderate dilation and tortuosity of veins, intraretinal hemorrhages, and cotton-wool spots. Note that the hemorrhages are restricted to the superotemporal quadrant. The presumed site of obstruction is designated by the *arrow*. *(Courtesy of Franco M. Recchia, MD.)*

and hypertension) leads to thickening of the arterial wall, which in turn leads to compression and inelasticity of the venous wall. These changes to the venous wall (endothelial damage) may produce turbulent blood flow and venous stasis, which predispose to venous thrombosis.

At the cellular level, retinal ischemia caused by impairment of normal retinal circulation leads to the local upregulation and release of hypoxia-related factors into the retina and into the eye. The most salient of these are vascular endothelial growth factor (VEGF) and various mediators of inflammation. VEGF has 2 profound effects on the retinal vasculature: (1) increased vessel-wall permeability, leading to macular edema; and (2) growth of new blood vessels *(neovascularization)*. Pro-inflammatory factors may worsen vascular leakage and macular edema.

Risk factors and causes of RVO

Retinal vein occlusion is most commonly associated with increasing age (90% of patients are >50 years old) and hypertension. Every patient with RVO should undergo medical evaluation in addition to a comprehensive ocular examination. In the absence of known cardiovascular disease, a search for other causative or predisposing systemic conditions should be considered, especially in patients younger than 50 years or in patients with simultaneous bilateral CRVO. The Eye Disease Case-Control Study and other studies have enumerated risk factors associated with BRVO and CRVO:

- increasing age
- systemic arterial hypertension
- cigarette smoking

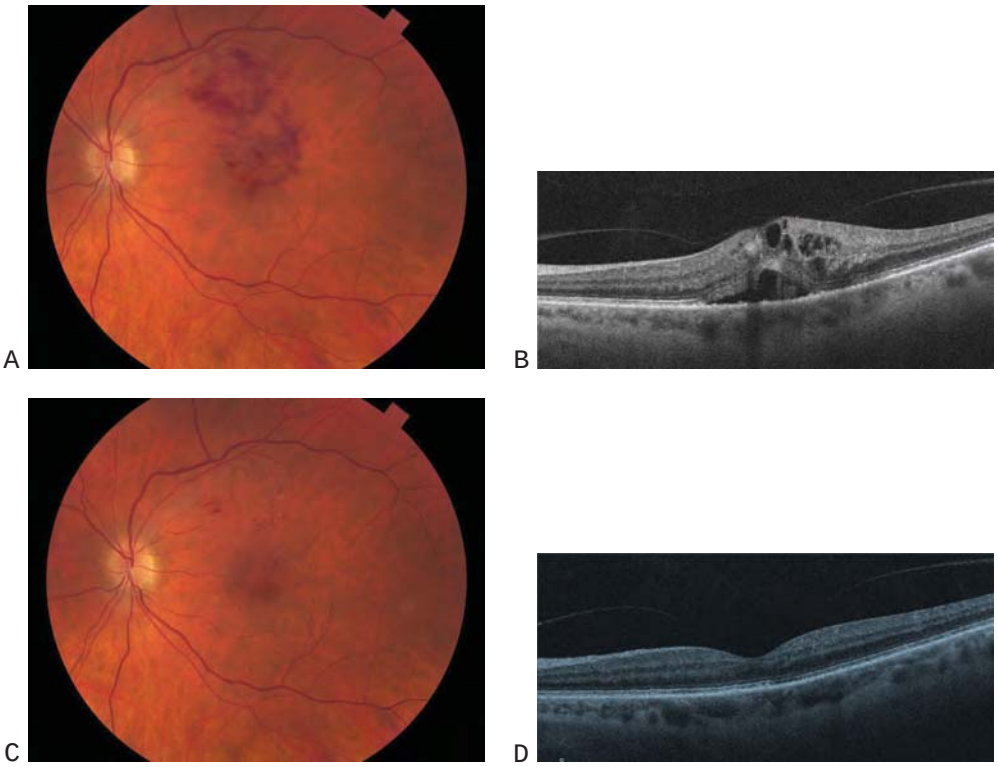

Figure 6-4 **A,** Fundus photograph of a macular BRVO. At presentation, corrected distance visual acuity (CDVA; also called *best-corrected visual acuity*) was 20/40. Intraretinal hemorrhages are confined to the superior macula and involve the fovea. **B,** OCT shows intraretinal and subretinal edema and an incidental finding of vitreofoveal adhesion. After 3 intravitreal injections of aflibercept, VA had improved to $20/20^{-2}$, with improvement in retinal hemorrhages **(C)** and resolution of macular edema **(D).** *(Courtesy of Franco M. Recchia, MD.)*

- open-angle glaucoma
- diabetes mellitus
- hyperlipidemia
- hypercoagulability
- hypothyroidism

Although rare, predisposing hypercoagulable and inflammatory conditions may be present. However, when CRVO occurs in patients older than 50 years or patients with known cardiovascular risk factors, an extensive systemic workup is generally unnecessary.

American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern Guidelines. *Retinal Vein Occlusions.* American Academy of Ophthalmology; 2019. www.aao.org/education/preferred-practice-pattern/retinal-vein-occlusions-ppp

Goldman DR, Shah CP, Morley MG, Heier JS. Venous occlusive disease of the retina. In: Yanoff M, Duker JS, eds. *Ophthalmology.* 4th ed. Elsevier/Saunders; 2014:526–534.

Hayreh SS. Retinal vein occlusion. *Indian J Ophthalmol.* 1994;42(3):109–132.

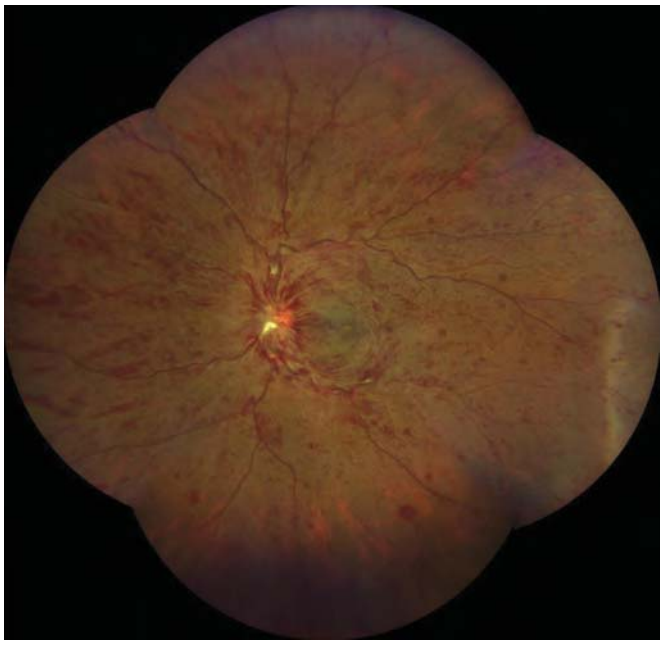

Figure 6-5 Typical findings of a central retinal vein occlusion (CRVO): dilation and tortuosity of veins and intraretinal hemorrhages involving all 4 retinal quadrants, edema of the optic nerve head, and scattered cotton-wool spots. *(Courtesy of Franco M. Recchia, MD.)*

Risk factors for branch retinal vein occlusion. The Eye Disease Case-Control Study Group. *Am J Ophthalmol*. 1993;116(3):286–296.

Risk factors for central retinal vein occlusion. The Eye Disease Case-Control Study Group. *Arch Ophthalmol*. 1996;114(5):545–554.

Complications of RVO

The most common complications of RVO are intraocular neovascularization and the sequelae thereof. Neovascularization is driven by VEGF, the levels of which are correlated with the extent of retinal ischemia. In BRVO, neovascularization occurs most commonly at the border between the affected ischemic retina and normal perfused retina; it is seen less frequently at the ONH and, in rare instances, in the anterior segment. In CRVO, neovascularization occurs most commonly in the anterior segment and can also occur within the retina or at the ONH.

Spontaneous resolution of RVO can occur and is usually associated with the development of alternative paths of venous outflow *(collateral vessels)*. In BRVO, capillaries extending across the median raphe dilate, helping to compensate for the compromised venous drainage. In CRVO, small vessels that normally connect the retinal circulation to the choroidal circulation near the ONH expand, resulting in the undulating appearance of optociliary shunt vessels (Fig 6-7). These mechanisms redirect venous drainage to the choroid, vortex veins, and superior and inferior ophthalmic veins in the orbit, bypassing the occluded central retinal vein. The presence of collateral vessels, however, does not

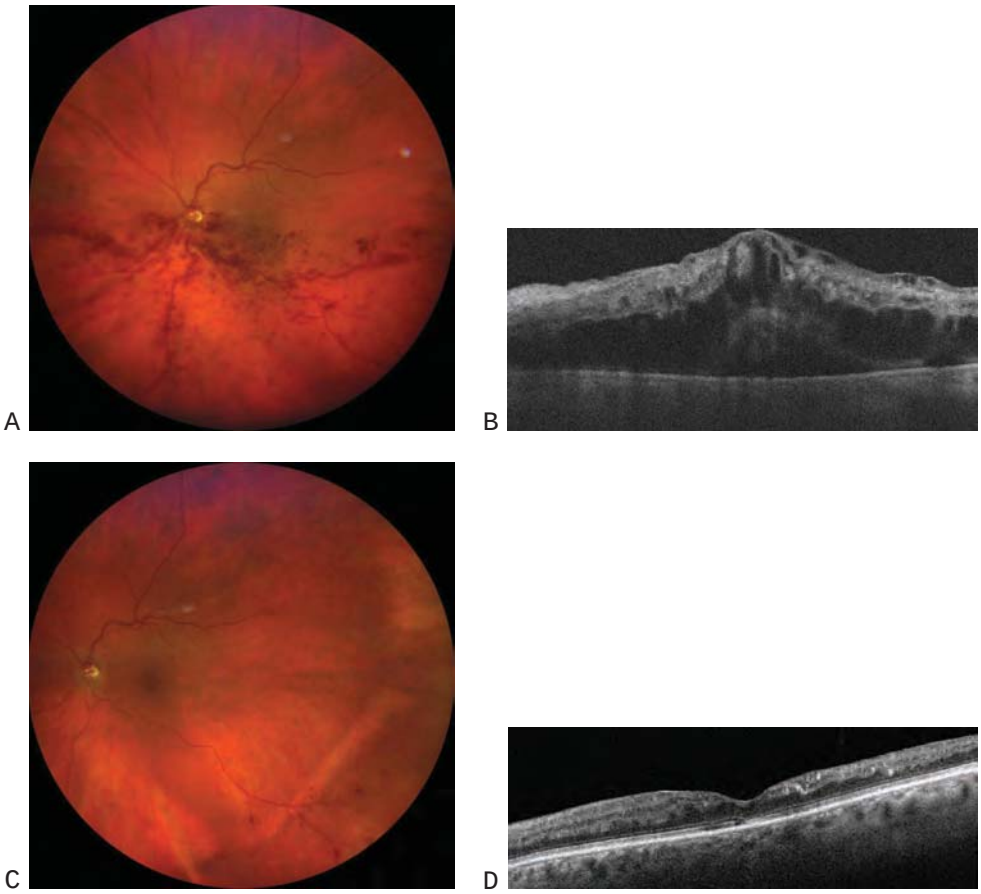

Figure 6-6 Typical findings of a hemicentral retinal vein occlusion (HRVO). **A,** Fundus photograph at presentation shows dilation and tortuosity of veins and intraretinal hemorrhages confined to the 2 inferior retinal quadrants. **B,** OCT at presentation shows inner hyporeflectivity consistent with intraretinal edema and outer hyporeflectivity consistent with subfoveal fluid. Fundus photograph **(C)** and OCT **(D)** taken 10 months after presentation show diminution of retinal hemorrhage and resolution of macular edema after 6 treatments with intravitreal aflibercept. Thinning of the inner retina and discontinuity of the ellipsoid zone are demonstrated on OCT; these anatomical changes will likely limit the degree of visual recovery. *(Courtesy of Franco M. Recchia, MD.)*

consistently equate with functional improvement. Chronic, untreated venous occlusive disease commonly leads to the development of retinal microvascular changes characterized by microaneurysms, telangiectasias, and macular edema.

Pharmacologic management of RVO

Anti-VEGF drugs have become the first-line treatment for macular edema associated with RVO because of their excellent efficacy and safety profiles. Improvement and maintenance of visual acuity are optimized by administering anti-VEGF treatment immediately upon diagnosis of RVO-related macular edema and continuing treatment long enough to

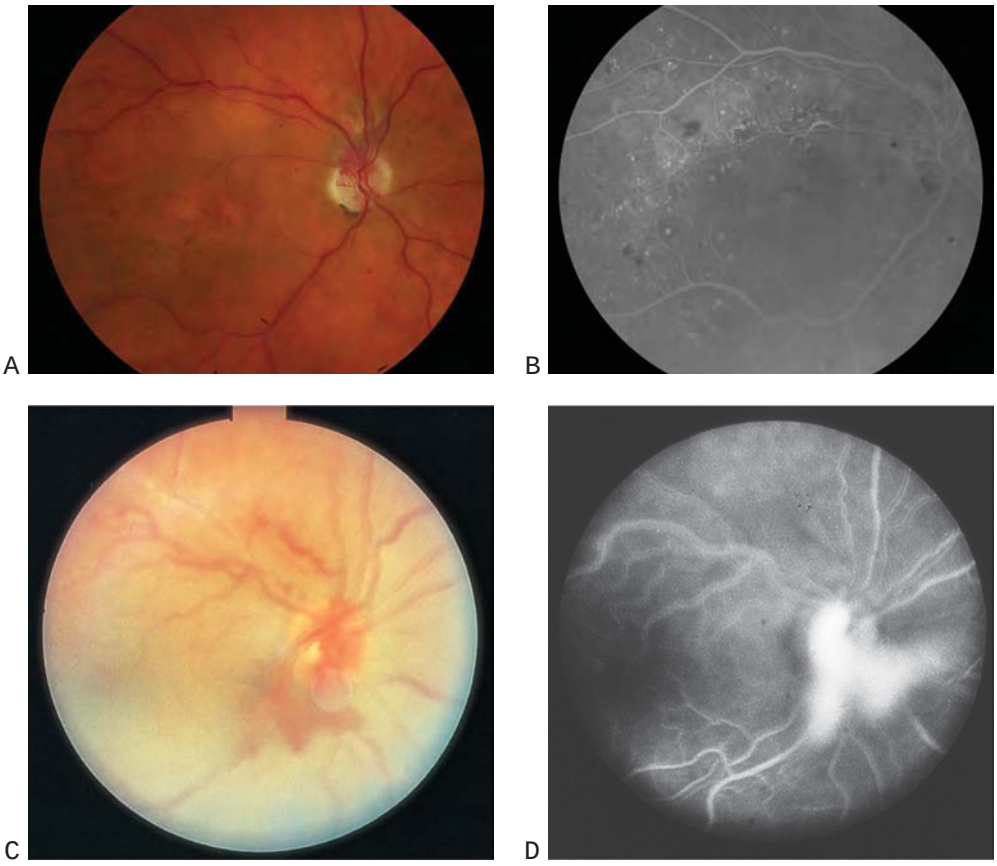

Figure 6-7 Characteristic retinal changes seen in a chronic retinal vein occlusion (RVO). **A,** Color photograph shows collateral vessels (specifically optociliary shunt vessels) on the superior optic nerve head, macular atrophy, and epiretinal membrane. **B,** Corresponding fluorescein angiogram shows areas of nonperfusion, telangiectasias, and mild macular edema. The collateral optic nerve head vessels can be contrasted with neovascularization of the disc shown in **C** and **D.** *(Parts A and B courtesy of Franco M. Recchia, MD; parts C and D courtesy of Gary C. Brown, MD.)*

prevent recurrence of macular edema. Intraocular corticosteroids are also effective at reducing macular edema. Because studies are increasingly not separating BRVO and CRVO when evaluating pharmacologic treatment of macular edema secondary to retinal venous occlusive disease, they are discussed together in this section.

Laser photocoagulation, pars plana vitrectomy, and other surgical techniques are also used in selected cases of BRVO and CRVO. See the discussions of surgical management in the specific sections for those entities.

Table 6-1 summarizes the major clinical trials that inform contemporary management of RVO and their salient findings. Because the study acronyms are generally more familiar to readers than are the study titles, the acronyms are used in the chapter text; for the complete titles, please refer to the table.

Table 6-1 Clinical Trials for Retinal Vein Occlusion

Study Acronym, Title (Year Completed)	Outcome Measure(s)	Number of Patients	Treatment Arms	Main Conclusions
Trials Evaluating Laser				
CVOS, Central Vein Occlusion Study (1994)	Visual acuity at 3 y	155	1. Grid macular laser q4mo PRN 2. Observation	Laser reduced angiographic macular edema but did not improve visual acuity.
	Incidence of anterior segment neovascularization	181	1. Prompt PRP 2. PRP deferred until appearance of NVI or NVA	PRP is recommended when at least 2 clock-hours of NVI or any degree of NVA is observed.
BVOS, Branch Vein Occlusion Study (1984)	Visual acuity at final study visit (mean 3.1 y)	139	1. Grid macular laser q4mo PRN 2. Observation	In patients with macular edema of >3 mo and BCVA ≤20/40, grid laser improved BCVA.
	Development of retinal NV and vitreous hemorrhage (mean 2.8 y)	319	1. Scatter peripheral laser q4mo PRN 2. Observation	Patients in whom retinal NV develops should be treated with scatter laser photocoagulation to the involved retinal sector. Risk of posterior segment NV correlates with extent of retinal ischemia.
Trials Evaluating Corticosteroid				
SCORE, The Standard Care vs Corticosteroid for Retinal Vein Occlusion, for BRVO (2008)	Gain in >15 letters of BCVA at 12 mo	352 with BRVO, 59 with hemi-CRVO	1. Intravitreal triamcinolone, 1 mg q4mo if re-treatment criteria were met 2. Intravitreal triamcinolone, 4 mg q4mo if re-treatment criteria were met 3. Grid macular laser photocoagulation	Early visual acuity gains with steroid treatment were not sustained. Cataract progression and need for IOP-lowering medications were greater following steroid treatment and were dose dependent.

Study Acronym, Title (Year Completed)	Outcome Measure(s)	Number of Patients	Treatment Arms	Main Conclusions
SCORE, The Standard Care vs Corticosteroid for Retinal Vein Occlusion Study (2008)	Gain in >15 letters of BCVA at 12 mo	271 with CRVO	1. Intravitreal triamcinolone, 1 mg q4mo 2. Intravitreal triamcinolone, 4 mg q4mo 3. Observation	Intravitreal corticosteroid was more likely to produce gains in visual acuity. Cataract progression and/or ocular hypertension occurred in one-third of eyes by 12 mo.
GENEVA, Global Evaluation of Implantable Dexamethasone in Retinal Vein Occlusion With Macular Edema (2008)	Time to achieve gain of >15 letters in BCVA	830 with BRVO, 437 with CRVO	1. Single intravitreal dexamethasone implant, 0.7 mg 2. Single intravitreal dexamethasone implant, 0.35 mg 3. Sham injection	Improvement in BCVA was greatest with dexamethasone implant at 60 d, but effectiveness waned by 6 mo. Risk of ocular hypertension was 16% after 1 dexamethasone injection.
COMRADE C, Clinical Efficacy and Safety of Ranibizumab Versus Dexamethasone for Central Retinal Vein Occlusion: A European Label Study (2014)	Mean change in BCVA at 6 mo	144	1. Single intravitreal dexamethasone implant, 0.7 mg 2. Intravitreal ranibizumab, 0.5 mg (monthly ×3, then PRN)	Ranibizumab (monthly loading, then PRN) was superior to a single injection of dexamethasone (mean BCVA gain of 16 letters vs 9 letters, respectively).
FDA Registration Trials for Anti-VEGF Medications				
BRAVO, Ranibizumab for Macular Edema Following Branch Retinal Vein Occlusion (2008)	Mean change in BCVA at 6 mo	397	1. Monthly intravitreal ranibizumab, 0.3 mg 2. Monthly intravitreal ranibizumab, 0.5 mg 3. Sham injection	Monthly treatment with ranibizumab is superior to sham treatment. Mean gains of 16 and 18 letters for the 0.3-mg and 0.5-mg ranibizumab groups, respectively, compared with 7 letters for sham group; 61% of eyes treated with 0.5-mg ranibizumab gained at least 15 letters.

(Continued)

Table 6-1 *(continued)*

Study Acronym, Title (Year Completed)	Outcome Measure(s)	Number of Patients	Treatment Arms	Main Conclusions
CRUISE, Ranibizumab for Macular Edema Following Central Retinal Vein Occlusion (2008)	Mean change in BCVA at 6 mo	392	1. Monthly intravitreal ranibizumab, 0.3 mg 2. Monthly intravitreal ranibizumab, 0.5 mg 3. Sham injection	Monthly treatment with ranibizumab is superior to sham treatment. Mean gains of 13 and 15 letters for the 0.3-mg and 0.5-mg ranibizumab groups, respectively, compared with 0.8 letters for sham group; 48% of eyes treated with 0.5-mg ranibizumab gained at least 15 letters.
VIBRANT, Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion (2012)	Gain in >15 letters of BCVA at 6 mo	183	1. Monthly intravitreal aflibercept, 2 mg 2. Macular laser photocoagulation	Monthly treatment with aflibercept is superior to laser. 53% of eyes treated with aflibercept gained ≥15 letters vs 28% of eyes treated with laser.
GALILEO/COPERNICUS, Vascular Endothelial Growth Factor Trap-Eye for Macular Edema Secondary to Central Retinal Vein Occlusion (2010)	Gain in >15 letters of BCVA at 6 mo	189	1. Monthly intravitreal aflibercept, 2 mg 2. Sham injection	Monthly treatment with aflibercept is superior to sham treatment. 56% of eyes treated with aflibercept gained ≥15 letters vs 12% in the sham group.
Trials Comparing Pharmacologic Treatments				
SCORE2, Effect of Bevacizumab vs Aflibercept on Visual Acuity Among Patients With Macular Edema Due to Central Retinal Vein Occlusion (2016)	Mean change in BCVA at 6 mo	305 with CRVO, 57 with hemi-CRVO	1. Intravitreal bevacizumab, 1.25 mg 2. Intravitreal aflibercept, 2 mg	Bevacizumab was noninferior to aflibercept (mean gain of 18 letters in each group).

Study Acronym, Title (Year Completed)	Outcome Measure(s)	Number of Patients	Treatment Arms	Main Conclusions
CRAVE, Bevacizumab Versus Ranibizumab in the Treatment of Macular Edema Due to Retinal Vein Occlusion (2015)	Change in central foveal thickness at 6 mo	98	1. Monthly intravitreal bevacizumab, 1.25 mg 2. Monthly intravitreal ranibizumab, 0.5 mg	Both bevacizumab and ranibizumab reduced mean retinal thickness and improved visual acuity.
LEAVO, Clinical Effectiveness of Intravitreal Therapy With Ranibizumab vs Aflibercept vs Bevacizumab for Macular Edema Secondary to Central Retinal Vein Occlusion (2016)	Change in visual acuity at 100 wk	463	1. Intravitreal bevacizumab, 1.25 mg 2. Intravitreal ranibizumab, 0.5 mg 3. Intravitreal aflibercept, 2 mg Doses were monthly for the first 3 months, then given as needed if re-treatment criteria were met.	Mean gain of 12.5 ETDRS letters for ranibizumab, 15.1 letters for aflibercept, and 9.8 letters for bevacizumab. Visual results may be worse with bevacizumab when compared with other 2 agents.
MARVEL, A Randomised, Double-Masked, Controlled Study of the Efficacy and Safety of Intravitreal Bevacizumab Versus Ranibizumab in the Treatment of Macular Oedema due to Branch Retinal Vein Occlusion (2015)	Change in BCVA at 6 mo	75	1. Intravitreal bevacizumab, 1.25 mg 2. Intravitreal ranibizumab, 0.5 mg	Mean BCVA gain was similar between bevacizumab (18 letters) and ranibizumab (15.6 letters).

BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; d = day(s); ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = intraocular pressure; mo = month(s); NV = neovascularization; NVA = neovascularization of the anterior chamber angle; NVI = neovascularization of the iris; PRN = pro re nata (as needed); PRP = panretinal photocoagulation; q4mo = every 4 months; VEGF = vascular endothelial growth factor; wk = week(s); y = year(s).

Intravitreal anti-VEGF therapy The initial studies of anti-VEGF therapy for macular edema caused by RVO were the BRAVO and CRUISE trials. In these studies, monthly injection of either 0.5 mg or 0.3 mg of ranibizumab was superior to sham injection for improving visual acuity. Similar results were achieved with intravitreal aflibercept (also called VEGF Trap-Eye) in the VIBRANT, COPERNICUS, and GALILEO studies (see Figs 6-4 and 6-6). The benefits were maintained during the second 6 months of these aflibercept studies, during which as-needed treatment was administered.

Bevacizumab, which is commonly used off label for retinal disease, has also demonstrated efficacy in the management of cystoid macular edema (CME) secondary to RVO (Fig 6-8). In SCORE2, bevacizumab was shown to be noninferior to (not worse than) aflibercept in the treatment of macular edema secondary to CRVO.

More recently, in the LEAVO study, the 3 most commonly used anti-VEGF agents were compared in a prospective multicenter noninferiority trial in the United Kingdom. Aflibercept treatment was noninferior to ranibizumab treatment at 100 weeks. However, bevacizumab was *not* noninferior to ranibizumab and, by post hoc analysis, was not noninferior to aflibercept. In other words, change in visual acuity may be worse with the use of bevacizumab than with the use of ranibizumab or aflibercept.

In current clinical practice, anti-VEGF regimens for RVO include fixed monthly dosing, as-needed treatment, and treat-and-extend approaches. Clinical trials have shown no additive benefit of macular grid or peripheral scatter laser photocoagulation for BRVO in patients treated with anti-VEGF agents.

Brown DM, Campochiaro PA, Bhisitkul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. *Ophthalmology.* 2011;118(8):1594–1602.

Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: twelve-month outcomes of a phase III study. *Ophthalmology.* 2011;118(10):2041–2049.

Hykin P, Prevost AT, Vasconcelos JC, et al. Clinical effectiveness of intravitreal therapy with ranibizumab vs aflibercept vs bevacizumab for macular edema secondary to central retinal vein occlusion: a randomized clinical trial. *JAMA Ophthalmol.* 2019;137(11):1256–1264.

Scott IU, VanVeldhuisen PC, Ip MS, et al; SCORE2 Investigator Group. Effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion: the SCORE2 randomized clinical trial. *JAMA.* 2017;317(20):2072–2087.

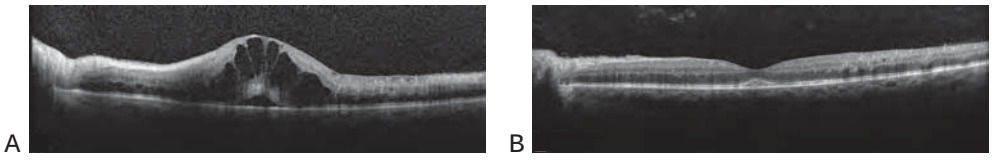

Figure 6-8 Cystoid macular edema (CME) secondary to CRVO, before and after treatment. **A,** Spectral-domain OCT (SD-OCT) scan shows severe CME with foveal detachment in a patient with a nonischemic CRVO. VA was 20/200. **B,** One month after intravitreal injection of bevacizumab 1.25 mg, the cystic changes and foveal detachment resolved, and VA was 20/25. *(Courtesy of Colin A. McCannel, MD.)*

Intravitreal corticosteroids Intravitreal corticosteroids are efficacious for RVO, but their risks include cataract formation and steroid-induced elevation of intraocular pressure (IOP) (in 20%–65% of individuals). The SCORE trial found that intravitreal triamcinolone injection in eyes with BRVO was comparable in efficacy to macular grid laser treatment in terms of visual acuity gain of 3 or more lines; however, because eyes receiving triamcinolone were more likely to develop a cataract or experience elevated IOP, macular grid laser therapy was recommended. In the CRVO arm of the SCORE study, intravitreal steroid was associated with improved visual acuity.

The GENEVA study explored the use of a 0.7-mg dexamethasone intravitreal implant to treat macular edema secondary to RVO. The dexamethasone implant (Ozurdex, Allergan, Inc) is a small, biodegradable pellet injected into the vitreous cavity. Visual improvement was noted between 30 and 90 days, with the greatest response at day 60. The COMRADE study compared the dexamethasone implant against monthly ranibizumab treatment. The efficacy of the 2 treatments was similar early, but at months 4–6, the eyes treated with ranibizumab had significantly better visual acuity.

Haller JA, Bandello F, Belfort R Jr, et al; OZURDEX GENEVA Study Group. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. *Ophthalmology.* 2010;117(6):1134–1146.e3.

Hoerauf H, Feltgen N, Weiss C, et al; COMRADE-C Study Group. Clinical efficacy and safety of ranibizumab versus dexamethasone for central retinal vein occlusion (COMRADE C): a European label study. *Am J Ophthalmol.* 2016;169:258–267.

Scott IU, Ip MS, VanVeldhuisen PC, et al; SCORE Study Research Group. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6. *Arch Ophthalmol.* 2009;127(9):1115–1128. Published correction appears in *Arch Ophthalmol.* 2009;127(12):1655.

Systemic anticoagulation Systemic anticoagulation is not recommended for the treatment of RVO. Case series suggest that patients may experience worse outcomes as a result of increased bleeding in the retina.

Branch Retinal Vein Occlusion

In BRVO, venous thrombosis and obstruction occur most commonly at an arteriovenous crossing in the superotemporal quadrant. When the occlusion does not occur at an arteriovenous crossing, other inflammatory and infectious causes should be considered.

Prognosis for patients with BRVO

In acute disease, the presence or absence of macular or foveal involvement determines the visual prognosis. Before the availability of pharmacologic intervention, the BVOS found that the incidence of neovascularization from the retina or optic nerve was 36% in eyes with extensive retinal ischemia; extensive ischemia was defined as an area of at least 5 disc diameters in size (Fig 6-9). Vitreous hemorrhage developed in 60%–90% of such eyes if laser photocoagulation was not performed.

Over the long term, permanent vision loss may be related to macular ischemia, lipid residues (hard exudates) in the fovea, pigmentary macular disturbances, subretinal

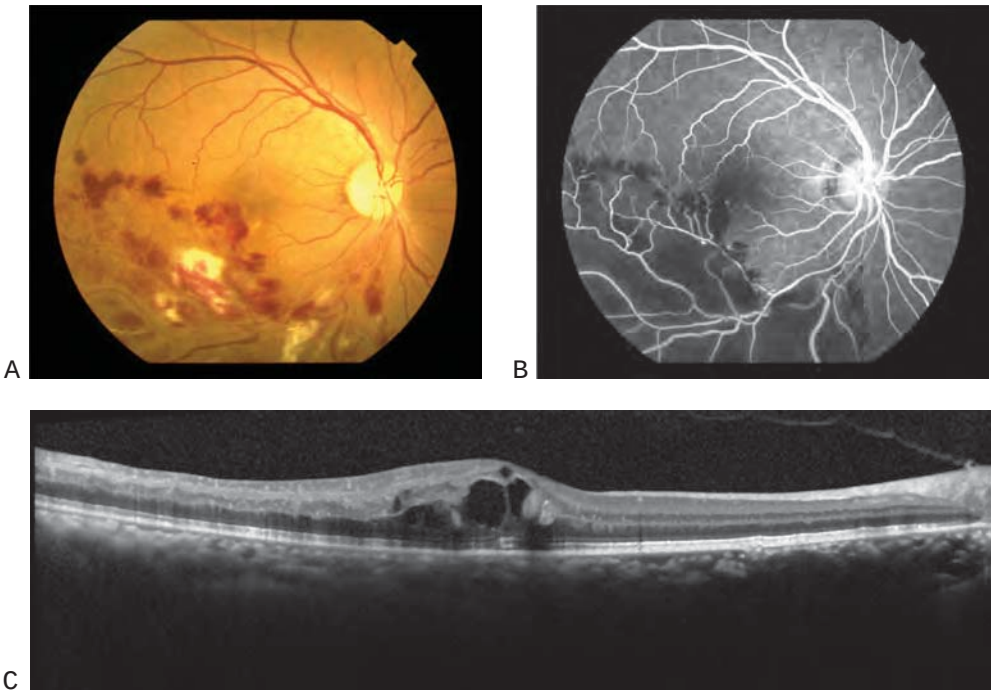

Figure 6-9 Branch retinal vein occlusion (BRVO) with ischemia. **A,** Fundus photograph shows inferotemporal BRVO. **B,** Fluorescein angiography image corresponding to **A** reveals pronounced retinal capillary nonperfusion in the distribution of the retina drained by the obstructed vein. **C,** SD-OCT image of the same eye reveals CME. *(Courtesy of Neal H. Atebara, MD.)*

fibrosis, CME, and epiretinal membrane formation. The last 2 conditions can be treated, and treatment may restore some visual function. Less common treatable causes of vision loss include vitreous hemorrhage, traction (also called *tractional*) retinal detachment, and rhegmatogenous retinal detachment. Traction retinal detachment typically arises from fibrosis and contraction of prior retinal neovascularization. Rhegmatogenous retinal detachment typically develops following a retinal break induced by vitreous traction in areas adjacent to or beneath the retinal neovascularization and fibrosis.

Treatment of BRVO

Pharmacologic management Pharmacologic management is currently the mainstay of BRVO management. See the earlier section "Pharmacologic management of RVO" for more detail.

Ehlers JP, Kim SJ, Yeh S, et al. Therapies for macular edema associated with branch retinal vein occlusion: a report by the American Academy of Ophthalmology. *Ophthalmology.* 2017;124(9):1412–1423.

Surgical management of BRVO In BRVO, macular laser photocoagulation and scatter panretinal photocoagulation may address macular edema and retinal neovascularization, respectively, by local destruction of ischemic retina and reduction in local pro-inflammatory and proangiogenic factors.

MACULAR LASER SURGERY Grid laser photocoagulation may be applied to areas of macular edema caused by the obstructed vein (Fig 6-10). The BVOS found that laser-treated eyes with intact foveal vasculature, macular edema, and visual acuity in the 20/40–20/200 range were more likely to gain 2 lines of visual acuity (65%) than untreated eyes (37%). At 3-year follow-up, treated eyes were more likely to have 20/40 or better visual acuity than untreated eyes (60% vs 34%, respectively), with a mean visual acuity improvement of 1.3 ETDRS (Early Treatment Diabetic Retinopathy Study) lines versus 0.2 line, respectively. In the BVOS, laser treatment of macular edema was delayed for at least 3 months to permit the maximum spontaneous resolution of intraretinal blood and edema. Although this practice may still be appropriate for macular laser therapy, treatment with pharmacologic agents should commence immediately upon diagnosis of BRVO.

SCATTER PHOTOCOAGULATION The BVOS showed that scatter photocoagulation to the area of retinal capillary nonperfusion is effective in causing regression of the new vessels in eyes with

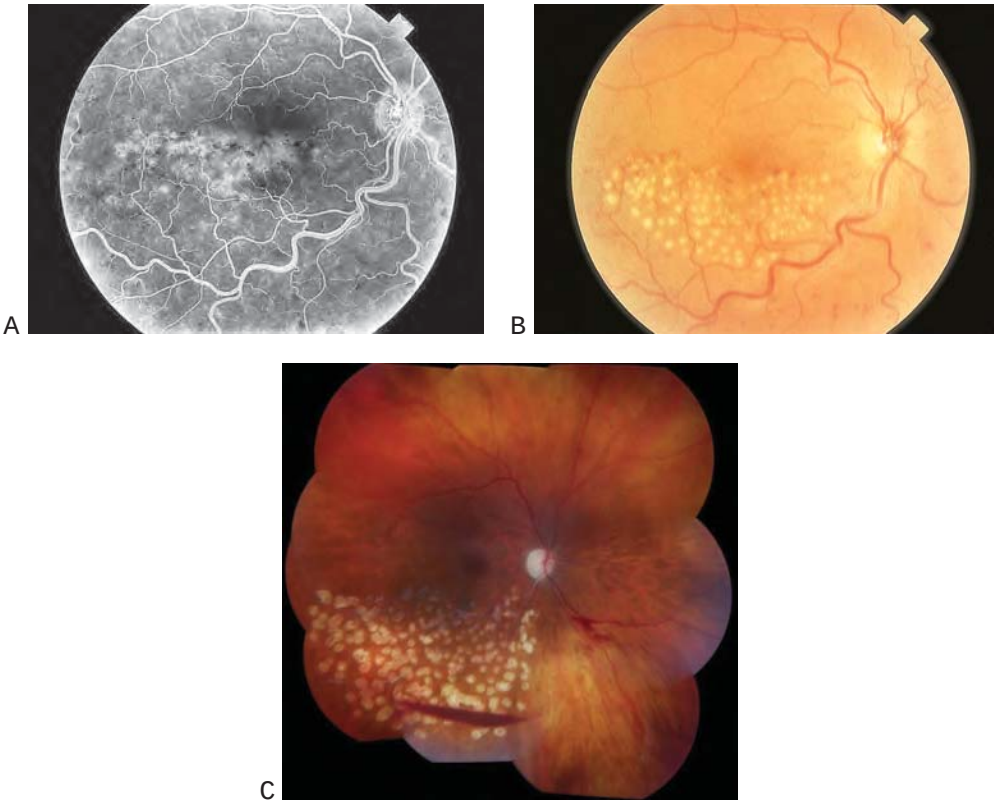

Figure 6-10 Two examples of laser photocoagulation for BRVO. **A,** Grid treatment for macular edema. The area of treatment corresponds to the area of leakage, as demonstrated by hyperfluorescence on fluorescein angiography. **B,** The laser spots spare the fovea. **C,** Peripheral scatter laser to an area of inferotemporal retinal ischemia (note the sclerotic vessels) as treatment for neovascularization of the disc and vitreous hemorrhage. Residual preretinal hemorrhage is seen inferiorly, but the neovascularization has regressed. *(Parts A and B courtesy of Gary C. Brown, MD; part C courtesy of Franco M. Recchia, MD.)*

retinal, ONH, or iris neovascularization (see Fig 6-9); it also reduced the risk of vitreous hemorrhage from 60% to 30%. Although the BVOS found that patients with large areas of nonperfusion were at significant risk of developing neovascularization, the study concluded that ischemia alone was not an indication for treatment, provided that follow-up could be maintained.

Neovascularization of the iris occurs in approximately 2% of eyes with BRVO. In these cases, scatter laser photocoagulation in the distribution of the occluded vein should be considered to prevent the development of neovascular glaucoma.

PARS PLANA VITRECTOMY Vitrectomy may be indicated for eyes that develop vitreous hemorrhage or retinal detachment (also see Chapters 16 and 19).

Central Retinal Vein Occlusion

In CRVO, vision loss is most commonly sudden and painless, with presenting visual acuity ranging from 20/20 to hand motions. Less commonly, patients may experience premonitory symptoms of transient obscuration of vision before overt retinal manifestations appear. Histologic studies suggest that most forms of CRVO arise from thrombosis of the central retinal vein at or posterior to the level of the lamina cribrosa. When thrombosis is more anterior, fewer collaterals are available, resulting in greater ischemia.

The CVOS was a multicenter prospective clinical study conducted in the early 1990s that elucidated the natural history of CRVO, the incidence of neovascular complications, and the utility of laser photocoagulation, as well as developing precise definitions of ischemic and nonischemic CRVO.

Nonischemic (perfused) CRVO is characterized by visual acuity of 20/200 or better, minimal or no afferent pupillary defect, and mild visual field changes. Ophthalmoscopy shows some dilation and tortuosity of all branches of the central retinal vein as well as dot- and flame-shaped hemorrhages in all quadrants of the retina (Fig 6-11). Macular edema and slight ONH swelling may be present (Activity 6-1). Fluorescein angiography usually demonstrates prolongation of the retinal circulation time with breakdown of capillary permeability but minimal areas of nonperfusion (<10 disc areas on standardized 7-field photography). Anterior segment neovascularization is rare in mild CRVO.

ACTIVITY 6-1 OCT Activity: Macular OCT of an eye with CRVO, severe CME, and foveal detachment.
Courtesy of Colin A. McCannel, MD.

Ischemic (nonperfused) CRVO is defined as at least 10 disc areas of retinal capillary nonperfusion on fluorescein angiography. Ischemic cases are usually associated with poor vision (worse than 20/200), an afferent pupillary defect, dense central scotoma, and peripheral visual field constriction. Marked venous dilation, more extensive hemorrhage, retinal edema, and variable numbers of cotton-wool spots are more frequent than in nonischemic CRVO (Fig 6-12). Fluorescein angiography demonstrates prolonged arteriovenous circulation time and widespread capillary nonperfusion. Because of inner retinal dysfunction due to ischemia, the b-wave to a-wave amplitude ratio is decreased in electroretinographic bright-flash dark-adapted testing. The CVOS showed that the natural history of ischemic CRVO is generally poor; only approximately 10% of eyes achieve vision better than

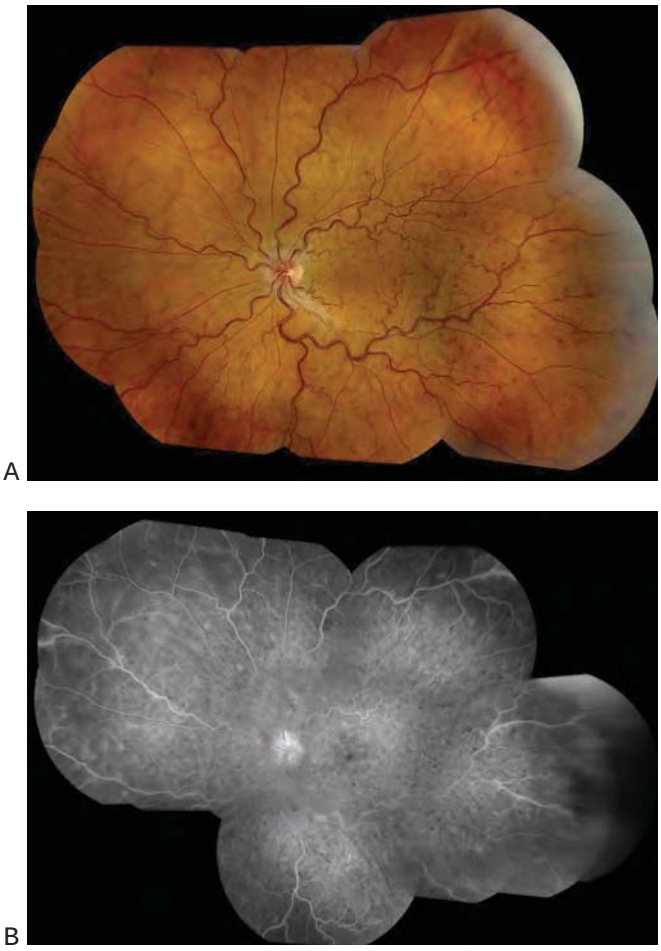

Figure 6-11 Perfused CRVO. A 38-year-old woman with a history of migraines presented with VA of 20/80. **A,** Montage of color fundus images shows prominent dilation and tortuosity of veins in all 4 retinal quadrants. **B,** Corresponding fluorescein angiography shows peripheral capillary nonperfusion, but this eye would be classified as perfused, according to Central Vein Occlusion Study criteria, on the basis of the intact perfusion in the postequatorial retina. *(Courtesy of Franco M. Recchia, MD.)*

20/400. With anti-VEGF treatment, however, the prognosis may now be somewhat better in all but the most severe cases.

Iris neovascularization in CRVO

Among eyes with severely ischemic CRVO, the incidence of anterior segment neovascularization (of the iris or angle) approaches 60%. Neovascularization of the iris (NVI) can occur as early as 2 weeks and as late as 6 months after the onset of symptoms, with the peak at approximately 2 months after presentation. The CVOS found that poor visual acuity is the risk factor most predictive of NVI. Other risk factors include large areas of retinal capillary nonperfusion and intraretinal blood. If NVI is not detected and treated promptly, neovascular glaucoma may develop.

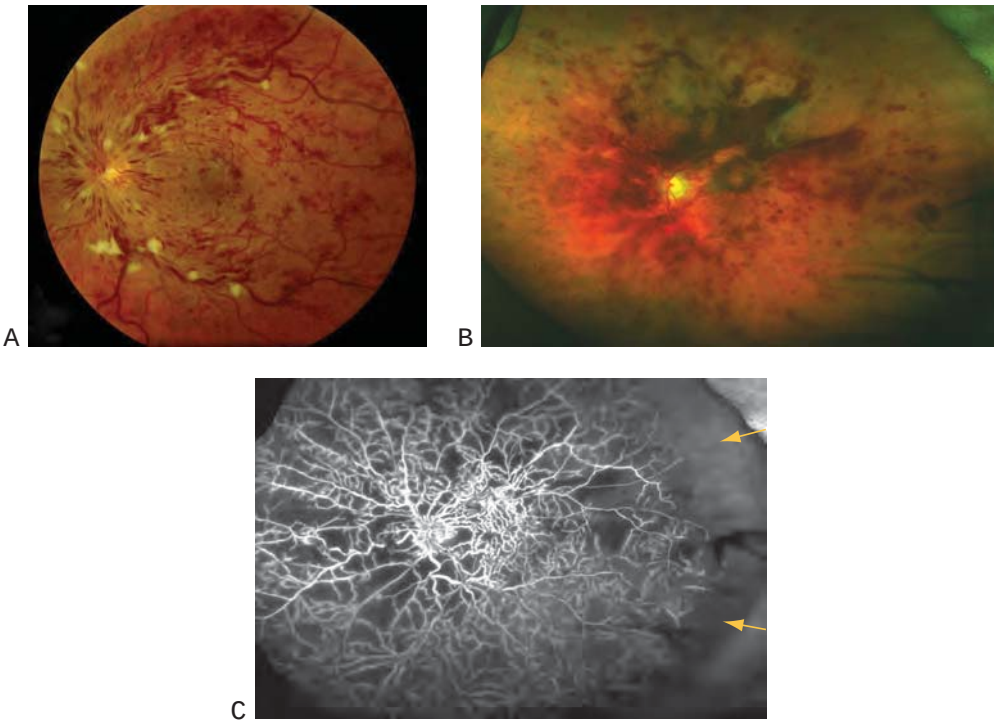

Figure 6-12 Two examples of a nonperfused (ischemic) CRVO. **A,** Fundus photograph of a nonperfused CRVO; patient's VA is counting fingers. There are diffuse retinal hemorrhages, numerous cotton-wool spots, and blurring of optic nerve head margins. Poor VA at presentation along with these clinical findings is consistent with severe nonperfusion. **B,** Ultra-wide-field fundus photograph of severe ischemic CRVO in an eye with VA of hand motions. The veins are dilated, and extensive retinal hemorrhages are present. **C,** Ultra-wide-field fluorescein angiography image corresponding to **B** taken 40 seconds after injection reveals widespread retinal capillary nonperfusion *(arrows)*. *(Part A courtesy of Franco M. Recchia, MD; parts B and C courtesy of Colin A. McCannel, MD.)*

Baseline and early natural history report. The Central Vein Occlusion Study. *Arch Ophthalmol.* 1993;111(8):1087–1095.

Klein R, Moss SE, Meuer SM, Klein BE. The 15-year cumulative incidence of retinal vein occlusion: the Beaver Dam Eye Study. *Arch Ophthalmol.* 2008;126(4):513–518.

Differential diagnosis of CRVO

Hyperviscosity retinopathy can mimic the appearance of CRVO. However, the retinal findings in hyperviscosity retinopathy are generally bilateral. Blood hyperviscosity is usually related to dysproteinemia (eg, associated with Waldenström macroglobulinemia or multiple myeloma) or blood dyscrasias (eg, polycythemia vera). In many cases, the hyperviscosity can be reversed by treating the underlying condition. Diagnostic testing may include complete blood count, serum protein electrophoresis, and measurement of whole-blood viscosity. *Ocular ischemic syndrome* (discussed later in the chapter) can also resemble CRVO, but hemorrhages in this syndrome are limited to the deeper retinal layers, and vascular tortuosity is absent.

American Academy of Ophthalmology Retina/Vitreous Panel. Preferred Practice Pattern Guidelines. *Retinal Vein Occlusions.* American Academy of Ophthalmology; 2019. www.aao.org/education/preferred-practice-pattern/retinal-vein-occlusions-ppp

Natural history and clinical management of central retinal vein occlusion. The Central Vein Occlusion Study Group. *Arch Ophthalmol.* 1997;115(4):486–491. Published correction appears in *Arch Ophthalmol*. 1997;115(10):1275.

Evaluation and management of CRVO

Visual acuity, visual field, and relative afferent defect testing and dilated ophthalmoscopy can be useful in determining whether the vein occlusion is nonischemic or ischemic. Fluorescein angiography and OCT provide valuable additional data. It is important to perform gonioscopy at presentation and during follow-up to check for angle neovascularization. Eyes that initially appear perfused sometimes develop progressive ischemia. In the CVOS, 16% and 34% of CRVOs initially classified as nonischemic converted to ischemic by 4 months and 36 months, respectively. Patients presenting with CRVO may also have elevated IOP or frank open-angle glaucoma, either in the affected eye alone or in both eyes.

Follow-up In the absence of treatment, patients with CRVO should be monitored monthly during the first 6 months for evidence of progression and development of macular edema, anterior segment neovascularization, or neovascular glaucoma. Patients treated with intravitreal anti-VEGF agents may need to be observed even longer after discontinuation of treatment.

Stem MS, Talwar N, Comer GM, Stein JD. A longitudinal analysis of risk factors associated with central retinal vein occlusion. *Ophthalmology.* 2013;120(2):362–370.

Treatment of CRVO

Pharmacologic management Pharmacologic management is currently the mainstay of CRVO management. See the earlier section "Pharmacologic management of RVO" for more detail.

Yeh S, Kim SJ, Ho AC, et al. Therapies for macular edema associated with central retinal vein occlusion: a report by the American Academy of Ophthalmology. *Ophthalmology.* 2015;122(4):769–778.

Surgical management of CRVO Laser therapy does not appear to provide benefit in CRVO, although other surgical techniques may be useful in select cases.

MACULAR LASER SURGERY The CVOS showed that grid laser photocoagulation in CRVO with macular edema does not improve visual acuity, and therefore it is no longer recommended.

PANRETINAL PHOTOCOAGULATION The CVOS found that immediate prophylactic panretinal photocoagulation (PRP) did not result in a statistically significant decrease in the incidence of NVI; in fact, NVI developed in 20% of participants who received the prophylactic PRP. Although the CVOS investigators recommended delaying laser therapy until at least 2 clock-hours of NVI are present, PRP is often performed at the first sign of NVI.

A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. The Central Vein Occlusion Study Group N report. *Ophthalmology.* 1995;102(10):1434–1444.

PARS PLANA VITRECTOMY CRVOs complicated by vitreous hemorrhage may benefit from pars plana vitrectomy to improve vision or to accomplish retinal ablative treatment in the management of anterior segment neovascularization. If neovascular glaucoma is present, a glaucoma drainage implant may be placed concurrently.

OTHER SURGICAL APPROACHES Several surgical approaches have been investigated over the last 3 decades. These approaches include creation of a peripheral laser anastomosis between a retinal vein and the choroidal circulation, radial relaxing incision of the optic nerve scleral ring to decompress the central retinal vein, and retinal vein cannulation with infusion of tissue plasminogen activator. These approaches are not recommended because of their lack of efficacy and/or high complication rates.

Ocular Ischemic Syndrome and Retinopathy of Carotid Occlusive Disease

Ocular ischemic syndrome (OIS) comprises the ocular symptoms and signs attributable to chronic severe ocular hypoperfusion caused by ipsilateral carotid obstruction or ophthalmic artery obstruction.

Symptoms and Signs of OIS

Symptoms of OIS typically include gradual vision loss that develops over a period of weeks to months, aching pain that is localized to the orbital area of the affected eye and is worse in upright position, and prolonged recovery of vision after exposure to bright light. Anterior segment signs include NVI in two-thirds of eyes and an anterior chamber cellular response in about one-fifth of eyes (Fig 6-13). Although iris and angle neovascularization are common,

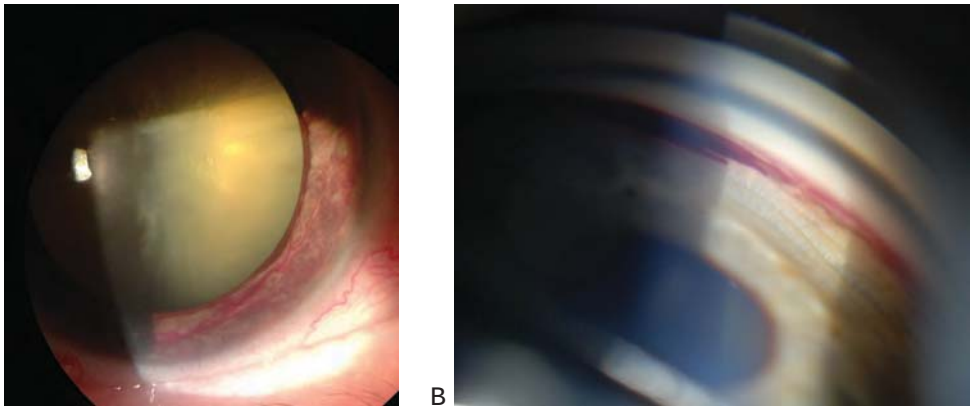

Figure 6-13 Anterior segment neovascularization in ocular ischemic syndrome (OIS). **A,** Slit-lamp photograph of diffuse neovascularization of the iris. **B,** Gonio photograph shows neovascularization of the anterior chamber angle (right part of image) as well as fresh blood in the angle and on the iris (left part of image). *(Images originally published on the Retina Image Bank website. © American Society of Retina Specialists. Part A: Pauline Merrill, Illinois Retina Associates, NVI; 2012, image number 2096. Part B: Jason S. Calhoun, Dept. of Ophthalmology, Mayo Clinic Jacksonville; 2013, image number 7327.)*

only one-half of eyes with this condition show an increase in IOP; low or normal IOP in the other eyes is most likely the result of impaired aqueous production.

OIS can cause a retinopathy similar in appearance to that of a partial occlusion of the central retinal vein; thus, it was originally called *venous stasis retinopathy*. Typical retinal findings include narrowed arteries; dilated but not tortuous veins; hemorrhages; microaneurysms; and neovascularization of the ONH, retina, or both (Fig 6-14). A helpful method for differentiating between OIS and CRVO is to measure the retinal artery pressure with an ophthalmodynamometer. An eye with CRVO will have normal artery pressure, whereas one with carotid occlusive disease will have low artery pressure, and the artery will collapse easily.

Fluorescein angiography reveals delayed choroidal filling in 60% of eyes, prolonged arteriovenous transit time in 95% of eyes, and prominent vascular staining (particularly of the arteries) in 85% of eyes. Electroretinography (ERG) demonstrates global decreased amplitude, reflecting damage caused by impaired blood supply to both the photoreceptors and the inner retina. An electronegative ERG occurs when the blood supply to the inner retina is compromised (as in CRVO or central retinal artery occlusion) while the supply to the photoreceptors is preserved. In cases of suspected OIS, urgent referral for carotid evaluation is needed.

Etiology and Course of OIS

The most common etiology of OIS is atherosclerosis. Typically, a 90% or greater ipsilateral obstruction is necessary to cause OIS. Other causes include Eisenmenger syndrome, carotid artery dissection, giant cell arteritis, and other inflammatory conditions. Most patients are older than 55 years. Approximately 20% of cases involve both eyes.

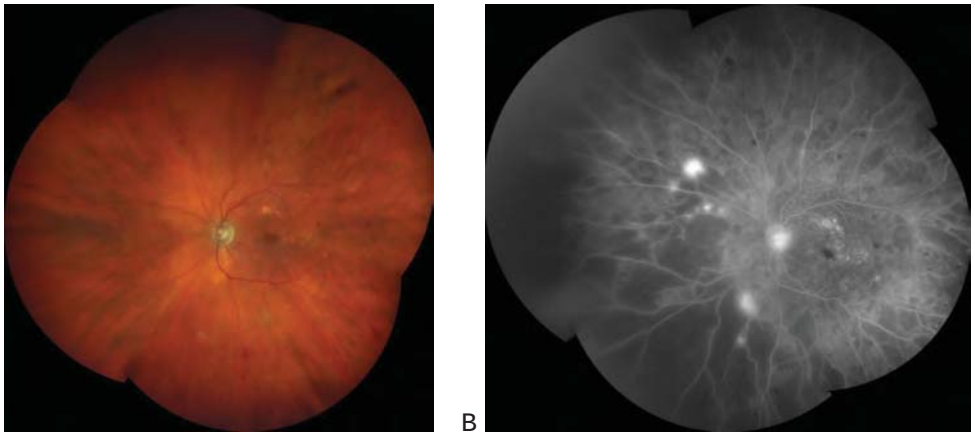

Figure 6-14 Retinal findings in OIS. An 80-year-old man with a history of coronary artery disease and diabetes mellitus presented with 2 weeks of aching pain and photosensitivity in his left eye. **A,** Fundus photograph shows dilated retinal veins without tortuosity and scattered blot (round, deep) retinal hemorrhages in the equatorial area. Retinal scars from previous focal macular laser treatment for diabetic macular edema are also present. **B,** Fluorescein angiography revealed delayed arterial perfusion (not shown), hypofluorescence consistent with diffuse capillary nonperfusion, and focal hyperfluorescence and leakage consistent with retinal neovascularization. *(Courtesy of Franco M. Recchia, MD.)*

When rubeosis iridis is present in OIS, visual acuity will decline to 20/200 or worse in more than 90% of cases within 1 year after diagnosis. Approximately one-half of patients with OIS also have ischemic cardiovascular disease; the stroke rate in these patients is higher than that of the general population, and the 5-year mortality is approximately 40%, mostly resulting from complications of cardiovascular disease.

Treatment of OIS

The most definitive treatment for OIS appears to be carotid artery stenting and endarterectomy. Unfortunately, these procedures are ineffective when there is 100% obstruction. In eyes with iris neovascularization and low or normal IOP as a result of impaired ciliary body perfusion and decreased aqueous formation, carotid reperfusion can lead to increased aqueous formation and a severe rise in IOP. Full-scatter PRP results in regression of anterior segment neovascularization in approximately two-thirds of cases. Anti-VEGF therapy has also been shown to cause regression of anterior segment neovascularization in patients with OIS.

Brown GC, Sharma S. Ocular ischemic syndrome. In: Schachat AP, Wilkinson CP, Hinton DR, Sadda SR, Wiedemann P, eds. *Ryan's Retina.* 6th ed. Elsevier/Saunders; 2018:chap 62.

Arterial Occlusive Disease

The blood supply to the inner layers of the retina is derived entirely from the central retinal artery unless a cilioretinal artery is present. Retinal ischemia results from disease processes that affect the vessels anywhere from the common carotid artery to the intraretinal arterioles. The signs and symptoms of arterial obstruction depend on the vessel involved: occlusion of a peripheral arteriole may be asymptomatic, whereas an ophthalmic artery occlusion can cause total blindness.

Cotton-Wool Spots

Acute obstruction in the distribution of the radial peripapillary capillary net leads to the formation of an NFL infarct, or *cotton-wool spot,* which causes impaired axoplasmic transport in the NFL (Fig 6-15). These inner retinal ischemic spots are superficial, white, and typically one-fourth disc area or less in size. They usually fade in 5–7 weeks, although spots present in association with diabetic retinopathy often remain longer. A subtle retinal depression caused by inner retinal ischemic atrophy may develop in an area of prior ischemia. The effect on visual function, including visual acuity loss and visual field defects, is related to the size and location of the occluded area.

The most common cause of cotton-wool spots is diabetic retinopathy (discussed in Chapter 5). Other causes, which should be investigated, are listed in Table 6-2. If even 1 cotton-wool spot is discovered in the fundus of an otherwise apparently healthy eye, the clinician should initiate a workup for the most likely underlying etiologies.

Brown GC, Brown MM, Hiller T, Fischer D, Benson WE, Magargal LE. Cotton-wool spots. *Retina.* 1985;5(4):206–214.

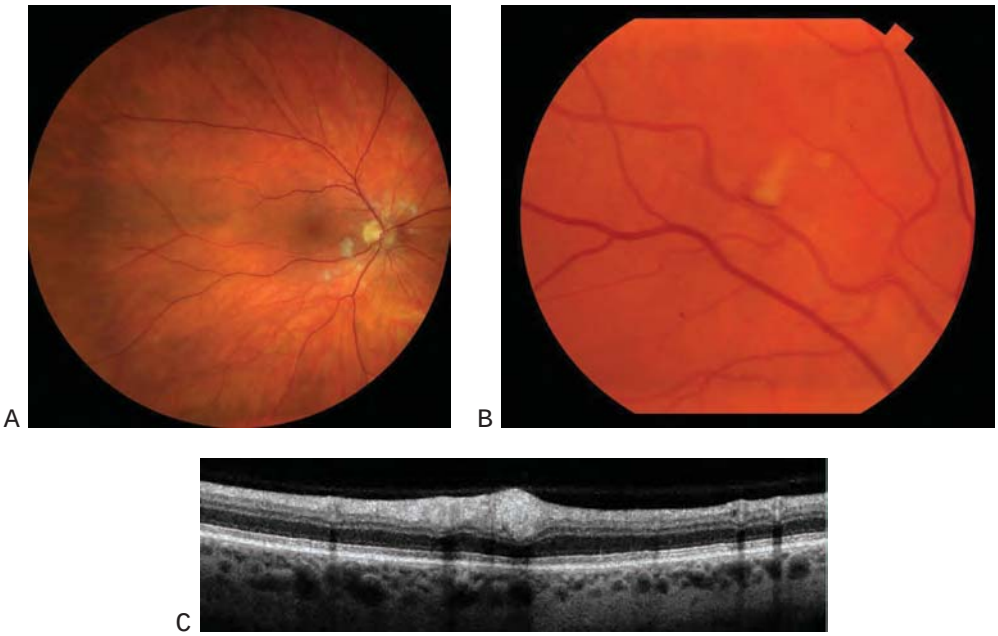

Figure 6-15 Examples of cotton-wool spots. **A,** Wide-field color fundus photograph of the right eye shows multiple fluffy, ill-defined white parapapillary lesions consistent with cotton-wool spots. Their superficial location is demonstrated by the obscuration of retinal vessels by some of the larger lesions. **B,** Fundus photograph shows an isolated cotton-wool spot just outside the superotemporal macula of the right eye. **C,** OCT through the lesion in **B** shows hyperreflectivity in the inner retina. *(Courtesy of Franco M. Recchia, MD.)*

Table 6-2 Causes of Cotton-Wool Spots

Diabetic retinopathy
Systemic arterial hypertension
HIV-associated retinopathy
Anemia (severe)
Radiation retinopathy
Sickle cell retinopathy
Cardiac embolic disease
Carotid artery obstructive disease
Vasculitis
Collagen vascular disease
Leukemia
Purtscher and Purtscher-like retinopathy
Giant cell arteritis

Branch Retinal Artery Occlusion

Although an acute branch retinal artery occlusion (BRAO) may be subtle and unapparent on initial ophthalmoscopic examination, within hours to days it can lead to edematous opacification caused by infarction of the inner retina in the distribution of the affected vessel (Fig 6-16). In time, the occluded vessel recanalizes, perfusion returns, and the

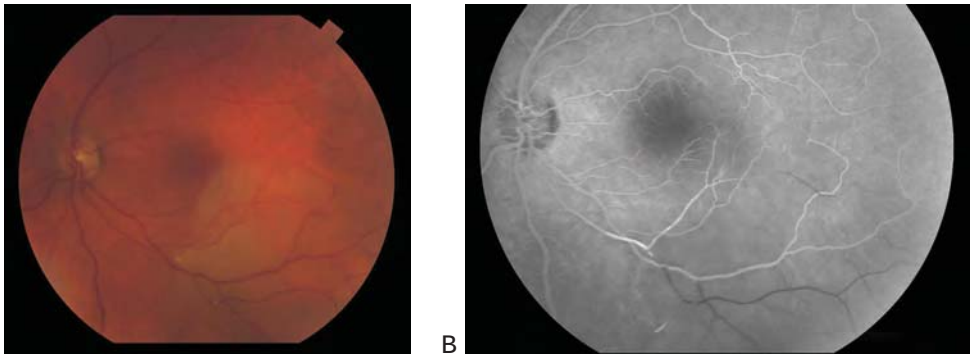

Figure 6-16 Branch retinal artery occlusion (BRAO). **A,** Fundus photograph shows a BRAO associated with 2 intra-arterial emboli: 1 at the first bifurcation of the inferotemporal arteriole, and 1 at its second bifurcation. Retinal whitening distal to these sites of occlusion signals acute retinal edema in response to retinal ischemia. **B,** In the corresponding fluorescein angiogram, blood flow is absent in the arterioles distal to the emboli, and the retina appears darker because of lack of capillary blood flow. *(Courtesy of Franco M. Recchia, MD.)*

edema resolves; however, a permanent visual field defect remains. A retinal arterial occlusion that occurs outside the posterior pole may be clinically asymptomatic.

Occlusion at any point along the arterial tree can be caused by embolization of the affected vessel. There are 3 main types of emboli:

- cholesterol emboli (so-called *Hollenhorst plaques*) arising in the carotid arteries (see Fig 6-16)
- platelet-fibrin emboli associated with large-vessel arteriosclerosis (Fig 6-17)
- calcific emboli arising from diseased cardiac valves

In rare cases, emboli might be caused by cardiac myxoma, long-bone fractures *(fat emboli),* infective endocarditis *(septic emboli),* and intravenous drug use *(talc emboli).* Although the occurrence is rare, migraine can cause ocular arterial occlusions in patients younger than 40 years.

Conditions other than embolic events, including infectious, inflammatory, and thrombophilic causes, can lead to retinal artery occlusion, especially in younger patients with no cardiovascular comorbidity (Table 6-3). Diagnosis can be facilitated by a detailed history and review of systems and complete ophthalmologic examination.

Initial management is directed toward determining the underlying systemic disorder. Patients with retinal arterial occlusion should be referred *urgently* to an emergency department or stroke center for evaluation of cerebrovascular disease and cardiac valvular disease. No specific ocular therapy has been found to be consistently effective in improving visual acuity.

Hayreh SS, Podhajsky PA, Zimmerman MB. Branch retinal artery occlusion: natural history of visual outcome. *Ophthalmology.* 2009;116(6):1188–1194.e944.

Wang JJ, Cugati S, Knudtson MD, et al. Retinal arteriolar emboli and long-term mortality: pooled data analysis from two older populations. *Stroke.* 2006;37(7):1833–1836.

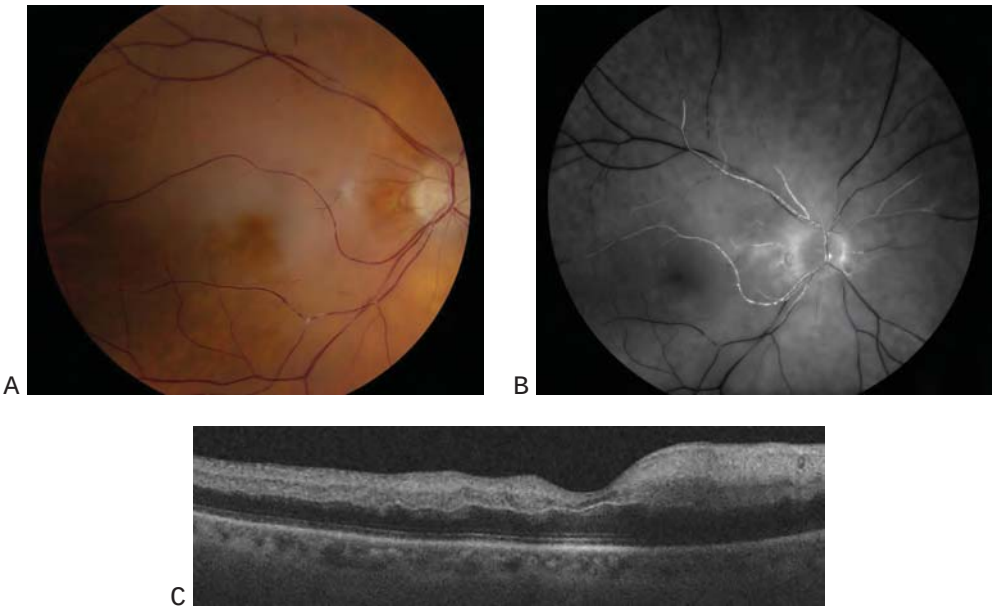

Figure 6-17 Central retinal artery occlusion (CRAO) caused by multiple emboli. **A,** The right eye shows diffuse retinal whitening, a cotton-wool spot, arteriolar attenuation, and multiple intra-arterial refractile lesions in both superior and inferior arterial distributions. **B,** Fluorescein angiography shows markedly delayed arterial filling and "boxcarring" of blood flow within retinal arterioles. Subsequent computed tomography angiography revealed an ulcerative atherosclerotic plaque in the right internal carotid artery. **C,** Simultaneous OCT shows inner retinal hyperreflectivity due to retinal edema with corresponding hyporeflectivity of the outer retina. *(Courtesy of Franco M. Recchia, MD.)*

Table 6-3 Nonembolic Conditions Associated With Retinal Artery Occlusion

Infectious
Acute retinal necrosis
Bartonellosis (cat-scratch disease)
Endocarditis
Endogenous endophthalmitis
HIV
Ocular or neurosyphilis
Ocular toxoplasmosis
Orbital cellulitis/subperiosteal abscess
Systemic COVID-19 disease
Inflammatory
Behçet syndrome
Churg-Strauss syndrome (eosinophilic granulomatosis)
Crohn disease
Granulomatosis with polyangiitis (formerly called *Wegener's granulomatosis*)
Neurosarcoidosis
Susac syndrome
Systemic lupus erythematosus
Thrombophilic
Antiphospholipid syndrome
Genetic polymorphisms or deficiencies in various clotting factors
Lupus anticoagulant antibodies
Pregnancy

Central Retinal Artery Occlusion

Sudden, complete, and painless loss of vision in 1 eye is characteristic of central retinal artery occlusion (CRAO). Three-fourths of patients present with visual acuity in the range of counting fingers. The retina becomes opaque and edematous, particularly in the posterior pole, where the nerve fiber and ganglion cell layers are thickest (Fig 6-18; see also Fig 6-17). The orange reflex from the intact choroidal vasculature beneath the foveola thus stands out in contrast to the surrounding opaque neural retina, producing a *cherry-red spot*. Even before the cherry-red spot appears, OCT imaging reveals a normal macular profile with diffuse hyperreflectivity and loss of internal layer definition (Fig 6-19, Activity 6-2; see also Fig 6-18). A cilioretinal artery may preserve some degree of macular vision (see Chapter 1, Fig 1-8).

ACTIVITY 6-2 OCT Activity: SD-OCT scan of an eye with CRAO and cilioretinal artery sparing.
Courtesy of Colin A. McCannel, MD.

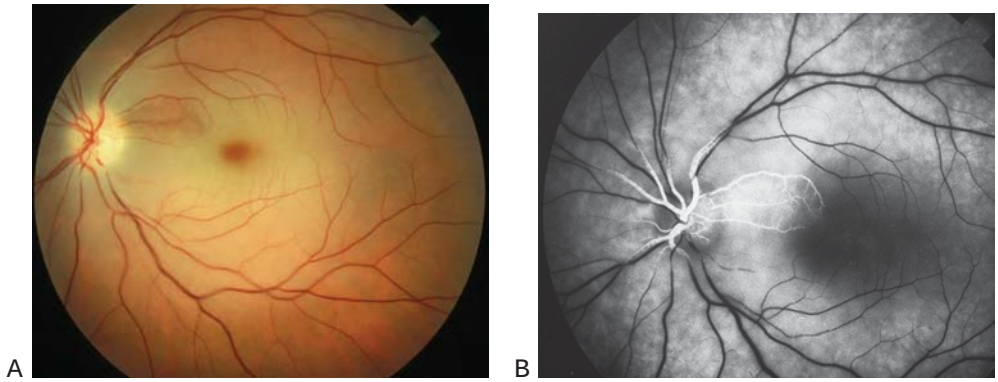

Figure 6-18 CRAO. **A,** Fundus photograph shows superficial macular opacification and a cherry-red spot in the foveola. **B,** Angiography image reveals preservation of a sector of superonasal macula related to cilioretinal vessels, which are perfused in this image. The patient had hand motions VA. *(Courtesy of Hermann D. Schubert, MD.)*

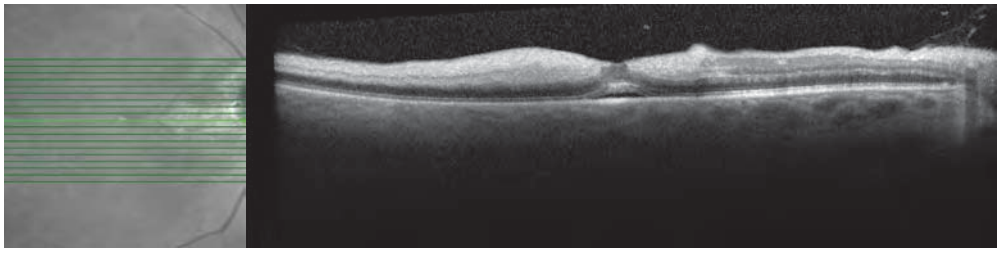

Figure 6-19 SD-OCT scan of a case of CRAO (similar to that seen in Figure 6-18) with cilioretinal artery sparing shows hyperreflectivity in the area of clinical opacification of the inner two-thirds of the retina in the affected areas *(X).* All retinal layers are identifiable in the area of retina perfused by the cilioretinal artery, adjacent to the optic nerve head. The foveal retina is spared from opacification, resulting in the appearance of a cherry-red spot on examination. Subfoveal fluid *(asterisk)* is variably present in these cases. *(Courtesy of Colin A. McCannel, MD.)*

With time, the central retinal artery reopens or recanalizes, and the retinal edema clears; however, the effect on visual acuity is usually permanent because the inner retina has been infarcted. In one study, 66% of eyes had final visual acuity worse than 20/400, and 18% of eyes had 20/40 or better. Most eyes in which visual acuity recovers to 20/40 or better have a patent cilioretinal artery. Vaso-occlusive vision loss to the level of no light perception is usually caused by choroidal vascular insufficiency from partial or complete ophthalmic artery occlusion or occlusions of the parent ciliary arteries in conjunction with occlusion of the central retinal artery (Fig 6-20). Studies in nonhuman primates have suggested that irreversible damage to the sensory retina begins after 90 minutes of complete CRAO. Nevertheless, clinical return of vision can occur in some instances even if the obstruction has persisted for many hours.

CRAO is most often caused by emboli originating anywhere between the heart and the ophthalmic artery or by atherosclerosis-related thrombosis occurring at the level of the lamina cribrosa. Emboli within the carotid distribution can cause transient ischemic attacks, amaurosis fugax, or both. Bright cholesterol emboli (Hollenhorst plaques), typically located at retinal artery bifurcations, suggest a carotid atheromatous origin and may be an indication for endarterectomy if accompanied by relevant symptoms and findings. Systemic etiologic considerations, such as those listed earlier in this chapter for BRAO, are important and require evaluation.

Giant cell arteritis (GCA) accounts for approximately 1%–2% of CRAO cases. When an embolus is not readily visible in an eye with CRAO, a thorough evaluation for GCA should be considered. The risk of GCA increases with advancing age, starting at 55 years. The erythrocyte sedimentation rate (ESR), C-reactive protein level, and fibrinogen levels, all of which are

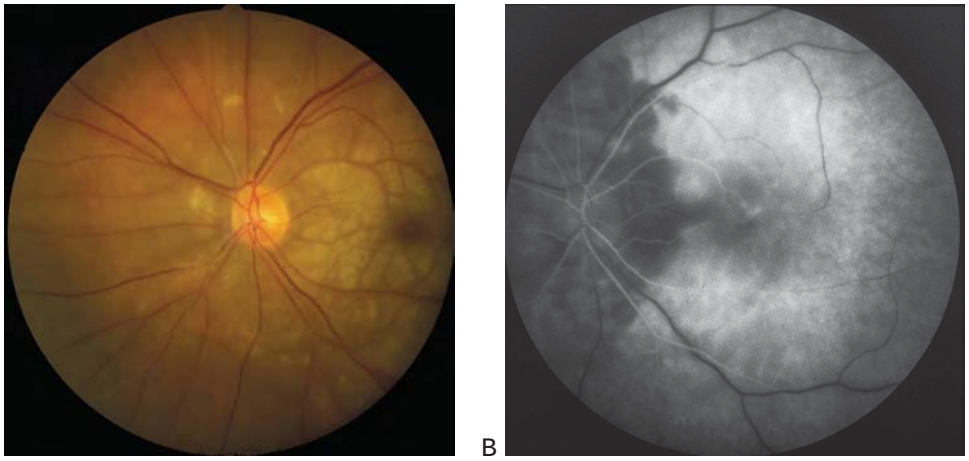

Figure 6-20 Central retinal and parent short ciliary artery occlusion. **A,** Fundus photograph of acute central retinal and short ciliary artery obstruction. Severe retinal opacification is present. The patient's VA was no light perception. **B,** Fluorescein angiography image taken 3 minutes after injection reveals hypofluorescence of the retinal vessels, the nasal choroid, and the optic nerve head, corresponding to an occlusion of the central retinal artery and nasal parent ciliary artery. Occlusion of the latter results in ischemia in the distribution of the short posterior ciliary arteries, with a vertical watershed of choroidal perfusion. *(Courtesy of Hermann D. Schubert, MD.)*

markers of inflammation, are usually elevated. A complete blood count may detect an elevated platelet count, which is suggestive of GCA; the blood count also aids in the interpretation of the ESR. If GCA is suspected, high-dose systemic corticosteroid therapy should be instituted promptly because the second eye can become involved by ischemia within hours to days after the first. In addition, a temporal artery biopsy should be performed within 14 days to confirm the diagnosis and determine the need for prolonged corticosteroid treatment. See BCSC Section 5, *Neuro-Ophthalmology,* for further discussion of GCA.

Ahn SJ, Woo SJ, Park KH, Jung C, Hong JH, Han MK. Retinal and choroidal changes and visual outcome in central retinal artery occlusion: an optical coherence tomography study. *Am J Ophthalmol.* 2015;159(4):667–676.

Atkins EJ, Bruce BB, Newman NJ, Biousse V. Translation of clinical studies to clinical practice: survey on the treatment of central retinal artery occlusion. *Am J Ophthalmol.* 2009;148(1):172–173.

Callizo J, Feltgen N, Pantenburg S, et al; European Assessment Group for Lysis in the Eye. Cardiovascular risk factors in central retinal artery occlusion: results of a prospective and standardized medical examination. *Ophthalmology.* 2015;122(9):1881–1888.

Falkenberry SM, Ip MS, Blodi BA, Gunther JB. Optical coherence tomography findings in central retinal artery occlusion. *Ophthalmic Surg Lasers Imaging.* 2006;37(6):502–505.

Park SJ, Choi NK, Yang BR, et al. Risk and risk periods for stroke and acute myocardial infarction in patients with central retinal artery occlusion. *Ophthalmology.* 2015;122(11):2336–2343.e2.

Management of CRAO

The most important step in initial management is identification of the underlying systemic etiologic factors and an *urgent* referral to an emergency department for a stroke workup. In 2011 and 2013, the National Stroke Association and the American Heart Association included "retinal cell death" in their consensus statement defining central nervous system infarction (stroke). The leading cause of death in patients with retinal arterial obstruction is cardiovascular disease, with an elevated risk of myocardial infarction within the first 7 days after onset of the obstruction. Studies have reported that as many as 78% of patients may have undiagnosed risk factors.

Patients should preferably undergo neuroimaging evaluation within 24 hours of symptom onset and be evaluated at an emergency department associated with a stroke center. Carotid ultrasonography is useful as a first-line screening test, but it depends on the availability of an experienced ultrasonographer and can image only the extracranial portion of the carotid tree. Computed tomography angiography or magnetic resonance angiography is therefore recommended for a more definitive imaging study.

In addition to a stroke workup, patients with isolated acute retinal ischemia should undergo brain imaging, ideally brain magnetic resonance imaging with diffusion-weighted imaging, analogous to the management of patients with acute cerebral ischemia. Multiple small cerebral infarctions are seen on diffusion-weighted magnetic resonance imaging of the brain in up to 31% of patients with acute RAO. The presence of these silent (asymptomatic) cerebral infarctions is associated with a higher chance of identifying an embolic cause for the acute retinal ischemia (Fig 6-21).

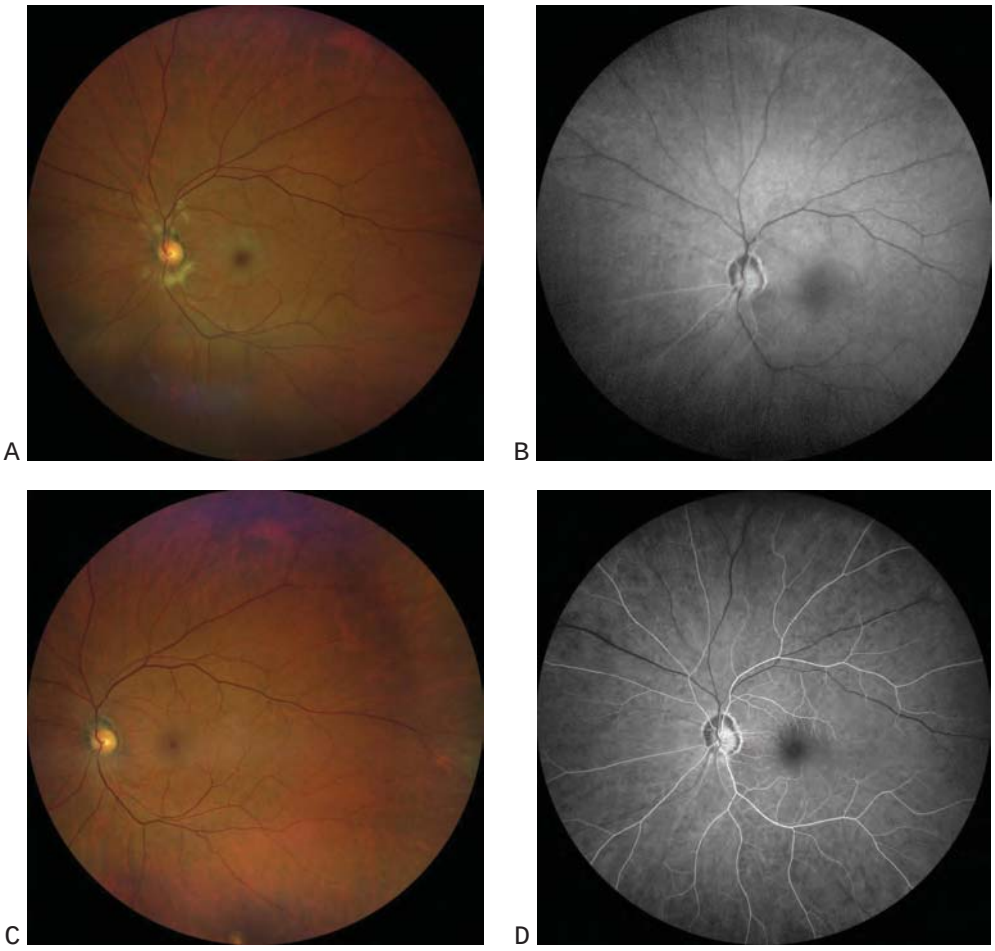

Figure 6-21 Acute retinal ischemia. This 64-year-old man with diabetes, hypertension, hyperlipidemia, and coronary artery disease presented with a 3-day history of a central blind spot in his left eye and VA of counting fingers. **A,** Fundus photograph shows parapapillary cotton-wool spots, macular whitening, and a cherry-red spot. **B,** Fluorescein angiography shows arterial filling beginning at 1 minute 19 seconds after dye injection. Stroke workup was performed immediately and revealed 90% carotid occlusion, which was treated with carotid endarterectomy (CEA). Three weeks after CEA, VA had improved to 20/40. **C,** There was resolution of retinal whitening and improvement in retinal perfusion. **D,** Dye appearance at 33 seconds after infusion demonstrates the improved perfusion. *(Courtesy of Franco M. Recchia, MD.)*

At present, there is no proven treatment for symptomatic RAO. Case reports and uncontrolled studies have suggested the utility of digital massage of the affected eye, anterior chamber paracentesis, vasodilation, breathing into a paper bag, carbogen therapy (a mixture of 95% oxygen and 5% carbon dioxide), topical IOP-lowering medications, hyperbaric oxygen, and transvitreal Nd:YAG embolysis. However, there are no level I data to support any specific therapy. Treatment with antifibrinolytic agents (typically, tissue plasminogen activator [tPA])

can be considered in select circumstances. In a recent white paper based on meta-analysis and literature review, the American Heart Association recommends the following:

- intravenous tPA for patients without systemic contraindication and who are evaluated within 4.5 hours of onset of visual symptoms; or
- intra-arterial tPA, through superselective catheterization of the ipsilateral ophthalmic artery, for patients who are not candidates for intravenous therapy and who are evaluated within 6 hours of onset of visual symptoms.

NVI develops in approximately 18% of eyes within 1–12 weeks after acute CRAO (mean interval, approximately 4 weeks). Treatment of NVI is highly effective in avoiding neovascular glaucoma. Full-scatter PRP results in regression of anterior segment neovascularization in approximately two-thirds of cases. Anti-VEGF therapy, either alone or in conjunction with PRP, is also effective. The current American Academy of Ophthalmology recommendations for acute management of RAO can be found at https://www.aao.org/education/preferred-practice-pattern/retinal-ophthalmic-artery-occlusions-ppp.

Patients in whom RAO is diagnosed incidentally as a chronic or remote event should still be evaluated for cerebrovascular disease and for modifiable vascular risk factors. However, unlike the procedures for acute RAO, such evaluation likely does not need to be immediate.

Biousse V, Nahab F, Newman NJ. Management of acute retinal ischemia: follow the guidelines! *Ophthalmology.* 2018;125(10):1597–1607.

Hayreh SS, Podhajsky PA, Zimmerman MB. Retinal artery occlusion: associated systemic and ophthalmic abnormalities. *Ophthalmology.* 2009;116(10):1928–1936.

Mac Grory B, Schrag M, Biousse V, et al. Management of central retinal artery occlusion: a scientific statement from the American Heart Association. *Stroke*. 2021;52(6):e282–e294. Published correction appears in *Stroke.* 2021;52(6):e309.

Cilioretinal Artery Occlusion

A distinct clinical entity is the occlusion of the cilioretinal artery, which arises from the short posterior ciliary vessels rather than the central retinal artery. These vessels, which are present in approximately 18%–32% of eyes, usually contribute to some portion of the macular circulation. Most commonly, their occlusion occurs in patients with a CRVO; it is postulated that the increased hydrostatic pressure associated with CRVO can reduce blood flow in the cilioretinal artery to the point of stagnation (Fig 6-22). When cilioretinal artery occlusion occurs in isolation, GCA should be considered.

Hayreh SS, Fraterrigo L, Jonas J. Central retinal vein occlusion associated with cilioretinal artery occlusion. *Retina.* 2008;28(4):581–594.

Ophthalmic Artery Occlusion

Ophthalmic artery occlusion is very rare. Clinically, the disorder typically produces vision loss to the level of light perception or no light perception because simultaneous nonperfusion of the choroid and retina results in ischemia of all retinal layers. Both the inner retina

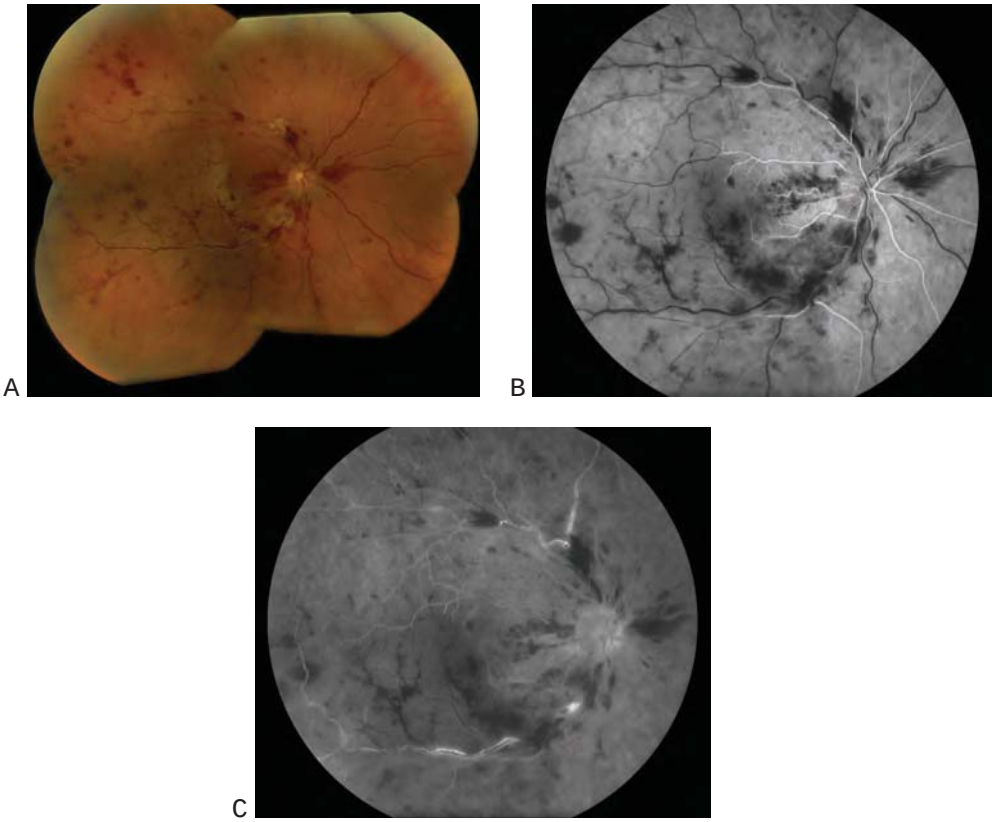

Figure 6-22 Cilioretinal artery occlusion. This 53-year-old woman presented with acutely decreased VA of 20/400 in her right eye. Medical history was notable for 2 first-trimester spontaneous abortions, and systemic workup ultimately revealed high levels of circulating anticardiolipin antibodies. **A,** Montage of color fundus photographs shows elements of both RVO (venous dilation and tortuosity, intraretinal hemorrhages at various layers, and cotton-wool spots) and cilioretinal artery occlusion (whitening in the temporal macula). **B,** Fluorescein angiography in the early arteriovenous phase shows multiple areas of arterial occlusion and peripheral nonperfusion. Note that in this case, the occlusions do *not* occur at arteriolar bifurcations, as would be expected in embolic occlusive disease. **C,** Angiogram taken in the late recirculation phase shows staining of the retinal veins, persistent arteriolar occlusion (notably, in branches of the inferotemporal arcade), and leakage consistent with macular edema. *(Courtesy of Franco M. Recchia, MD.)*

and outer retina become opacified from the infarction; thus, a cherry-red spot may not be present because there is a lack of contrast between the foveal and perifoveal retina.

Ophthalmic artery occlusion may be caused by internal carotid artery dissection, orbital mucormycosis, or embolization. A growing number of ophthalmic artery occlusions caused by cosmetic facial-filler injections, particularly into the periocular and brow area, have been reported as the popularity of such procedures has increased (Fig 6-23). In autopsy studies of patients who died during active GCA, up to 76% had some degree of vasculitis affecting the ophthalmic artery; clinically, however, ophthalmic artery occlusion is rare in GCA.

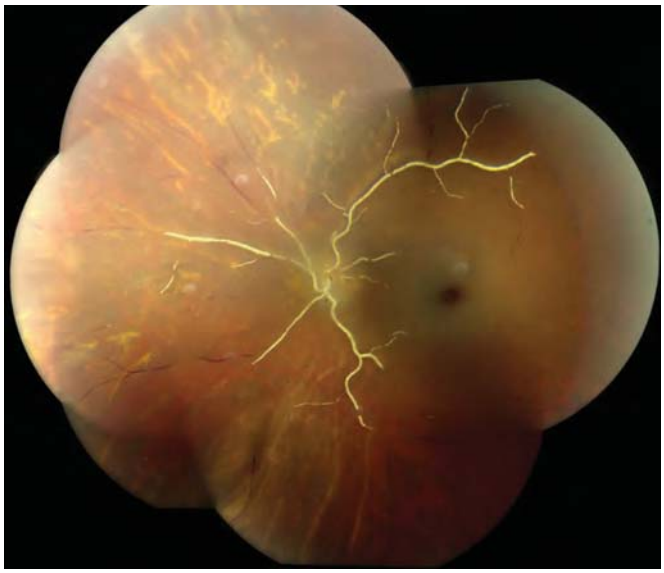

Figure 6-23 Ophthalmic artery occlusion. Fundus photograph montage of the left eye of a 44-year-old woman after ipsilateral injection of synthetic calcium hydroxyapatite gel into her left lateral lower eyelid for cosmetic purposes. Sudden loss of vision ensued to the level of no light perception. An ophthalmic artery occlusion occurred from presumed retrograde flow of the cosmetic filler into the ophthalmic artery by way of anastomotic arteries in the orbit bridging the internal and external carotid circulations. The white filler material is visible in the retinal circulation and choroidal blood vessels. *(Courtesy of Kathryn Sun, MD, PhD; Thomas F. Essman, MD; and Brenda Schoenauer, CDOS.)*

Paracentral Acute Middle Maculopathy

Paracentral acute middle maculopathy (PAMM) refers to macular lesions with changes in the inner nuclear layer on SD-OCT. The primary etiology in PAMM may be ischemia of the deep capillary system, which is responsible for blood supply to the middle retina.

The typical presentation is acute onset of diminished central visual acuity (although Snellen measurement of 20/20 is possible) or paracentral scotoma. Ophthalmoscopically, the lesions may appear only as subtle parafoveal gray-white spots or wedges. Compared with cotton-wool spots, the retinal whitening associated with PAMM lesions is more distinct, duller gray-white, less opaque, and deeper in the retina; also, it is not distributed along the NFL. However, these lesions are evanescent and may resolve before clinical examination takes place. In such cases, the characteristic hyperreflective bands on SD-OCT should still be detectable (Fig 6-24). Over time, PAMM lesions typically resolve with thinning of the inner nuclear layer, resulting in persistent paracentral scotomata.

PAMM is primarily a disease of retinal ischemia and often seen in association with retinal vascular occlusion. Evaluation in suspected cases includes imaging and systemic workup for cardiovascular risk factors and sickle cell disease.

Chu S, Nesper PL, Soetikno BT, Bakri SJ, Fawzi AA. Projection-resolved OCT angiography of microvascular changes in paracentral acute middle maculopathy and acute macular neuroretinopathy. *Invest Ophthalmol Vis Sci.* 2018;59(7):2913–2922.

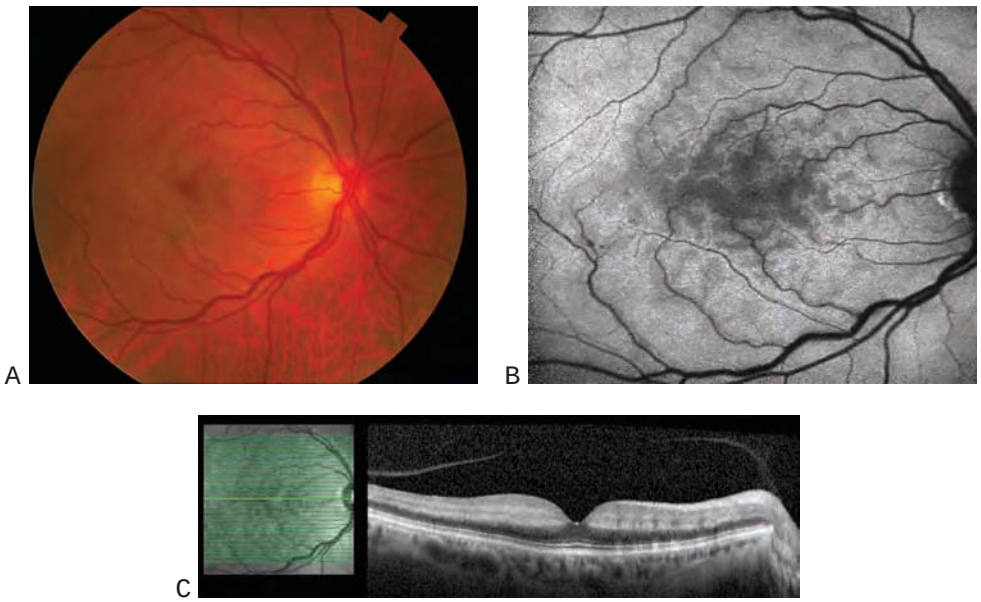

Figure 6-24 Paracentral acute middle maculopathy (PAMM). A 57-year-old woman presented with acute visual defects that she described as "lacy patterns" in her vision. **A,** Fundus photograph shows ill-defined grayish lesions in the macula, corresponding to intraretinal opacification. **B,** Fundus autofluorescence highlights the blocking defect of the perivenular retinal opacification. **C,** SD-OCT shows hyperreflectivity of the inner nuclear layer, more patchy nasally and more continuous temporally. These clinical and imaging findings are consistent with PAMM. *(Courtesy of Amani Fawzi, MD.)*

Arterial Macroaneurysms

Retinal arterial macroaneurysms are acquired ectasias of the first 3 orders of retinal arterioles. Large macroaneurysms can actually traverse the full thickness of the retina. Vision loss may occur from embolic or thrombotic occlusion of the end arteriole *(white infarct)* or from hemorrhage in any retinal layer. Other retinal findings may include capillary telangiectasia and remodeling, as well as retinal edema and exudate involving the macula (Fig 6-25). Often, there are multiple arterial macroaneurysms, although only 10% of cases are bilateral. Arterial macroaneurysms are associated with systemic arterial hypertension in approximately two-thirds of cases and may occur in the area of previous vascular occlusions. Systemic blood pressure should be measured at the time of diagnosis, and the patient should be referred for further evaluation.

Typically, the macroaneurysm closes and scleroses spontaneously, with accompanying resorption of related hemorrhage. Reopening of the macroaneurysm and rebleeding are rare. Thus, initial management is usually observation. Laser photocoagulation treatment may be considered if increasing edema in the macula threatens central vision. In most instances, closure can be achieved with moderate-intensity laser treatment of the retina, performed immediately adjacent to the macroaneurysm, using 2–3 rows of large-spot-size (200–500 μm) applications. Some specialists prefer direct treatment. Caution

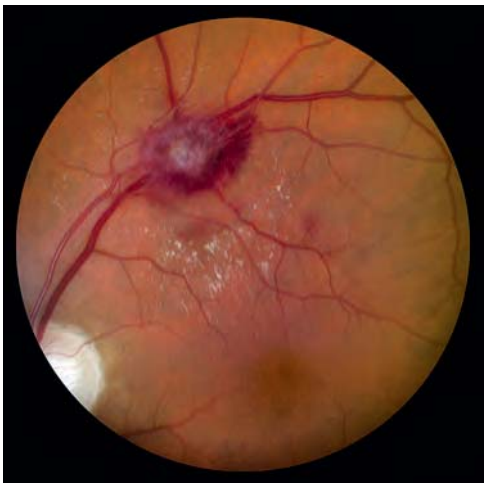

Figure 6-25 Fundus photograph of a retinal arterial macroaneurysm with some exudate in the superior macula, resulting from leakage of the lesion, and mild hemorrhage. *(Courtesy of Colin A. McCannel, MD.)*

should be used when treating macroaneurysms that occur in macular arterioles because thrombosis with retinal arterial obstruction distal to the macroaneurysm may result.

Lee EK, Woo SJ, Ahn J, Park KH. Morphologic characteristics of retinal arterial macroaneurysm and its regression pattern on spectral-domain optical coherence tomography. *Retina.* 2011;31(10):2095–2101.

Pitkänen L, Tommila P, Kaarniranta K, Jääskeläinen JE, Kinnunen K. Retinal arterial macroaneurysms. *Acta Ophthalmol.* 2014;92(2):101–104.