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REVIEW ARTICLE

Retinal vein thrombosis: pathogenesis and management

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Summary. Retinal vein occlusion (RVO) is the most common retinal vascular disease after diabetic retinopathy. Owing to its multifactorial nature, however, management of this condition remains a challenge. Of the two main types of RVO, branch retinal vein occlusion (BRVO) is more prevalent than central retinal vein occlusion (CRVO). Most patients develop the disease at an elderly age, and more than half of them have associated systemic disorders (e.g. hypertension, hyperlipidemia and/or diabetes mellitus). There is no evidence to suggest routine testing for heritable thrombophilias in patients with RVO. The main cause of the visual impairment is macular edema, while neovascularization of the retina and optic disc are the most serious complications leading to vitreous hemorrhage, retinal detachment and neovascular glaucoma. Macular grid laser photocoagulation is an effective treatment for macular edema in patients with BRVO and a visual acuity of 20/40 or less. Other treatment options for reducing the edema are intravitreal steroids, anti-VEGF drugs and vitrectomy. The recently introduced intravitreal application of steroids and anti-VEGF drugs may prove to be a better approach for improving visual acuity. Finally, scatter panretinal laserphotocoagulation can effectively treat neovascularization and its secondary complications.

Keywords: pathogenesis, prognosis, retinal vein occlusion, treatment.

Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disease after diabetic retinopathy. Of the two main types of RVO, central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), the latter is more prevalent. BRVO, however, typically occurs at an arteriovenous crossing, where, in most cases, the artery passes anterior to the vein. Another type of RVO is hemi-vein occlusion, presenting as occlusion of only one trunk of the central retinal vein [1].

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This review focuses on the pathogenesis of RVO, with particular emphasis on the association with cardiovascular risk factors and thrombophilic disorders. Key ocular signs and treatment management are also outlined.

Classification of different types of RVO

Most of the published studies divide RVO into two groups: CRVO and BRVO. A further type called hemi-vein occlusion was previously diagnosed as BRVO, and in some studies still is [2]. In most of the current studies hemi-CRVO is defined as a particular form of CRVO [1]. Hayreh [3] describes three primary types of RVO, each of which comprises two sub-types, making a total of six different forms of RVO.

1 CRVO is divided into two types: non-ischemic and ischemic CRVO. These two forms have different pathogenesis, clinical features, prognosis and management.
2 Hemi-CRVO, like CRVO, is of two types: ischemic and non-ischemic.
3 BRVO is divided, depending on which venous branch is affected, into two forms: major BRVO and macular BRVO.

In the past several different eponyms, including papillophlebitis, mild retinal and papillary vasculitis, and benign retinal vasculitis have been decribed in the literature. These resulted mostly from the misconception that RVO does not develop in young persons [3]. The differentiation between different types of RVO and so-called 'retinal venous stasis' is in some studies confusing. Some authors described venous stasis as a presence of hyperviscosity syndrome in Waldenstrom's macroglobulinemia [4]. In other studies a secondary RVO due to increased venous pressure in patients with carotico-cavernous sinus fistula [5] or in patients with optic neuritis [6] has been reported.

In the differential diagnosis, ocular ischemic syndrome, diabetic and radiation retinopathy and venous occlusion due to systemic vasculitis have to be excluded.

Epidemiology

The most recently published study summarizing the prevalence of RVO as reported in studies from the United States, Europe, Asia and Australia has shown an age- and sex-standardized prevalence of 5.20 per 1000 (95% confidence

interval [CI] 4.40–5.99) for any form of RVO [7]. This study combined data regarding 68 751 individuals from 15 studies, with participants' ages ranging from 30 to 101 years. The prevalence of BRVO was 4.42 per 1000 (95% CI 3.65–5.19) and of CRVO was 0.80 per 1000 (95% CI 0.61–0.99) [7]. Prevalence varied by ethnicity and increased with age, but did not differ by gender. Prevalence of CRVO was lower than BRVO in all ethnic populations.

Hayreh *et al*. [1] showed that the probability of developing a second episode of occlusion in the other eye within 4 years is about 7% [1].

Pathogenesis

The exact pathogenesis of RVO remains unclear. The condition may be due to a combination of three systemic changes known as Virchow's triad: hemodynamic changes (venous stasis), degenerative changes of the vessel wall and blood hypercoagulability [8].

Hyperopia and glaucoma have been reported as local ophthalmic risk factors [9].

There are differences in the role of each single risk factor in pathogenesis of CRVO and BRVO. For example, hypermetropia, arteriosclerosis and high blood pressure are more common in BRVO, whereas raised intraocular pressure is more common in CRVO [10]. This demonstrates that CRVO and BRVO are different entities with different prognosis and management [3]. Not infrequently, studies in the literature consider retinal venous occlusions as a single clinical entity; this is a limitation.

Systemic risk factors

RVO presents mainly in older individuals, over 50% of cases occurring in persons older than 65 [1]. There is strong evidence from large studies of increased risk of this disease in patients with systemic arteriosclerotic vascular disease [11–16]. Table 1 shows the most important systemic risk factors.

An increased risk of RVO has been shown in patients with hypertension, diabetes mellitus, dyslipidemia [11–16], high body mass index and smoking [13]. Others risk factors are different forms of vasculitis, neoplasia and drug intake (Table 1) [8]. The condition can also occur in younger persons but the association with systemic cardiovascular disease is less common in these cases [17]. The exact pathogenesis in younger patients is poorly understood, with some authors suggesting the possible greater role of thrombophilia [18,19].

Table 1 Systemic risk factors associated with retinal vein occlusion

Hypertension, hyperlipidemia, diabetes mellitus
Atherosclerotic vascular disease: coronary artery disease, high body mass index, smoking
Vasculitis: systemic lupus erythematosus, sarcoid, syphilis
Neoplasia: polycythemia rubra vera, multiple myeloma, leukemia
Drugs: oral contraceptives, diuretics

O'Mahoney *et al*. [20] performed a meta-analysis of 21 studies on the correlation between RVO and systemic cardiovascular risk factors. The prevalence of systemic hypertension was found to be 63.6% in patients with RVO compared with 36.2% in controls. This was equivalent to an odds ratio (OR) of 3.5 (95% CI 2.5–5.1). For both types of RVO a significant association was found between hypertension and CRVO (OR, 3.8; 95% CI 1.9–7.4) and BRVO (OR 3.0; 95% CI 2.0–4.4). For any form of RVO, hyperlipidemia was more than twice as common among patients (35.1%) than controls (16.7%), equivalent to an OR of 2.5 (95% CI 1.7–3.7). Similar significant risk estimates were seen for persons with CRVO and BRVO.

Diabetes mellitus was slightly more prevalent among patients with any form of RVO (14.6%) than unaffected controls (11.1%), equivalent to an OR of 1.5 (95% CI 1.1–2.0). Although CRVO (OR 2.0; 95% CI 1.2–3.4) was significantly associated with diabetes mellitus, BRVO (OR 1.1; 95% CI 0.8–1.5) was not [20].

Cheung *et al*. [16] investigated the prevalence of RVO and its association with cardiovascular, inflammatory and hematologic risk factors in a multiethnic cohort (whites, blacks, Hispanics and Chinese). They found a similar prevalence of RVO across different racial and ethnic groups. Further, the results showed significant association between RVO and older age (OR 1.34; 95% CI 1.00–1.81, per decade increase) and renal dysfunction (OR 1.85; 95% CI 1.01–3.39). No significant association, however, was reported with direct measures of subclinical atherosclerosis (e.g. carotid intima media thickness and coronary artery calcium scores) or endothelial dysfunction (soluble intercellular adhesion molecule-1) or markers of inflammation (C reactive protein, interleukin-6) or coagulation (D-dimer) [16].

Degenerative changes of vessel wall

As mentioned above, CRVO typically occurs in the area of the lamina cribrosa. In this site the vein and artery share a common adventitial sheath. For this reason, mechanical narrowing of the lumen of the thin-walled vein due to an arteriosclerosis-related rigid and hyperplasic thick arterial wall has been assumed to play a role in CRVO pathogenesis.

The typical localization of BRVO is an arteriovenous (AV) crossing. The histological changes in the vessel wall at the A/V crossing have been investigated in several studies [21,22]. Jefferies *et al*. [21], however, showed that there was no histological evidence for the expected venous compression at the crossing. Seitz [22] described the clinical-histological sequelae in one eye with BRVO a few hours after onset. There was no blood-thrombus obliterating the venous lumen at the A/V crossing but the endothelium was damaged. Mechanical compression of the vein through the rigid artery in the A/V crossing may result in turbulent blood flow, producing injury to venous endothelium that leads to occlusion of the vein [21,23,24].

Hematological disorders

Some studies have revealed an association between RVO and hyperviscosity due to high hemotocrit [25,26]. Higher blood viscosity increases erythrocyte aggregation under conditions of low blood flow [25]. Improvement of the microcirculation through reduced blood viscosity is the mechanism of action of hemodilution, which is discussed below.

The literature on the association between thrombophilic factors and RVO is very inconsistent.

One major reason is the limited number of investigated patients. No single currently published study has achieved the required sample size for detecting the association between RVO and thrombophilia with adequate statistical power [19]. To date no multicentre prospective study has been completed. Hence, to clarify the role of thrombophilic disorders in patients with RVO, a meta-analysis of all published studies remains the only option. Five meta-analyses investigating the association between RVO and thrombophilia have been published to date [19,26–30]. Table 2 presents the thrombophilic disorders that are suspected to be risk factors for RVO.

In several studies and three meta-analyses, a statistically significant association between RVO and increased serum levels of homocysteine (Hcy) has been found [27–29]. Hcy appears to have a deleterious effect on vascular endothelium and may induce increased platelet aggregation and thrombosis. Hyperhomocysteinemia may be caused by dietary habits, prescription medicines or mutations in genes encoding enzymes affecting homocysteine metabolism [31]. No association between RVO and the gene mutation (C677T) in the enzyme methylentetrahydrofolate reductase (MTHFR), causing impaired activity leading to hyperhomocysteinemia, has been found [28,29]. Given the heterogeneity of studies and the risk of publication bias, no recommendation can be made with regard to routine investigation and treatment of elevated Hcy in the setting of RVO. There is no evidence to suggest routine testing for the MTHFR C677T genotype in patients with RVO [29].

The most frequently analyzed thrombophilic disorder in patients with RVO is factor V Leiden (FV Leiden). Two published meta-analyses [19,27] have shown a moderately higher prevalence of FV Leiden in RVO patients than in controls (OR 1.49; 95% CI 0.62–3.57 [27]; and OR 1.66; 95% CI 1.19–2.32). There was no association with prothrombin gene mutation, or with protein C and S or antithrombin deficiency [30].

Some authors hypothesize that the role of thrombophilia is more important in younger patients [32–34] but the definition of 'younger patients' is not clear and varies in the literature from 45 to 60 years. In other studies no differences in the prevalence of thrombophilic disorders have been reported for patients of different ages [35,36].

Rehak *et al*. [37] compared the prevalence of thrombophilia in RVO according to systemic risk factors and age. The results suggest that the role of thrombophilia is potentially more important in patients without cardiovascular risk factors. The correlation with younger age could not be confirmed in this study.

Antiphospholipid syndrome (APS) is an acquired thrombophilia and autoimmune disease characterized by antiphospholipid antibodies and at least one clinical criterion, the most common being venous or arterial thrombosis or recurrent fetal loss [38,39]. The results of the most current meta-analysis [30] have shown a significantly higher prevalence of APS in patients with RVO compared with controls (risk difference = 14.6%; 95% CI 5.1%–24.1%). Lupus anticoagulants and increased level of anticardiolipin antibodies are both associated with RVO [30].

Due to high risk of recurrent thromboembolism, APS is a potentially life threatening disorder. Therefore, APS is treated using vitamin K antagonists in the long term [39]. The role of antiphospholipid antibodies in the etiology of RVO and the impact of anticoagulation in patients with RVO positive for antiphospholipid antibodies has to be clarified in further studies before the recommendation for screening for APS in RVO patients can be made.

Several authors have recommended screening for thrombophilia in younger patients or in patients without systemic risk factors [8,19,33,34,37]. Diagnosis of thrombophilia does not alter the management of RVO. There is only weak evidence for use of anticoagulation or thrombolysis in patients with RVO and this kind of treatment is not generally recommended [40]. To date, the benefit of anticoagulation for visual prognosis in RVO patients positive for thrombophilic disorders has not been investigated. Given the lack of therapeutic consequences, routine screening for thrombophilia in patients with RVO is not reasonable.

Table 2 Most important thrombophilic disorders discussed in the etiology of retinal vein occlusion

Anti-phospholipid syndrome (APS)
Hyperhomocysteinemia
Resistance to activated protein C (factor V Leiden mutation)
Protein C and protein S deficiency
Deficiency of antithrombin
Prothrombin gene mutation (G20210A)

Symptoms and clinical signs

Patients with CRVO usually present with sudden, painless, unilateral loss of vision. However, patients with BRVO can be asymptomatic, especially if BRVO is in nasal retinal quadrants, or they may present with blurred vision, usually involving the sector of visual field corresponding to the area of the occluded venous branch. Generally, macular edema is the most important cause of reduced vision in patients with RVO [41].

The fundus appearance in RVO can vary according to severity of the venous occlusion. Table 3 presents clinical findings typical for the acute and late stages of RVO.

Characteristic clinical features (Fig. 1) are flame-shaped, dot or blot retinal hemorrhages, and dilated tortuous veins with or without optic disc edema. The breakdown of the blood-retina barrier leads to leakage of plasma into the surrounding retina.

Table 3 Clinical findings characteristic for acute and late stages of retinal vein occlusion (RVO)

Acute RVO	Chronic RVO
Intraretinal hemorrhages	Cystoid macular edema
Hard exudates	Atrophy of retinal pigment epithelium
Cotton-wool spots	Epiretinal membrane
Optic disc edema	Shunt vessels
Macular edema	Neovascularization of retina and/or optic disc and/or rubeosis iridis
Dilated, tortuous retinal veins	Late complications of neovascularizations: vitreous hemorrhages retinal detachment neovascular glaucoma

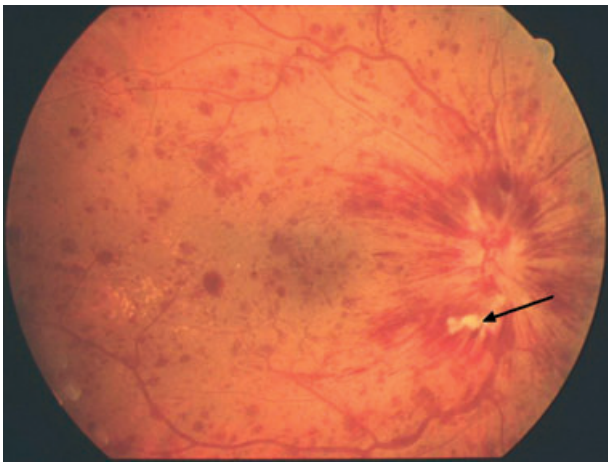

Fig. 1. Clinical features of central retinal vein occlusion showing intraretinal hemorrhages, dilated tortuous veins and cotton-wool spots (arrow).

Yellow lipid deposits localized at the junction of the normal and edematous retina are called hard exudates. Cotton-wool spots are caused by ischemia of the nerve axons. In CRVO the retinal hemorrhages and exudates are distributed throughout all four quadrants (Fig. 1). BRVO occurs more frequently in the superotemporal (66% of cases) and inferotemporal (22–43% of cases) quadrants [42].

Fluorescein angiography (FAG) is useful for confirming the venous occlusion caused by delayed filling of the involved vein. FAG can also detect the retinal non-perfusion zones in the occluded area (Fig. 2), although the ischemic areas are often obscured by the intraretinal hemorrhages. The enlarged foveal avascular zone is a sign of macular ischemia. FAG can distinguish neovascularization from venous collaterals (shunt vessels), which typically occur in the chronic stage of RVO as well.

According to the FAG findings, CRVO is divided into the two following types [3,41]:

1 *non-ischemic CRVO* (also called venous stasis retinopathy), which accounts for about 75% of all CRVO patients and is characterized by the appearance of areas of retinal ischemia smaller than 10 areas of the optic disc; and

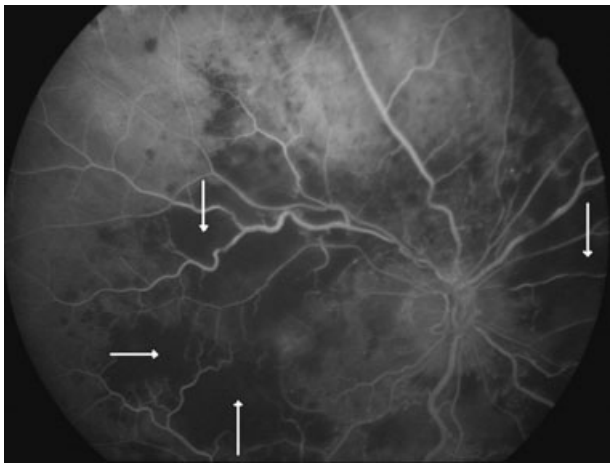

Fig. 2. Fluorescein angiography findings in patients with ischemic central retinal vein occlusion presenting areas of capillary non-perfusion (dark areas marked with arrows).

2 *ischemic CRVO* (also called hemorrhagic retinopathy), which is defined by the appearance of neovascularization on the surface of the iris (rubeosis iridis) or FAG-confirmed areas of retinal ischemia larger than 10 areas of the optic disc.

To characterize the form of the CRVO, the FAG should be carried out in the diagnostic setting and also according to the progression of retinal hemorrhages or suspected neovascularization. In patients with BRVO without suspected neovascularization, FAG is indicated in cases with macular edema longer than 3 months and a visual acuity* (VA) of 20/40 or less. In these patients grid photocoagulation is recommended, except for patients with macular ischemia.

Another useful investigation to differentiate ischemic and non-ischemic CRVO is a flicker ERG (electroretinogram) [43].

Currently, exact measurement of macular edema is available using optical coherence tomography (OCT). The latest generation of spectral-domain OCT enables a very accurate measurement of retinal volume in the macular region (retinal map) and exact remeasurement of the same area in follow-up visits. This information is superior to the FAG findings and facilitates the evaluation of treatment response.

Visual prognosis and complications of RVO

RVO is a sight-threatening disease. Visual loss may result from chronic macular edema and macular ischemia. Secondary complications (vitreous hemorrhages, retinal detachment and/or neovascular glaucoma) are due to retinal neovascularization [41]. As the natural history and prognosis vary considerably, CRVO and BRVO will be discussed separately.

In general, BRVO has a good prognosis; 50–60% of eyes have been reported to have a final visual acuity (VA) of 20/40

*The numerator refers to the distance in feet from which a person can reliably distinguish a pair of objects. The denominator is the distance from which an 'average' person would be able to distinguish these objects.

or better even without any treatment [44]. A poor visual prognosis has been reported in patients with chronic macular edema or macular ischemia [41,45]. Generally, it is difficult to determine visual prognosis for patients with BRVO in the acute phase of the disease. Rehak and Rehak [46] analyzed the results of published studies reporting on visual outcomes in patients with BRVO without and with laser treatment.

The results showed that in the group of eyes with an initial VA 20/50 or better, no eye without treatment and only 13% of eyes with laser treatment had a final VA of 20/200 or worse, whereas in the group of eyes with an initial VA 20/200 or worse, 83% and 50% of eyes (respectively) had a final VA of 20/200. The authors conclude that cases of BRVO with an initial VA of 20/200 or worse have a statistically significant poorer visual prognosis than those with an initial VA of 20/50 or better [46]. Five disk areas or more of capillary non-perfusion is a major risk for the development of neovascularization, which occurs in $<25\%$ of cases with major BRVO [47].

Ota *et al*. [48] suggested that the status of integrity of the photoreceptor layer in the fovea detected by OCT might be used for the prediction of visual outcome in patients with BRVO.

The visual prognosis for patients with ischemic and non-ischemic CRVO differs. Fifty-one per cent of eyes with non-ischemic CRVO gained a VA 20/40 or better without any treatment. The reduced baseline VA and extent of initial retinal ischemia correlated strongly with poor final VA [49]. Conversion of non-ischemic into ischemic CRVO has been observed in 10–33% of primary non-ischemic cases [49–51]. Ischemic CRVO has a worse prognosis than the non-ischemic type; 73–93% of patients had a final VA of 20/200 or worse [49,52].

The late complications of all types of RVO are retinal neovascularization, traction retinal detachment, rubeosis iridis and neovascular glaucoma. There is a higher risk of developing rubeosis iridis and associated neovascular glaucoma in patients with ischemic CRVO (more than 60% of patients) [52].

Treatment

A number of treatment modalities have been advocated for the management of RVO. To date, however, no causal treatment has been shown in large randomized studies to be effective. For this reason, current treatments focus on the sequelae of RVO, such as macular edema and retinal neovascularization. Most studies that have investigated the interventions for RVO suffer from methodological limitations (e.g. insufficient statistical power, absence of a control group, and inclusion of patients with different types of RVO that have a different natural history). Most of the available studies have a retrospective design or describe small case series. All these factors are responsible for very limited evidence and result in confusion in the clinical recommendations. In future, further randomized clinical trials with strict stratification of patient inclusion criteria are required.

Platelet inhibitor therapy, inhibition of erythrocyte aggregations, fibrinolytic therapy and isovolemic hemodilution

Treatment with oral acetylsalicylic acid and subcutaneous heparin have not proved to be effective in CRVO, while in BRVO no randomized clinical trials have been published [53,54]. Thrombolysis using recombinant tissue plasminogen activator (rt-PA) intravitreally or directly into the retinal vein has been demonstrated to improve VA in patients with CRVO [55], but owing to the high prevalence of local adverse events, there is no general acceptance of this technique [40,56]. Intravenous thrombolysis with low-dose rt-PA and concomitant heparinization significantly improved the final VA in patients with acute stage CRVO (within 11 days before treatment) compared with hemodilution [57]. This positive effect could not be observed in patients with BRVO.

Troxerutin and ticlopidine inhibit erythrocyte and platelet aggregation, respectively, thus reducing blood viscosity and increasing the retinal microcirculation [58,59]. Both of these substances improved the visual outcomes in patients with acute stage RVO [58] but the evidence for this treatment is limited [54].

Isovolemic hemodilution using hydroxyethylstarch or dextran has been investigated in several clinical trials but due to large variation in study protocols the evidence supporting their use remains incomplete [40,53,54].

Laser photocoagulation

Laser treatment is an established method for use in patients with RVO. Two main laser techniques can be used: macular grid photocoagulation for treatment of macular edema, and panretinal (scatter) laser photocoagulation for treatment of retinal and/or disc neovascularization. The results of prospective, randomized clinical trials evaluating the efficacy of these techniques over almost 20 years represent to date the highest level of evidence in relation to treatment of RVO [53,54].

Laser treatment in BRVO

The Branch Vein Occlusion Study [47] demonstrated that grid photocoagulation is an effective treatment for reducing macular edema and improving VA in patients with BRVO.

In this study, only eyes with recent BRVO, macular edema without ischemia, resolved foveal hemorrhage, a VA 20/40 or worse and no other ocular co-morbidities were included. After a 3-year follow-up, 65% of treated eyes improved by two or more lines from baseline, as opposed to 37% of untreated eyes. Grid laser photocoagulation is thus recommended for eyes with a VA 20/40 or worse and a BRVO of 3 months duration if fluorescein angiography reveals macular edema as the cause of vision loss without foveal hemorrhage or macular ischemia. The same study recommended performing peripheral scatter photocoagulation of the ischemic retina if there is retinal or disc neovascularization. Further, the study also demonstrated that, if all eyes with large retinal non-perfusion were treated, 64% of

these patients would never develop neovascularization. Therefore waiting is generally advocated until neovascularization actually develops before scatter photocoagulation is considered [47].

Laser treatment in CRVO

The Central Vein Occlusion Study [60,61] evaluated the effectiveness of grid laser photocoagulation for improving VA in eyes with macular edema and a VA 20/50 or worse. Although there was a large reduction in macular edema on fluorescein angiogram, no difference in final VA has been shown between treated and untreated eyes (final VA 20/200 and 20/160 respectively) [61].

The study also compared the efficacy of prophylactic panretinal photocoagulation in eyes with ischemic CRVO with that of frequent observation [60]. Untreated eyes developing neovascularization were treated with panretinal photocoagulation and previously treated eyes underwent additional panretinal photocoagulation. Neovascularization developed in 20% of prophylactically treated eyes and 35% of untreated eyes but the difference was not statistically significant. Therefore, there is no evidence for the prophylactic panretinal photocoagulation in ischemic CRVO and these eyes should be only observed. The examination of chamber angle (gonioscopy) and dilated fundus examination should be performed in the first 6 months every 4 weeks and if neovascularizations are detected the panretinal photocoagulation is indicated [60].

Surgical treatment

Surgical techniques decompress the retinal vein in the area of the occlusion. In radial optic neurotomy (RON) an incision of the lamina cribrosa at the edge of the optic nerve is made and the pressure on the central vein is relieved. Sheathotomy, a technique for BRVO, creates an incision in the adventitial sheath at the point of A/V crossing and separates the vein from the overlying artery. In both of these techniques the principal step is a pars plana vitrectomy. Even though the data are equivocal, overall, the majority of the reports have suggested that these treatments improve VA [53,54]. However, some studies comparing vitrectomy alone with vitrectomy combined with sheathotomy and/or RON have pointed out the absence of any difference in clinical outcome [62–64]. It is suggested that the key role in this surgery is played by simple vitrectomy [63,64] and possible mechanisms of action include improved retinal oxygenation, and removal of vitreomacular traction and cytokines responsible for the vascular permeability [63]. Overall, given the only moderate visual outcome and possible sight-threatening complications, surgical techniques are not generally recommended.

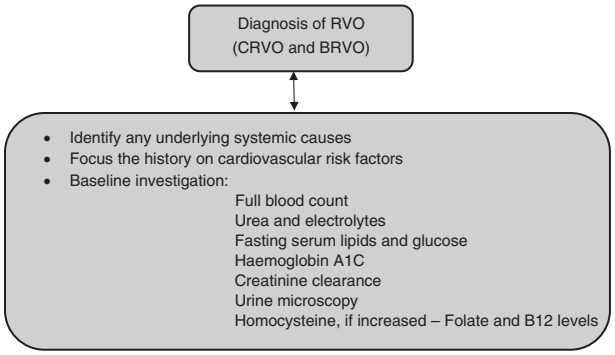

Chart 1 Algorithm of investigations in patients with retinal vein occlusion.

Intravitreal application of steroids and anti-VEGF drugs

Intravitreal drug application is a treatment option for macular edema associated with RVO that targets the disease at the causal molecular level. A main mechanism of edema formation is breakdown of the blood-retinal barrier formed by vascular endothelial and pigment epithelial cells [65]. Further, the retinal ischemia is one of the most important upregulators of vascular endothelial growth factor (VEGF) and other inflammatory factors (e.g. interleukin-1 or prostaglandins) that increase vascular permeability [66]. Dysfunctional fluid clearance from the retinal tissue may also contribute to the development of retinal edema [67]. The mechanism of action of steroids is multifactoral and not completely understood. Theories range from a non-specific anti-inflammatory effect leading to suppression of VEGF and other inflammatory factors to providing a stabilizing influence on the retinal vasculature by increasing the tight junctions of the retinal capillary endothelium [68].

Corticosteroids

Intravitreal triamcinolone acetonide (IVTA) has been shown to successfully decrease macular edema and improve VA in both CRVO and BRVO but the efficacy is greatest following the first injection and tends to diminish after repeated injections. However, several adverse side-effects, including elevation in intraocular pressure or cataract formation, have been reported [69–71]. To date, the largest randomized published study, SCORE (Standard Care vs. Corticosteroid for Retinal Vein Occlusion) [72], compared the efficacy and safety of 1- and 4-mg doses of triamcinolone with standard care (grid photocoagulation) in eyes with BRVO. No significant difference was identified in terms of final VA between the laser group and triamcinolone groups; however, the rate of adverse events (elevated intraocular pressure and cataract) was highest in the group treated with 4 mg of triamcinolone. For these reasons, grid photocoagulation should remain the standard technique for patients with BRVO [72]. A biodegradable dexamethasone implant (Ozurdex®; Allergan Inc., Irvine, CA, USA) that delivers the drug to the posterior segment for a period of 3–4 months has also shown promising results in the treatment of macular edema [73].

Anti-VEGF drugs

Intravitreal injection of anti-VEGF drugs (bevacizumab, ranibizumab or pegaptanib) is the most recently used treatment

Table 4 Summary of clinical recommendation for patients with central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO)

Intervention	CRVO	BRVO
Erythrocyte and platelet anti-aggregating therapy	Routine use of ticlopidine and troxerutine to improve VA or prevent neovascularization is not recommended	
Fibrinolysis	Routine use is not recommended. Limited evidence for intravenous application of low-dose rt-PA and concomitant heparinization in patients with acute stage CRVO (first 11 days)	Routine use is not recommended
Isovolemic hemodilution	Routine use of hemodilution to improve VA or prevent neovascularization is not recommended	
Grid laser photocoagulation	For treatment of macular edema due to CRVO is not recommended	Indicated in patients with macular edema and VA 20/40 or worse of 3 months duration (not recommended in cases with macular ischemia)
Scatter laser photocoagulation	Prophylactic treatment in patients without neovascularization is not recommended if gonioscopy and dilated fundus examination can be performed every 4 weeks. In cases with neovascularizations should be performed promptly to avoid secondary complications	Recommended if retinal or disc neovascularizations are present
Pars plana vitrectomy	Routine use is not recommended	
Intravitreal steroids	Intravitreal injections of steroids or steroid-implants may improve VA in patients with macular edema	Application of triamcinolone is not superior to grid laser photocoagulation. Steroids may improve VA, but the rate of adverse events is higher compared with grid laser or anti-VEGF drugs
Intravitreal anti-VEGF drugs	Currently no large randomized trials are available. In small studies the application of anti-VEGF drugs seems to be a promising treatment option. The prospective randomized clinical trials are ongoing	

option for patients with macular edema secondary to RVO. Most of the relevant studies have used bevacizumab in dosages from 1 to 2.5 mg [46,74,75]. More recently several case series and small studies have demonstrated significantly improved VA in RVO patients treated by repeated intravitreal injection of anti-VEGF drugs [74–79]. Intracameral bevacizumab has also been reported as a successful treatment for rubeosis iridis and neovascular glaucoma [79]. The most important limitation of currently available studies is the very limited number of included patients, and evaluation of different types of RVO. Some of the studies described only three patients [79]. These factors limit the evidence and results of large randomized trials with clearly defined inclusion criteria are required before clinical recommendations can be made.

Conclusions: algorithm of investigations and treatment in patients with RVO

RVO is a complex retinal vascular disorder that commonly leads to severe visual impairment. A large percentage of patients with RVO have a history of cardiovascular disease, hypertension, hyperlipidemia and/or diabetes mellitus. Evaluation of a new patient with RVO (see Chart 1) must include as a first line, examination of blood pressure, lipid profile and glucose levels because RVO may be a presentation of significant vascular morbidity.

Diagnosis of thrombophilia does not alter the management of RVO. Given the lack of therapeutic consequence, screening for heritable thrombophilia in patients with RVO is not required.

Table 4 summarizes the clinical recommendation for treatment of patients with CRVO and BRVO. The highest evidence level is present for laser treatment. Grid laser photocoagulation is recommended in patients with BRVO if VA is 20/40 or worse over a period of 3 months.

Currently, a number of large clinical trials are underway to investigate the effects of intravitreal anti-VEGF drugs.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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