Retinal vein thrombosis: risk factors, pathogenesis and therapeutic approach

Domenico Prisco, MD; Rossella Marcucci, PhD MD

Department of Medical And Surgical Critical Area, Section of Clinica Medica Generale e Cliniche Specialistiche, University of Florence; Thrombosis Center, AO Careggi, Florence, Italy.

Key Words
Retinal thrombosis, hemostasis, homocysteine, risk factor.

Abstract
Retinal vein occlusion (RVO) is a relatively common disease, often associated with the presence of diseases related to internal medicine. It is well known that RVO is associated with common systemic vascular disorders such as hypertension, arteriosclerosis and diabetes. Several studies using hospital-based controls have shown an increased risk of RVO in patients with arteriopathy, or high levels of plasma glucose and arterial blood pressure. Patients are categorized into six types of RVO based on the site of occlusion and on the type of consequent vascular damage. Central retinal vein occlusion (CRVO) is the most frequently-occurring and clinically relevant type of RVO. In addition to the well-known classical risk factors, new haemostasis-related ones have been investigated in patients affected by CRVO. While data concerning a number of parameters remain contradictory, high levels of type 1 plasminogen activator inhibitor (PAI-1) and hyperhomocysteinemia appear to play a significant role in the pathogenesis of this disease. Although based on a limited number of studies, this new knowledge could eventually provide important indications regarding prognosis and therapeutic strategies. There is no established treatment for CRVO. Treatment consists primarily of managing any identified underlying systemic disease. The increasing role of hypercoagulability in patients with CRVO supports the use of antithrombotic drugs in the treatment of this disease. Vitamin treatment to correct hyperhomocysteinemia should also be taken into consideration. However, the approach to CRVO treatment with antithrombotic drugs is not evidence-based yet. There is urgent need of intervention trials to evaluate the role of these drugs in CRVO patients.

Introduction
One of the most common retinal vascular occlusive disorders is retinal vein occlusion (RVO) which is usually associated with visual loss of variable degree. RVO may be localized in large, medium, and small-calibre veins. Accordingly, retinal vessel involvement may have different extent, from branch retinal vein occlusion (BRVO), to hemicentral retinal vein occlusion, and central retinal vein occlusion (CRVO). Based upon the type of the vascular damage associated with the occlusion, we may observe oedematous, ischaemic or miscellaneous types. Clinical and fundoscopy characteristics, prog-
nosis and, at least in part, therapeutic approach depend on both the site of vessel occlusion and the type of consequent vascular damage.

RVO is a relatively frequent disease and may be associated with many different systemic diseases. In particular, CRVO is the more relevant picture which may often need a diagnostic and therapeutic involvement not only of the ophthalmologist but also of the internist [1, 2].

**Central retinal vein occlusion**

CRVO is the second most frequent disease after diabetes mellitus causing a visual loss. The tract of central retinal vein passing through lamina cribrosa is the most frequent site of occlusion. Several reasons are responsible of this localization: 1) as years go by, collagen tissue of lamina cribrosa becomes more thick and stiff causing a compression of the vascular wall; 2) degenerative processes at the expense of central retinal artery may cause compression on the near venous wall; 3) the consequently turbulent flow enhances the risk of endoluminal thrombus formation. Patients with CRVO may complain of decreased vision or floaters at the time of presentation. Sometimes CRVO is preceded by episodes of amaurosis fugax. Visual acuity can range from 20/15 to light perception. Decreased visual acuity can be secondary to macular capillary nonperfusion, macular edema, retinal haemorrhage, retinal detachment, vitreous haemorrhage or neovascular glaucoma. Fluorescein angiography reveals normal retinal arterial and choroidal filling, delayed retinal venous filling, variable staining of the retinal veins, and variable retinal vascular leakage resulting in retinal edema. The Central Vein Occlusion Study (CVOS), a prospective cohort study of 725 patients with randomized clinical trials of specific subgroups, found that visual outcome depends largely on initial visual acuity. Older age, male sex, and the number of risk factors (systemic vascular risk factors and glaucoma) were correlated with poorer visual outcome. In addition, 34% of eyes with initially perfused CRVO developed ischaemic CRVO during the three-year follow-up (15% converted during the first four months of follow-up) [3].

CRVO in young adults is uncommon: only 10-15% of patients with CRVO are under 40 years of age. As regard as prognosis, after the patient's first vein occlusion, the chance of a vascular occlusion in the fellow eye is approximately 1% per year, based on the CVOS results. If the patient's initial visual acuity is 20/40 or better, the patient may be informed that there is a good likelihood of retaining good acuity. If the visual acuity is 20/50 to 20/200, the prognosis is variable: visual acuity may improve (about a 1 in 5 chance), may stay at the same general level (almost half of cases), or may get worse. If the initial visual acuity is worse than 20/200, prognosis for vision poor (80% remain at that level or worse); the primary concern is prevention of neovascular glaucoma by early detection of the development of iris neovascularization and its prompt treatment [4].

**Pathogenesis and risk factors of CRVO**

Open-angle glaucoma is the most frequent local alteration predisposing to CRVO as it compromises venous outflow by increasing intra-ocular pressure. A popular theory exists that raised intraocular pressure causes external compression of the central retinal vein as it passes through the lamina cribrosa. This would result in turbulent blood flow distal to the constriction and subsequent thrombus formation. An association with CRVO and raised intraocular pressure has been described but turbulent flow has not been documented by on Doppler studies. CRVO is detected in 4% to 4.5% of eyes with primary open angle glaucoma and primary open angle glaucoma or ocular hypertension have been reported in 4% to 43% of patients with CRVO.

An inflammatory aetiology was first suggested in some types of CRVO, in particular in young patients. Local inflammation has been detected pathologically and immunological diseases have been associated with CRVO, but a definite inflammatory process has not been determined. Focal phlebitis, optic disc swelling, and vitreous cells are present in a significant number of patients, and underline again the possible role of an inflammatory process. Some patients experience prompt resolution with the use of periocular steroids, further indicating that inflammation may play a role at least in some of them.

Starting from the pathological findings of Von Michel in 1878, several authors have, at various times, supported or contested the presence of a thrombus in CRVO. Over the last years, new data supporting the role of thrombosis in CRVO have become available. An issue taken into consideration in the pathogenesis of CRVO is blood viscosity. In hyperviscosity syndromes retinal features which are indistinguishable from CRVO may be observed. Red cell deformability plays an important role in determining blood viscosity in the presence of slow venous flow and high vascular resistance, conditions which are present in the central retinal vein at the level of lamina cribrosa. The increase of hematocrit and blood viscosity are two possible determinants of hyperviscosity in patients with CRVO, in particular in those with ischaemic type. Blood viscosity determinants are altered in CRVO patients as compared with controls; in particular a specific abnormality is the reduced red cell deformability [2].

It is well known that RVO is associated with common systemic vascular disorders such as hypertension, arteriosclerosis and diabetes [1]. Two larger studies using hospital-based controls have shown an increased risk of CRVO in patients with arteriosclerosis, or high levels of plasma glucose and arterial
blood pressure. On the contrary, the risk was inversely related to regular exercise, alcohol intake, and high density lipoprotein levels. A population-based study involving 3654 Australians found significant associations between RVO and hypertension, stroke and angina (as well as glaucoma). Among young adults with CRVO, approximately 25% are hypertensive, significantly less than older patients with CRVO, among whom the prevalence of hypertension is approximately 60%. Diabetes mellitus is present in 3-9% of CRVO patients under 50 years of age, as compared to 4-34% of older patients [1]. In a recent study of Hayreh et al. who prospectively investigated 1090 consecutive RVO patients it was documented that in BRVO there was a significantly higher prevalence of arterial hypertension, peripheral vascular disease, venous disease, peptic ulcer and other gastrointestinal disease than in CRVO.

Over the past years a limited number of studies has evaluated the possible role of different haemostatic factors in the pathogenesis of CRVO (table 1). However, most of the available studies have assessed one or just a few haemostatic factors, often in a limited number of patients. In a case-control study, we have thoroughly evaluated the most important thrombophilic risk factors in 100 patients with CRVO [5]. At present only a few other studies on hypercoagulability are available with a separate analysis on patients with CRVO.

The available data on haemostatic alterations in RVO patients have been recently reviewed [4,6]. A hypercoagulable state documented by the presence of higher levels of prothrombin fragment 1+2, activated factor VII and D-dimer than in controls was reported in patients with CRVO. As a hypercoagulable state documented by the presence of higher levels of prothrombin fragment 1+2, activated factor VII and D-dimer than in controls was reported in patients with CRVO.

Among the haemostasis-related risk factors for venous thrombosis, only anecdotal reports exist of deficiencies of natural anticoagulants (antithrombin, protein C and S).

On the contrary, several studies documented a high prevalence of activated protein C resistance (APCR) in CRVO patients ranging from 12 to 26%, but other authors did not confirm these data. Conflicting results have been reported also on factor V (FV) Leiden mutation prevalence in CRVO patients. Some authors failed to find a high prevalence of FV Leiden in CRVO with respect to controls, whereas others demonstrated a significant association between this genetic disorder and CRVO. Differences in populations investigated may, at least in part, account for such discrepancies. In our study we found that both FV Leiden and APCR were risk factors for CRVO at univariate analysis [5]. However, at multivariate analysis differences were no longer significant.

Prothrombin gene G20210A mutation has been poorly investigated in CRVO. Most available data, in agreement with our study, have excluded a role of this mutation as a risk factor for CRVO.

Mild hyperhomocysteinemia is a well-recognized risk factor for arterial and venous thrombotic events. Contrasting data have been reported on the prevalence of hyperhomocysteinemia and of C677T MTHFR (+/+) genotype among patients with CRVO. In our study homocysteine plasma levels but not MTHFR gene polymorphism were significant risk factors for CRVO after multivariate analysis [5]. Considering all available data in the literature in the majority of studies, a role of hyperhomocysteinemia (but not of C677T MTHFR(++) genotype) as a risk factor for RVO has been found [4]. This may depend on the different role played by vitamin status, which is one of the determinants of homocysteine blood levels. However, the role of folic acid, vitamin B12 and vitamin B6 status in RVO is presently unknown. Thus, our study supported a role of hyperhomocysteinemia in CRVO in an Italian population.

There is also limited evidence that elevated plasminogen activator inhibitor-1 (PAI-1) and lipoprotein(a) [Lp(a)] may be risk factors for RVO. In our study both factors were significantly higher in CRVO patients than in controls but, after multivariate analysis adjusted for classical and thrombophilic risk factors, only high PAI-1 levels remained an independent risk factor for CRVO. In these patients an increased PAI-1 concentration may have led to a relative reduction in fibrinolysis, which may play a role in the pathogenesis of RVO. Preliminary data from our group suggest that genetic determinants (such as PAI-1 4G/5G or ACE I/D polymorphisms) may

### Table 1. Haemostasis related risk factors in RVO's: data from literature

<table>
<thead>
<tr>
<th>Deficiencies of physiologic clotting inhibitors *</th>
<th>Antiphospholipid antibodies ^</th>
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<tbody>
<tr>
<td>Elevated levels of PAI-1</td>
<td>Activated protein C resistance ^</td>
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<tr>
<td>Factor V Leiden ^</td>
<td>Polymorphism G20210A of factor II gene ^</td>
</tr>
<tr>
<td>Hyperhomocysteinemia ^</td>
<td>Polymorphism C677T of MTHFR gene ^</td>
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<tr>
<td>Elevated levels of lipoprotein(a) ^</td>
<td>Polymorphism 4G/5G of PAI-1 gene</td>
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<tr>
<td>Plasminogen deficiency ^</td>
<td>Factor XII deficiency ^</td>
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<tr>
<td>*Case-reports</td>
<td>^ Contrasting results</td>
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### Table 2. Reported treatments of CRVO

- Systemic steroids
- Anticoagulants
- Antiplatelet drugs
- Fibrinolytic therapy
- Hemodilution
- Laser panretinal photocoagulation
- Laser-induced chorioretinal venous anastomosis
- Surgery
at least in part condition this finding.
Finally, the presence of antiphospholipid antibodies has been reported to predispose to CRVO.
As a general comment on the contrasting positive and negative reports in the literature on different haemostatic risk factors, we should note that they are likely to reflect type II error, in view of the small sample size of most published studies of CRVO.

**Therapeutic Approach**

Except for laser which has well defined indications, especially in the prevention of open angle glaucoma, there is no established treatment for CRVO [4,6]. Treatment consists primarily of managing any identified underlying systemic disease. A number of systemic approaches have been reported in the literature (table 2). However, no clear demonstration of their utility exists. Successes and beneficial effects claimed for different therapies in most cases simply represent the natural history of the disease.

Steroids are frequently used in oedematous forms of RVO. No clear benefit of antithrombotic drugs has been demonstrated. However, the recently emerging role of hypercoagulability in patients with CRVO has stimulated the use of different antithrombotic drugs in the treatment of this disease. Many doctors treat these patients with low-dose heparin or low molecular weight heparins in the acute phase and with antiplatelet agents in the chronic phase. Heparin doses should probably be those commonly used for prevention and not for therapy of venous thrombosis because these agents may be harmful for possible increase of the amount of retinal haemorrhages. No demonstration of the usefulness of antiplatelet drugs exist but they are prescribed to most patients with coexistent indications such as diabetes, hypertension or arterial disease. However, the approach to CRVO treatment with antithrombotic drugs is not evidence-based yet. There is urgent need of intervention trials to evaluate the role of these drugs in CRVO patients. Finally, vitamin treatment to correct hyperhomocysteine should also be taken into consideration.

**References**