

Clinical Risk Factors Underlying the Occurrence of Retinal Vein Occlusion

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ABSTRACT

Retinal vein occlusion (RVO) is the second commonest cause of retinal vascular disorder just after diabetic retinopathy. RVO is associated with a wide variety of systemic and local complicating factors. In over half of the cases with RVO, the age of the disease onset is over 65 years. The most recognized risk factors for RVO are the senility and accompanying systemic vascular diseases. Additional risk factors include thrombophilic mutations, systemic inflammatory conditions and ophthalmic risk factors. The aim of this review is to outline clinical risk factors underlying the occurrence of RVO.

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Key words: Branched Retinal Vein Occlusion; Central Retinal Vein Occlusion; Risk Factors

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INTRODUCTION

Retinal vein occlusion (RVO) is second most common sight-threatening retinal vascular disorder just after the diabetic

retinopathy^[1]. RVO can be evaluated as two primary categories, branch RVO (BRVO) and central RVO (CRVO), depending on the site of the occlusion. In all of the published studies, BRVO had been detected as more common than the CRVO, ranging from 3 to 10 times more prevalent^[1]. RVO is predisposed by various systemic and local pathobiological states^[2]. The aim of this review is to outline clinical risk factors underlying the occurrence of RVO.

THE CLINICAL RISK FACTORS FOR THE GENESIS OF CRVO

CRVO is a common retinal vascular disorder that presents with variable visual loss. More than 90% of the CRVO cases occur in the patients older than 50 years, but it has been reported in all of the age groups. CRVO is slightly more frequent in males than in females. CRVO does not have any particular racial preference^[3]. The Beaver Dam Eye Study Group reported the 15-year cumulative incidence of CRVO to be 0.5%^[4]. Thrombotic occlusion of the central retinal vein can occur from various pathological events such as the compression of the vein. The mechanical pressure due to the structural changes in the lamina cribrosa including glaucomatous cupping, orbital disorders, and inflammatory swelling in the optic nerve can cause CRVO. Moreover, hemodynamic disturbances associated with sluggish circulation, vessel wall alterations as in vasculitis and the changes within the blood constituents such as deficient fibrinolysis may complicate CRVO^[5].

Age

Advancing age is a very important risk factor for CRVO^[3]. The mean age for CRVO was 69.6 years^[6]. The meta-analysis by Rogers et al^[7] showed a 0.27 per 1000 prevalence of CRVOs in 40-to-49-year olds, 0.69 per 1000 in 50-to-59-year olds, 1.67 per 1000 in 60-to-69-year olds, 2.87 per 1000 in 70-to-79-year olds, and 5.44 per 1000 in those older than 80 years. The prevalence in subjects older than 80 is 20 times higher than people from 40 to 49 years^[7].

Hypertension

Hypertension (HT) is the most commonly risk factor for CRVO^[3]. Systemic HT accelerates the arterial stiffness that accompanies aging,

and hardening of the central retinal artery within the lamina cribrosa to compress the adjacent central retinal vein, leading to the turbulent blood flow and facilitating thrombosis^[8]. A longitudinal analysis demonstrated that both uncomplicated and complicated HT can be considered as the risk factors for CRVO. The impact of HT on the retinal arterial structure could place the patients at increased risk for the genesis of CRVO even before other systemic complications of HT are evident^[9].

Diabetes mellitus

CRVO is significantly associated with the presence of DM^[10]. DM itself affects the health of the retinal blood vessels. Diabetes alone, even without a retinal vein occlusion, can cause macular edema. Stem *et al*^[9] reported that the complicated DM could increase the risk of CRVO while uncomplicated DM had no effect on the risk of being diagnosed with CRVO.

Hyperlipidemia

Most of the studies suggested a significant association between the CRVO and hyperlipidemia (HLD)^[9]. For any clinical presentation of RVO, hyperlipidemia was twice more common than the controls, equivalent to a pooled odds ratio of 2.5. The significant risk estimates were observed for the patients with CRVO^[9]. HLD is an established risk factor for the atherosclerosis, and early HLD is associated with an increased arterial compliance, and later due course of the disease the arteries would become more rigid^[11]. Thus, the duration and severity of HLD may affect the extent of the atherosclerotic events in the central retinal artery, which could, in turn, affect the risk of developing the CRVO^[9].

Atherosclerotic systemic diseases

CRVO is associated with risk of ischemic heart disease and stroke^[12]. The association of the retinal arteriolar emboli with carotid artery plaque and increased carotid intima-media thickness had been demonstrated^[12]. Stem *et al*^[9] indicated that other diseases caused by atherosclerosis, such as peripheral artery disease and stroke, are associated with an increased CRVO risk. Therefore, atherosclerosis occurring elsewhere in the body may be a surrogate marker for the atherosclerosis occurring in the central retinal artery^[9].

The Eye Disease Case Control Study (EDCC) Group suggested that the increased body mass index shall be considered as a risk factor for RVO^[13]. The Group had found that the participants who rated themselves as presently above average in terms of physical activity had about 60% lower odds of CRVO than did those who rated themselves as below average (screening analysis)^[13]. The association of cigarette smoking with retinal arteriolar emboli has also been reported in the Beaver Dam study^[4].

Inflammatory disorders

The impact of inflammation was first suggested in some subtypes of CRVO especially in the younger patients. In that subgroup of patients, the presence of focal phlebitis, optic disc swelling, and vitreous cells make us think of the underlying inflammatory process^[14]. Even though a definitive inflammatory process has not been clarified yet, another point showing the role of the ongoing inflammation in RVO indirectly is anecdotal clinical cases that were treated with high-dose corticosteroids and intensive immunosuppressant agents and finally preserved their vision^[15].

Hypercoagulation diseases

A longitudinal analysis of the risk factors for CVO reported that

the diagnosis of a primary or secondary hypercoagulable state is associated with the genesis of CRVO^[9]. There is mounting evidence that some cases of RVO disease may be associated with thrombophilic or hypofibrinolytic states. Those include factor V and factor II mutations and the deficiency in anticoagulant proteins such as protein C, protein S, and antithrombin III. Other thrombophilic abnormalities, such as factor XII deficiency and hyperhomocystinemia, have also been reported^[16]. Janssen *et al*^[17] conducted a meta-analysis to more fully understand how specific coagulopathies affect the risk of developing an RVO. They suggested that hyperhomocystinemia and the presence of anti-phospholipid antibodies each had a significant association with RVO^[17]. Bashshur *et al*^[16] found a higher prevalence of anticardiolipin antibodies in the younger patients with RVO disease and no conventional risk factors. They reported that anticardiolipin antibodies behave in RVO disease and affect the clinical course of the disease. Hyperhomocystinemia is a risk factor for central retinal vein occlusion and may suggest a poor prognosis in the patients. Vine^[18] reported that of the 74 patients with a central retinal vein occlusion, 16 (21.6%) had total plasma homocysteine levels above the 95th percentile in the control group (odds ratio, 6.53; 95% confidence interval, 1.81–23.50).

The pathogenesis of CRVO among young hypercoagulable patients is quite different than that seen in the older patients with atherosclerosis^[9]. The study of 228 patients who developed RVOs indicated that thrombophilic disorders were common in the group of patients with RVO who were either \leq 45 years old or who lacked any cardiovascular risk factors^[19]. This data suggested that the patients with coagulopathies may experience unprovoked thrombus formation in the central retinal vein as a result of their underlying thrombophilia and possibly not as a consequence of the turbulent flow induced by compression of the vein by a nearby atherosclerotic artery. Most importantly, the patients diagnosed as RVO who are \leq 45 years old and have lack any cardiovascular risk factors should be screened for coagulation disorders.

The role of B-vitamins, namely folic acid, vitamin B6 and B12, as independent risk factors for arterial and venous thrombotic events had been repeatedly suggested. The association between low folic acid levels and the occurrence of RVO had been demonstrated in a meta-analysis^[20]. Sodi *et al*^[21] suggested that postmethionine hyperhomocystinemia, elevated factor VIII, and reduced folic acid and B6 plasma levels were more frequent in the patients with CRVO.

Drug therapy

Medications such as diuretics, sympathomimetics, oral contraceptives, and antipsychotics have been linked to the development of the CRVO^[22]. The use of those drugs may result in hemoconcentration, thrombophilia, or dehydration, which precipitate the development of CRVO^[22]. Angiotensin II receptor antagonists may increase dehydration especially when taken in combination with diuretics^[22]. Antihypertensive medications taken by the patients, including β -blockers and calcium channel blockers, have not been reported to cause conditions that complicate CRVO.

Koizumi *et al*^[23] found a significantly increased risk of CRVO in patients using aspirin and warfarin. The patients using clopidogrel had an odds ratio of more than 1, but the association did not reach statistical significance. The use of any antithrombotic conferred a highly significant OR of 3.13 for CRVO. Thus, most patients in whom CRVO develops that are already using antithrombotic agents suggests that these medications do not completely ameliorate the risk of thrombus development in the patients at CRVO risk^[23]. There are systemic factors that predispose patients to the increased risk for

thrombotic disease of the venous drainage of the retina and that this increased risk is not accounted for by entry of commonly accepted risk factors such as hypertension and diabetes into the regression model. The same factors may be associated with an increased tendency of using antithrombotic agents^[23]. Lipid-lowering agents such as statins have vaso-protective and anti-atherogenic properties, and in one study they were shown to actually halt the progression of atherosclerosis in patients requiring coronary angiography^[24].

Ocular risk factors

CRVO was associated with increased intraocular pressure (IOP), primary open-angle glaucoma and ocular hypertension^[25]. There is a strong correlation between glaucoma and CRVO because of the association of optic disk cupping with distortion of the retinal vessels at the disk, predisposing the vein to occlusion^[25]. The significant association of open-angle glaucoma and CRVO may be a manifestation of a common underlying vascular abnormality, such as systemic hypertension^[26]. Kim *et al*^[26] suggested that RVO and open-angle glaucoma may share common systemic risk factors reflecting a common pathogenic mechanism. They found that the retinal nerve fiber layer (RNFL) thinning, especially in the inferior-temporal and superior-temporal sectors in the fellow eyes, was more prominent in a subgroup of patients >60 years old. The arterial stiffness and atherosclerosis may explain both CRVO and thinning of the RNFL. The patients with thinner RNFL in the contralateral eye had the same IOP as the controls which suggested the possibility that OAG and RVO shared a common vascular abnormality^[26].

Papilledema due to raised pressure in the optic nerve sheath may cause further compression to central retinal vein and contribute to CRVO^[25]. Hyperopia and anatomic structure of the eye is also an important risk factor for CRVO. For instance, hyperopic eyes with a shorter axial length have a small lamina cribrosa and also narrow scleral canal, which may lead to a relative mechanical blockage in the vein^[14]. This blockage was thought to cause thrombus formation by leading to turbulence flow in the vein^[14]. Brown *et al*^[27] have speculated that eyes with a shorter axial length might be predisposed to crowding in the lamina cribrosa. Other factors including orbital tumor, orbital abscesses, cavernous sinus thrombosis, and retrobulbar sheath injection may cause compression to central retinal vein and contribute to CRVO.

THE CLINICAL RISK FACTORS FOR THE GENESIS OF BRVO

Branch retinal vein occlusion (BRVO) is a frequent retinal vascular disease with an incidence of 2.14/1000/year in the population over 40 years of age^[28]. BRVO usually occurs in patients older than 50 years and has no sex or racial predilection. The disease is usually unilateral occurring bilaterally only in 5-10% of the patients^[28]. BRVO is defined as a focal occlusion of a retinal vein at an arteriovenous crossing site. The main pathogenic mechanism for development of BRVO is arterial stiffness that causes venous compression in the common adventitial sheath^[3]. In all but a few rare cases, the BRVO occurs at the crossing sites where the artery is passing superficially to the vein^[29]. The upper temporal vascular arcade is more often involved than the lower temporal vascular arcade. Most BRVOs involve the area inside the temporal vascular arcades, whereas peripheral BRVOs are more rarely seen, partly because they tend to be asymptomatic^[29]. The most recognized risk factors for BRVO are age, cardiovascular disorders, thrombophilic state, systemic vascular diseases, and ocular conditions.

Age

Advanced age is the most important risk factor for BRVO^[3]. The meta-analysis revealed a 1.37 per 1000 prevalence of BRVOs in 40-to-49-year olds, 6.09 per 1000 in 50-to-59-year olds, 9.29 per 1000 in 60-to-69-year olds, 12.27 per 1000 in 70-to-79-year olds, and 11.93 per 1000 in those older than 80 years. The prevalence in subjects older than 80 is 8 times higher than people from 40 to 49 years^[7].

Hypertension

Systemic HT is the most common risk factor for BRVO^[3]. Blood pressure which is too high over a long period of time may end up the damaging of the blood vessels. This damage may eventually lead to many types of clinical vascular problems such as atherosclerosis and vein occlusion. Most studies indicated that hypertension and related hypertensive retinal arteriolar changes are the strongest and most consistent risk factors for the genesis of RVO^[13]. A meta-analysis disclosed that, in BRVO, the odds ratio for HT is 3.0 (95% CI: 2.0–4.4)^[10].

Diabetes mellitus

DM is known as a risk factor for BRVO^[30]. A meta-analysis showed that, in BRVO, the odds ratio for DM is 1.1 (95% CI: 0.8–1.5)^[7]. O'Mahoney *et al* reported DM was shown to be not significantly associated with BRVO^[10]. A longitudinal cohort study showed that there was no association between DM without end-organ damage and BRVO, individuals with end-organ damage from DM had a 36% increased hazard of BRVO compared with those without DM. But HT with DM had an increased hazard of developing a BRVO compared with those with none of these conditions^[31].

Hyperlipidemia

O'Mahoney *et al*^[31] observed that hyperlipidemia was more than twice as common among the RVO cases than the controls, equivalent to a pooled odds ratio of 2.5. Similar significant risk estimates were seen for persons with CRVO and BRVO. Another meta-analysis showed that, in BRVO, the odds ratio for HL 2.3 (95% CI: 1.5–3.5)^[10].

Atherosclerotic associated diseases

The cardiovascular risk factors appear to be important in developing BRVO^[6]. Higher body mass index (more than 30) was also more frequent in BRVO patients^[13]. The EDCC Study Group found that participants who rated themselves as presently above average in terms of physical activity had about 70% lower odds of BRVO than did those who rated themselves as below average (screening analysis)^[13].

Song *et al*^[32] showed that patients with RVO have an increased risk of asymptomatic ipsilateral carotid artery plaques, and those with BRVO often also have decreased aortic distensibility and elasticity, a finding frequently found in patients with atherosclerosis. A strong association of current cigarette smoking (odds ratios 4.4) with incident retinal branch vein occlusion was found in Beaver Dam study^[4].

Inflammatory disorders

Both systemic and local inflammations have been hypothesized to play a significant role in the etiology of BRVO^[14]. Local inflammation within the eye has also been implicated in the pathogenesis of BRVO. *In vivo* assessment of the vitreous fluid in patients with BRVO has demonstrated elevated levels of proinflammatory mediators and lower levels of anti-inflammatory cytokines^[33]. In particular,

in a major study on inflammatory immune mediators in a group of vitreoretinal diseases, patients with RVO had elevated levels of interleukin-6, interleukin-8, and monocyte chemoattractant protein-1, all of which are considered highly proinflammatory^[34].

BRVO can also occur as a complication of a local or systemic vasculitis. The disease has been reported as a complication of retinal vasculitis in cases of both familial and spotted Mediterranean fever^[35]. BRVO can be a result of direct infiltration of the eye leading to venous obstruction^[6]. Such as, sarcoidosis and ocular tuberculosis could also be considered as systemic risk factors for the development of BRVO. Thus, systemic inflammation seems to play an important role in BRVO^[6].

Hypercoagulation diseases

As far as the thrombophilic risk factors are concerned, it has been difficult to determine to what extent thrombophilias play a role in BRVO^[7]. A meta-analysis of RVOs examined the prevalence of hyperhomocysteinemia, methylenetetrahydrofolate reductase gene mutation, factor V Leiden mutation, protein C and S deficiency, antithrombin deficiency, prothrombin gene mutation, anticardiolipin antibodies, and lupus anticoagulant^[36]. Only hyperhomocysteinemia and anticardiolipin antibodies had major effects at odds ratios of 8.9 (95% CI: 5.7–13.7) and 3.9 (95% CI: 2.3– 6.7), respectively^[36]. Thrombin activatable fibrinolysis inhibitor was evaluated in another study and appeared to have no effect on BRVO development^[37]. Moreover, thrombophilic gene polymorphisms examined in 294 patients seemed to have no effect as well^[38]. In addition, a recent case–control study of 117 patients found no effect of hyperhomocysteinemia and anticardiolipin antibodies^[39]. Also, Lam et al^[40] detected risk factors for developing BRVO in 60 patients younger than 50 years, it is not completely clear what role thrombophilia plays in BRVO pathogenesis. Blood abnormalities play a controversial role in the pathogenesis of BRVO; erythrocyte volume, level of fibrinogen, and hematocrit seem to be important^[41].

Drug therapy

The presumptive mechanism for the oral contraceptive pill and other medication regimens resulting in reports of increased risk for BRVO lies primarily in hypercoagulability^[42]. Retinal artery hypertension, vessel wall dysfunction, and hyperviscosity may all play a role in BRVO development with anabolic steroid users^[43].

Ocular risk factors

Glaucoma and raised intraocular pressure may predispose to RVO because of the increased ocular pressure leading to venous stasis in blood flow, but are not considered as important risk factors for BRVO^[6]. Hyperopia is not only an important factor in CRVO but also in BRVOs. Appiah et al^[44] showed that hyperopia was significantly more prevalent in BRVO. Anatomical features of the optic disc may play a role in the pathogenesis of BRVO. We have previously^[28] determined the relationship between BRVO and various optic disc topography parameters determined by HRT, and suggested that anatomically small and crowded optic nerve head may be a risk factor for BRVO^[28].

BRVO was associated significantly with the presence of arteriovenous nicking. This finding is consistent with clinical experience^[45] and the data from the Beaver Dam Eye Study^[4] which suggested that localized arteriosclerotic processes may contribute to the stasis and occlusion in adjacent retinal veins, and may, in fact, explain some of the association between retinal vein occlusion and the risk factors classically associated with arterial or arteriolar disease^[12].

CONFLICT OF INTERESTS

The authors declare that they do not have conflict of interests.

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