• Review Article •

Intraocular pressure modifications in patients with acute central/hemicentral retinal vein occlusions

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Abstract

● Intraocular pressure (IOP) modifications in patients with acute central/hemicentral retinal vein occlusions (RVOs) consist in IOP reductions and increases. The IOP reduction is due to a transitional hyposecretory phase of the aqueous humor, that increases gradually until 3mo after the venous occlusion onset, and then finally disappears after month 4th. The IOP increases lead to the ocular hypertension and glaucoma. The possible pathogenetic correlations between ocular hypertension/glaucoma and acute central/hemicentral RVOs have been classified into three groups: 1) the venous occlusion precedes the ocular hypertension/glaucoma causing neovascular glaucoma and secondary angle-closure glaucoma without rubeosis; 2) the ocular hypertension and the glaucoma precede the venous occlusion and favor its appearance (ocular hypertension, primary angle-closure, primary angle-closure glaucoma, and open angle glaucomas); and 3) the venous occlusion and the ocular hypertension/glaucoma are mostly age dependent appearances due to common vascular and collagen alterations, lacking a causal connection between the 2 conditions.

● **KEYWORDS:** intraocular pressure; acute central/hemicentral retinal vein occlusion; neovascular glaucoma; ocular hypertension; primary angle-closure; open angle glaucoma; secondary nonrubeotic angle-closure glaucoma
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INTRODUCTION

Intraocular pressure (IOP) or ophthalmotonus is the pressure exerted by the intraocular liquids upon the walls of the ocular globe. The pressure is determined by the relation between the eye globe capacity and the volume of its contents. The intraocular liquids that constitute the eyeball contents are represented by the aqueous humor that fills the ocular chambers and impregnates the vitreous, and the blood within the uvea. The outer structural coat of the eye (*e.g.*, the cornea and the sclera) determines the ocular globe capacity. From the 3 mentioned factors above (aqueous humor, uveal blood, and corneoscleral coat), the most important one for the steady maintenance of a normal IOP is the aqueous humor which is maintained at a constant volume due to a steady rate of formation and outflow. That is, a normal IOP depends on the inflow and outflow of the aqueous humor. The mean normal IOP is 15.5 mm Hg ranging between 10 and 22 mm Hg[1].

The modifications of the IOP in patients with acute central/hemicentral retinal vein occlusions (central/hemicentral RVOs) are current topics in ophthalmology with multiple theoretical and practical implications. These IOP changes may decrease or increase the pressure.

The IOP reduction (ocular hypotension) is defined as an IOP reduction ≥2 mm Hg in an eye with acute central/hemicentral RVO compared to the IOP in the contralateral unaffected eye. Hayreh *et al*[2] reported IOP reductions in 48% of patients at their initial consultation, especially in the cases with ischemic forms of venous occlusion. This drop in the IOP is attributed to a transitory hyposecretory phase of the aqueous humor, which increases gradually for 3mo after the onset of the venous occlusion, and then finally disappears after the 4th month. The normalization of the IOP in all our patients with acute central/hemicentral RVO after the first bevacizumab intravitreal injections administered[3], suggests that the vascular endothelial growth factor (VEGF) may have direct hypotensive ocular effects, or alternatively that VEGF stimulates the expression of a hypotensive biochemical factor that decreases the IOP.

The definition of high IOP (>22 mm Hg) includes ocular hypertension (OH) and glaucoma events. The possible pathogenetic correlations between OH/glaucoma and acute central/hemicentral RVOs can be summarized as follows: 1) Venous occlusion precedes and causes OH/glaucoma; this would include cases with neovascular glaucoma (NVG) and those with secondary angle-closure glaucoma without

rubeosis. 2) OH and glaucoma precede the venous occlusion and favor its appearance; this includes cases of OH, primary angle-closure, primary angle-closure glaucoma (PACG), and open angle glaucomas (OAG). 3) Venous occlusion and OH/glaucoma are mostly age dependent appearances of common vascular and collagen alterations without a causal connection between the two conditions.

This review convers the above mentions forms of increased IOP associated with acute central/hemicentral RVOs. It comprises 4 sections, namely, NVG, primary angle-closure and PACG, OH/OAGs, and secondary angle-closure glaucoma without rubeosis.

NEOVASCULAR GLAUCOMA

Particularities NVG is a severe and aggressive form of secondary angle-closure glaucoma, defined by intraocular neovascularization (NV; iris, chamber angle or retina) with high IOP. The optic disc modifications are not specific and glaucomatous excavation of the optic nerve is not required for the diagnosis. It is a devastating and intractable ocular disorder, most commonly determined by a deep and severe retinal ischemia with a risk of blindness and of adverse evolution even after the medical or surgical normalization of the high IOP[4-7]. Visual loss is a common feature that can be attributed to conditions such severe ocular ischemia, glaucomatous optic nerve lesion, cataract formation, recurring hyphema with ensuing hematic impregnation of the cornea, and or phthisis bulbi[8-9].

Incidence The incidence of cases with rubeosis iridis and NVG in individuals with nonischemic central retinal vein occlusion (CRVO), has reached 10%[10]. Eyes with nonischemic CRVO can develop ocular NV and NVG if there is an associated diabetic retinopathy or ischemic ocular syndrome, the last 2 conditions are the sole causes of ocular NV and attributions to nonischemic vein occlusion are false. The cumulative risk of developing NVG in eyes with ischemic occlusion reaches a maximum of 45% after several years with the maximum risk present during the first 7 or 8mo. In cases of ischemic hemicentral RVO, NVG appears in 3% of individuals[10-12].

Prevention No therapy today can reverse a completely developed form of NVG (the angle-closure stage of NVG) and preventing further loss of vision that ensues in most cases. Although NVG is a serious complication it can often be prevented. Prophylaxis is always preferable to treatment of its complications. We consider 2 aspects for preventing NVG developing after venous occlusion[3,13]. The first and most important of them is the appropriate treatment of patients with acute occlusions (duration of disease symptoms <3mo) with intravitreal injections of anti-VEGF agents. Subsequently, a thorough screening for ocular NV development is mandatory, especially during the first 7-8mo after the onset of the venous occlusion, when the risk for NVG is at its maximum. This is the best time to intervene to prevent the occurrence of NVG. The second important aspect for NVG prevention is the treatment of those patients with venous occlusion and intraocular NV but normal IOP (pre-glaucoma stage of NVG). For those individuals the preventive treatment consists in administration of anti-VEGF agents, topical steroids, and cycloplegics; if the NV remains after these treatments, panretinal photocoagulation (PRP) is necessary to prevent or delay the development of intractable glaucoma. We favor long-term treatment with anti-VEGF agents and use PRP only in patients with CRVO and intraocular NV (unless this complication subsides after medical treatment[3]). The ophthalmic literature favors the view that anti-VEGF agents do not prevent the development of NVG and that they merely delay its occurrence[12,14] serving as an effective temporizing rather than a definitive treatment. However, following the principles presented above we achieved a cumulative incidence rate for NVG of 4.08% after the treatment of patients with acute central/hemicentral RVOs with bevacizumab (Avastin; Genentech, Inc.,South San Francisco, CA, USA). We encountered only 2 mild cases of NVG during our 3-year follow-up, and the conditions were rapidly reversed after medical treatment. We did not resort to PRP because the IOPs became normal, and the iris NV disappeared after treatment[3].

PRIMARY ANGLE-CLOSURE

Patients with central/hemicentral RVOs have a fairly high prevalence (21%-22%[15-17]) of one of the 2 variants of narrow anterior chamber angles (angular width ≤20 degrees), namely, moderately narrow (15-20 degrees) and extremely narrow (≤10 degrees) angles. This fact raises the possibility of correlation between the angle configuration and the development of central/hemicentral RVO. In addition, the anterior chamber depth is significantly shallower following the onset of CRVO[18].

Classification of Narrow Drainage Angles

Primary angle-closure suspect The eyes with narrow angles show the following features: normal IOP, no history or evidence of an acute IOP elevation, absence of peripheral anterior synechiae in the angle, no glaucomatous change of the optic nerve and visual field, and smaller than average size of the anterior segment of the ocular globe (smaller than normal axial length and anterior chamber depth, and the cornea thicker than that in eyes with normal angles[17]. The configuration of these eyes may represent a local risk factor predisposing to central/hemicentral RVO. Specifically, in eyes with narrow angles, the retinal vein and artery, which share the same adventitial sheath, are more crowded as they pass through the lamina cribrosa. This situation may narrow the lumen of

the vein, resulting in decreased blood flow, increased blood viscosity, and local turbulence that may cause thrombosis[16].

A primary angle-closure suspect (PACS) associated with central/hemicentral RVO requires observation without treatment. The eventual treatment is similar to that applied against primary angle-closure and is reserved for cases that progress from PACS to primary angle-closure.

Primary angle closure The characteristics of eyes with primary angle-closure include a narrow drainage angle and the presence of at least one of the following features[1,17] indicating trabecular obstruction by the peripheral iris: peripheral anterior synechiae; IOP>21 mm Hg; excessive pigment deposition on the trabecular meshwork surface (especially on the superior surface); ischemic sequelae of acutely raised IOP (distorsion of the radially orientated iris musculature, iris stromal atrophy, dilated nonresponsive pupil, focal necrosis of lens epithelium causing glaucomfleken); clear history of clinical signs or symptoms consistent with sudden IOP increase (headaches, congestion, blurred or halo vision, corneal edema or mild-dilated pupil); evidence of a surgical peripheral iridotomy; dark room provocation test resulting in an IOP increase ≥8 mm Hg from the baseline; and without glaucomatous change of the optic nerve and visual field.

Central/hemicentral RVO may occur after intermittent primary angle-closure attacks. The medical history of these patients is relevant. Specifically, they experience subacute attacks of angle closure and then recover their visual function with reversal of all signs and symptoms. Following such an attack a persistent blurred vision may prompt the ophthalmologist to suspect a venous occlusion. In eyes with narrow angles, intermittent angle closure episodes may trigger the onset of venous occlusion from collapse of the vein, and, as a result, endothelial lesions may lead to intimal proliferation at the level of the lamina cribrosa.

The treatment in patients with primary angle-closure associated with central/hemicentral RVO consists of peripheral iridotomy/iridectomy or trabeculectomy in cases in which the IOP level cannot be normalized with medical treatment alone.

Primary angle-closure glaucoma The PACG is defined as the presence of primary angle-closure and glaucomatous optic neuropathy (irreversible structural and/or functional glaucomatous lesion). Three risk factors for central/hemicentral RVO are angle closure[16], a permanently high IOP[19], and glaucomatous cupping of the optic disc[20].

The treatment of PACG associated with central/hemicentral RVO consists of trabeculectomy and phacoemulsification-intraocular lens implantation (as appropriately for patients with opaque lens).

The incidences of the PACS, primary angle-closure, and PACG in patients with central/hemicentral RVOs were 10.5%, 8.7%, and 1.75%, respectively[16]. The narrowing of the anterior chamber angle appears to be normal with aging. With advancing age, the angle may become occluded with progression of gonioscopic findings from PACS to primary angle-closure and from primary angle-closure to PACG.

OCULAR HYPERTENSION/OPEN ANGLE GLAUCOMAS

The high cumulative prevalence rates of OH (16.2%-29.4%) and OAGs [9.9%-19.6%; including primary open angle glaucoma (POAG) and pseudoexfoliative glaucoma] in patients with central/hemicentral RVOs indicate that OH and OAGs are risk factors for the occurrence of venous occlusions[2,19-22]. This association refers to the RVOs occurring at the optic cup (optic cup-sited RVOs; OC-RVOs) and to those appearing in the optic nerve head at the lamina cribrosa (optic nerve head-sited RVOs) in the absence of optic nerve head swelling (NONHS-RVOs). RVOs with optic nerve head swelling within the optic nerve head behind the lamina cribrosa have not been associated with high values of IOP, cup-to-disc ratio or prevalence of POAG[23]. The appearance of the optic nerve head swelling in RVOs shows that the venous occlusion caused sufficient ischemia immediately behind the lamina cribrosa to block axoplasmic transport.

Pathogenetic Factors Contributing to the Development of Venous Occlusion in Patients with Central/hemicentral RVOs Associated with the OH/OAGs[2,19-23]

High intraocular pressure A high IOP is a definite risk factor that may precipitate the onset of central/hemicentral RVO although no correlation has been found with the degree of IOP elevation. The venous return from the retina is disturbed by any IOP increase particularly at the point where the vein passes through the substance of the optic nerve, namely, the lamina cribrosa which is the most frequent site of venous occlusion. If the IOP increases above the venous pressure threshold it may cause a venous obstruction. Mechanical compression, an adverse local hemodynamic influence, increases, as a result of backward bowing of the lamina cribrosa deforming the channels that pass through it, and occluding the vein at the level of that for the NONHS-RVOs. If there is also a loss of tissue within a pathologically cupped optic disc, the main vein trunks are no longer protected by the optic nerve glial tissue and the high IOP gets directly transmitted through the vein wall into the lumen. Cell proliferation in the lumen of the vein at the level of the lamina cribrosa and displacement of the vessel in the anterior portion of the optic nerve have been suggested to be causes of central/hemicentral RVOs.

Both, the optic cup and optic nerve head-sited RVOs without optic nerve head swelling require similar treatments to control the IOP. The specific treatment of OC-RVOs should aim at reducing the IOP and alleviating other factors that may

cause increased optic disc cupping. Treating a high IOP is mandatory in cases of central/hemicentral RVOs associated with OH/OAGs. The OH of patients with unilateral central/hemicentral RVO increases the risk of venous occlusion and of development of structural and/or functional glaucomatous lesions in the uninvolved congener eye.

Glaucomatous cupping of the optic nerve head We discuss the role of the pathological cupping of the optic nerve head as a mechanical factor for causing central/hemicentral RVO. The cupping may cause mechanical displacement and stretching of the main venous trunk, which tends to be kinked as it bends around the sharpened rim of the glaucomatous cup. These anatomical changes may specifically affect the vein at the optic cup site (OC-RVOs), leading to weakening of the vein wall. Therefore, glaucomatous cupping is a major factor promoting venous occlusion at this site. Glaucomatous cupping leads to a loss of the glial tissue that supports the retinal vein and exposes it to ocular pressure changes.

Diffuse senile arteriosclerosis Arteriosclerotic changes may involve the trabecular meshwork, lamina cribrosa, and adventitial sheath of the retinal vessels; they are the most common causes of central/hemicentral RVOs and can also intervene in the pathogenesis of POAG.

TRANSIENT SECONDARY NON-RUBEOTIC ANGLE-CLOSURE GLAUCOMA FOLLOWING CRVO

This form of glaucoma must be distinguished from NVG because the treatments and prognoses may differ between the 2 conditions.

General Characteristics[24-25] 1) unilateral acute OH with angle-closure and flattening of the anterior chamber, which appears within 1mo of a CRVO attack; 2) the congener eye shows a deep anterior chamber, normal IOP, and a wide open (45º width) anterior chamber angle; 3) transient character; and 4) lack of the intraocular NV.

The shallowness of the anterior chamber is due to an abnormal accumulation of blood or transudative fluid from the retinal vessels, in the posterior segment of the eye, that pushes the vitreous and lens forward, blocks the pupil, and leads to angle-closure glaucoma. Vascular congestion and swelling of the ciliary body in the setting of a CRVO relaxes the zoules causing further anterior displacement of the lens. The swollen ciliary body can also narrow the angle by anterior displacement of the iris. The angle-closure is caused by an abnormal resistance to the aqueous humor flow through the pupil from the posterior to the anterior chamber, due to the anterior positioning of the lens. The mechanism is analogous to that of the PACG, with an anteriorly positioned lens, but on a permanent rather than a transient basis. The favorable effect of cycloplegics is due to tightening of the zonules, which favors posterior displacement of the iris-lens diaphragm[1,24].

These features justify the classification of the transient non-rubeotic angle-closure glaucoma following CRVO among the ocular conditions showing similarities with the classical malignant glaucoma without being identified with this form of malignant hypertension. Anti-VEGF agents are beneficial because they act synergistically reversing the increased vascular permeability mediated by VEGF and decreasing the amount of fluid in the posterior portion of the eyeball.

Choroidal hemorrhages, massive vitreous hemorrhages, uveal effusions, and PRPs are other causes of transient unilateral flattening of the anterior chamber, with or without angle-closure glaucoma[25].

The reported incidence of non-rubeotic angle-closure glaucoma in patients with CRVO is extremely low (0.68%)[24]. However, the disease could be more frequent than thought, but be only rarely diagnosed.

In conclusion, the IOP in central/hemicentral RVOs can undergo increases and reductions. The IOP reductions are anodyne and have little clinical relevance. On the contrary, IOP increases include well-individualized glaucoma entities such as acute central/hemicentral RVOs-emergent secondary glaucomas (*e.g.*, NVG and secondary angle-closure glaucoma without rubeosis) and some clinically well-defined forms of high IOP and glaucoma that precede and may lead to appearance of acute central/hemicentral RVOs (*e.g.*, OH, primary angle-closure, PACG, and open angle glaucoma).

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