

## Pathogenesis of Retinal Vein Occlusion

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Received: January 15, 2016

Revised: March 26, 2016

Accepted: October 12, 2015

Published online: June 28, 2016

### ABSTRACT

Retinal vein occlusion (RVO) has multiple pathogenetic mechanism that including local anatomical susceptibility, degenerative changes of the vessel wall and abnormal hematological abnormalities. All of these mechanisms could contribute to develop vascular obstruction. Anatomic features of arteriovenous crossings and common adventitial sheath shared by artery and vein could cause turbulent flow. Turbulence in vessel flow promotes endothelial phenotypic changes that cause endothelial f-actin expression increase. Intercellular adhesions and endothelial functions are affected by high f-actin levels. Damaged arteries and hypoxic tissues express endothelin-1 (ET-1). Endothelin-1 can diffuse from the neighboring veins and stimulate venous vasoconstriction. Vasoconstriction of veins lead to an increase in pressure. High blood viscosity is another important factor in pathogenesis of RVO. Pathogenesis of RVO is very complex and these factors can lead to a vicious cycle of worsening the other factor.

**Key words:** Central; Branch; Retinal vein occlusion; Endothelial dysfunction

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Uğurlu N, Uzel AGT, Şengül A. Pathogenesis of Retinal Vein Occlusion. *International Journal of Ophthalmic Research* 2016; 2(2): 130-132 Available from: URL: <http://www.ghrnet.org/index.php/ijor/article/view/1502>

### INTRODUCTION

Ocular vascular occlusive disorders collectively constitute the most common cause of visual disability<sup>[1]</sup>. Retinal vein occlusion (RVO) is the second most common retinal vascular disorder after diabetic retinopathy and is considered to be an important cause of visual loss<sup>[2,3]</sup>.

While the exact pathogenesis of RVO remains unclear and controversial, it has been suggested that multiple factors including local anatomical susceptibility, degenerative changes of the vessel wall and abnormal hematological abnormalities may all contribute to the development of vascular obstruction. While arterial disease is considered to be the predominant aetiology in both central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), the other risk factors are different in both presentations.

### LOCAL ANATOMICAL SUSCEPTIBILITY

In CRVO, obstruction of retinal blood flow in the region of lamina cribrosa and just posterior of it occur as a result of different contributing factors. Unique anatomical features of CRVO in the region of lamina cribrosa may predispose to obstruction.

Central retinal artery and central retinal vein share a common adventitial sheath at the lamina cribrosa. The central retinal vein could be compressed by right next to artery especially in eyes with arteriosclerotic vascular disease. Rigid and hyperplastic arteriosclerotic artery wall causes mechanical narrowing of thin-walled vein<sup>[4]</sup>. High blood velocities in the CRVO also lead to endothelial cell damage, endothelial proliferation and possible thrombus formation<sup>[5-7]</sup>. Narrowing of central venous lumen and

turbulent flow in this region results occlusion at the lamina cribrosa. The association between BRVO and arteriovenous (A/V) crossing was first reported by Koyanagi in 1928<sup>[8]</sup>. Branch RVOs occur almost invariably at a site where the artery crosses over the vein. In approximately 60-70% of eyes that are unaffected by BRVO the artery has been reported to be anterior to the vein whereas in 98-99% of eyes with BRVO it crosses the vein<sup>[9-11]</sup>.

Anatomic features of A/V crossings and secondary effects of arteriolar sclerosis may prone the crossing site to venous occlusion. The thin-walled vein lies between the rigid thick-walled artery and the highly cellular retina in the majority of A/V crossings. Common adventitial sheath shared by artery and vein and the narrowing of the venous provide the setting for BRVO<sup>[12-14]</sup>. Increased rigidity of the crossing artery induced by arteriolar sclerosis may increase the risk of occlusion. Studies investigating the vulnerability of A/V crossing sites to BRVO have reported focal thickening of the venous basement membrane and hyperplasia of extracellular matrix and adventitia at A/V crossings<sup>[15-19]</sup>.

However, an additional pathogenetic mechanism has recently been postulated for development of venous occlusion. Atherosclerotic arteries may be producing increased endothelin-1 (ET-1), which may diffuse across to the neighboring vein, stimulating venous vasoconstriction<sup>[19]</sup> and increase retinal venous pressure<sup>[20]</sup>. While vascular endothelial cells produce ET-1 under a physiological condition but also all cells under stress produce ET-1. Potential sources of ET-1 could be systemic circulation, diseased artery and hypoxic neighboring tissue<sup>[20]</sup>.

It was assumed that ocular perfusion pressure decreases progressively as a result of increased retinal vein pressure. If the critical limit for perfusion pressure is exceeded, hypoxic retina could secrete more ET-1. There would be dangerous vicious cycle that causes retinal hemorrhages and retinal edema<sup>[21-24]</sup>.

## DEGENERATIVE CHANGES OF THE VESSEL WALL

It has recently been postulated that retinal and choroidal endothelial cells has functional and structural site (like geometrics, phenotype and intracellular cytoskeleton) specific heterogeneity. Possible relationship between the site specific changes of vascular endothelial phenotype and endothelial dysfunction have been investigated in many literature. The endothelium is subjected to the mechanical forces due to shear stress related to blood flow. Endothelial cells converts these mechanical signals into chemical signals and it starts a series of signal transduction pathways and differentiation in endothelial cell phenotype. Endothelial phenotypic heterogeneity is a core property of the endothelium and has been described at the level of cell morphology, function, gene expression, and antigen composition. Endothelial phenotypic changes and endothelial dysfunction has been considered as playing important role in pathogenesis of many vascular diseases also in BRVO and CRVO<sup>[25]</sup>.

It has been proposed that as a result of turbulent blood flow in the retinal vein at A/V crossing induces endothelial damage and causes thrombus formation and venous occlusion<sup>[26-28]</sup>. Endothelium has important roles in regulating the response of hemodynamic changes and modification of cell shape<sup>[29-32]</sup>. At the A/V crossing regions age related changes of shape and intracellular structures have been recognized. These site specific changes has been reported much more frequent in elderly patients with systemic diseases like diabetes mellitus and systemic hypertension. It has been postulated that these site specific and age related changes in vascular endothelial cells

may have important role in BRVO<sup>[33]</sup>.

As mentioned above, the area of the lamina cribrosa is the specific localization of CRVO. Both environmental and genetic factors may cause endothelial phenotype changes<sup>[34]</sup>. Polygonal morphology of endothelial cells in prelaminar region were transiently changed to spindle shaped in the lamina cribrosa. Lamina cribrosa region is the site of greatest endothelial phenotypic changes identify. In patients with vascular comorbidities, endothelial f-actin expression also increases in central retinal vein<sup>[35]</sup>. The force transduction mechanisms in endothelial cells are a combination of force transmission via cytoskeletal elements and transduction of the physical forces to biochemical signals at mechanotransducer sites. F-actin microfilaments are basic structure at transmission and transduction. Endothelial f-actin intercellular adhesions and regulate the effect of endothelial cells on external mechanical forces induced internal mechanical stress. All these changes are suggested as part of high hemodynamic force in lamina cribrosa region contributing to CRVO.

## HEMATOLOGICAL DISORDERS

Two main hematological disorders in the pathogenesis of BRVO are dysregulation of the thrombosis-fibrinolysis balance and conditions leading to high blood viscosity<sup>[36-38]</sup>. They create more favorable environment to intravenous thrombus formation and venous occlusion. Association between BRVO and hyperviscosity due to high hemotocrit was demonstrated in literature<sup>[39-41]</sup>. Results of published studies conflicting and the role of coagulation factors in the development of RVO is not fully understood.

## CONCLUSION

Pathogenesis of RVO is complex and multifactorial. Different anatomical, vascular and inflammatory factors may contribute to its pathophysiology.

## COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

## REFERENCES

- 1 Hayreh SS. Ocular vascular occlusive disorders: natural history of visual outcome. *Prog Retin Eye Res.* 2014 Jul; **41**: 1-25. doi: 10.1016/j.preteyeres.2014.04.001. Epub 2014 Apr 21. Review.
- 2 Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc* 2000; **98**: 133-141.
- 3 Rehak J, Rehak M. Branch retinal vein occlusion: pathogenesis, visual prognosis, and treatment modalities. *Curr Eye Res* 2008; **33**: 111-131.
- 4 Green WR, Chan CC, Hutchins GM, et al. Central retinal vein occlusion: a prospective histopathologic study of 29 eyes in 28 cases. *Trans Am Ophthalmol Soc.* 1981; **79**: 371-422.
- 5 Williamson TH. A 'throttle' mechanism in the central retinal vein in the region of the lamina cribrosa. *Br J Ophthalmol* 2007; **91**: 1190-3.
- 6 Rehak J, Rehak M. Branch retinal vein occlusion: pathogenesis, visual prognosis, and treatment modalities. *Curr Eye Res.* 2008; **33**: 111-31
- 7 Kumar B, Yu DY, Morgan WH, et al. The distribution of angioarchitectural changes within the vicinity of the arteriovenous crossing in branch retinal vein occlusion. *Ophthalmology.* 1998; **105**(3): 424-7

- 8 Koyanagi Y. The role of arteriovenous crossing for occurring of retinal branch vein occlusion. *Klin Monatsbl Augenheilkd.* 1928; **81**: 219-231.
- 9 Duker JS, Brown GC. Anterior location of the crossing artery in branch retinal vein occlusion. *Arch Ophthalmol.* 1989; **107**(7): 998-1000
- 10 Takahashi K, Muraoka K, Kishi S, et al. Formation of retinochoroidal collaterals in central retinal vein occlusion. *Am J Ophthalmol.* 1998; **126**(1): 91-9
- 11 Weinberg D, Dodwell DG, Fern SA. Anatomy of arteriovenous crossings in branch retinal vein occlusion. *Am J Ophthalmol.* 1990; **109**(3): 298-302
- 12 Zhao J, Sastry SM, Sperduto RD, Chew EY, Remaley NA. Arteriovenous crossing patterns in branch retinal vein occlusion. *Ophthalmology.* 1993; **100**: 423-428.
- 13 Duker JS, Brown GC. Anterior location of the crossing artery in branch retinal vein obstruction. *Arch Ophthalmol.* 1989; **107**: 998-1000.
- 14 Jefferies P, Clemett R, Day T. An anatomical study of retinal arteriovenous crossings and their role in the pathogenesis of retinal branch vein occlusions. *Aust NZ J Ophthalmol.* 1993; **21**: 213-217.
- 15 Christoffersen NL, Larsen M. Pathophysiology and hemodynamics of branch retinal vein occlusion. *Ophthalmology* 1999; **106**: 2054-2062.
- 16 Staurenghi G, Lonati C, Aschero M, Orzalesi N. Arteriovenous crossing as a risk factor in branch retinal vein occlusion. *Am J Ophthalmol* 1994; **117**: 211-213.
- 17 Weinberg D, Dodwell DG, Fern SA. Anatomy of arteriovenous crossings in branch retinal vein occlusion. *Am J Ophthalmol* 1990; **109**: 298-302.
- 18 Duker JS, Brown GC. Anterior location of the crossing artery in branch retinal vein obstruction. *Arch Ophthalmol* 1989; **107**: 998-1000.
- 19 Fraenkl SA, Mozaffarieh M, Flammer J. Retinal vein occlusions: the potential impact of a dysregulation of the retinal veins. *EPMA J* 2010; **1**: 253-261.
- 20 Flammer J, Konieczka K. Retinal venous pressure: the role of endothelin. *EPMA J.* 2015 Oct 26; **6**: 21. doi: 10.1186/s13167-015-0043-1. eCollection 2015. Review
- 21 Kaur C, Foulds WS, Ling EA. Blood-retinal barrier in hypoxic ischaemic conditions: basic concepts, clinical features and management. *Prog Retin Eye Res.* 2008; **27**(6): 622-47. doi: 10.1016/j.preteyeres.2008.09.003.
- 22 Flammer J, Konieczka K, Flammer AJ. The primary vascular dysregulation syndrome: implications for eye diseases. *EPMA J.* 2013; **4**(1): 14. doi: 10.1186/1878-5085-4-14.
- 23 Xu W, Wang HY, Zhao XH, Wang PJ. Values of ocular hemodynamics and serum endothelin-1 in the early diagnosis of diabetic retinopathy. *Zhonghua Yi Xue Za Zhi.* 2013; **93**(1): 37-40.
- 24 Sasongko MB, Wong TY, Nguyen TT, Cheung CY, Shaw JE, Kawasaki R, et al. Retinal vessel tortuosity and its relation to traditional and novel vascular risk markers in persons with diabetes. *Curr Eye Res.* 2015; 1-7.
- 25 Yu DY, Yu PK, Cringle SJ, Kang MH, Su EN Functional and morphological characteristics of the retinal and choroidal vasculature. *Prog Retin Eye Res.* 2014 May; **40**: 53-93. doi: 10.1016/j.preteyeres.2014.02.001. Epub 2014 Feb 28.
- 26 Dallinger S, Dörner GT, Wenzel R, Graselli U, Findl O, Eichler HG, Wolzt M, Schmetterer L. Endothelin-1 contributes to hyperoxia-induced vasoconstriction in the human retina. *Investig. Ophthalmol. Vis. Sci.* 2000; **41**: 864e869.
- 27 Davies PF. Endothelium as a signal transduction interface for flow forces: cell surface dynamics. *Thromb. Haemost.* 1993; **70**: 124e128.
- 28 Deguchi S, Maeda K, Ohashi T, Sato M. Flow-induced hardening of endothelial nucleus as an intracellular stress-bearing organelle. *J. Biomech.* 2005; **38**: 1751-1759
- 29 Pries AR, Secomb TW, Gaetgens P. Structure and hemodynamics of microvascular networks: heterogeneity and correlations. *Am. J. Physiol.* 1995; **269**: H1713e-H1722.
- 30 Pries AR, Kuebler WM. Normal endothelium. *Handb. Exp. Pharmacol.* 2006; 1e
- 31 Pries AR. The vascular endothelium: structural, functional and pathophysiological aspects. *Biomed. Pharmacother.* 2008; **62**: 503.
- 32 Pries AR, Secomb TW. Origins of heterogeneity in tissue perfusion and metabolism. *Cardiovasc. Res.* 2009; **81**: 328e335.
- 33 Kang MH, Balaratnasingam C, Yu PK, Morgan WH, McAllister IL, Cringle SJ, Yu DY. Alterations to vascular endothelium in the optic nerve head in patients with vascular comorbidities. *Exp Eye Res.* 2013 Jun; **111**: 50-60. doi: 10.1016/j.exer.2013.03.005. Epub 2013 Mar 19.
- 34 Kang MH, Balaratnasingam C, Yu P, Morgan WH, McAllister IL, Cringle SJ, Yu DY. Morphometric characteristics of central retinal artery and vein endothelium in the normal human optic nerve head. *Investig. Ophthalmol. Vis. Sci.* 2011; **52**: 1359e1367.
- 35 Prasain N, Stevens T. The actin cytoskeleton in endothelial cell phenotypes. *Microvasc. Res.* 2009 Jan; **77**(1): 53-63.
- 36 Chen HC, Wiek J, Gupta A, Luckie A, Kohner EM. Effect of iso-osmotic haemodilution on visual outcome in branch retinal vein occlusion. *Br J Ophthalmol.* 1998; **82**: 162-167.
- 37 Janssen MCH, de Heijer M, Cruysberg JRM, Wollersheim H, Bredie SJH. Retinal vein occlusion: A form of venous thrombosis or a complication of atherosclerosis? *Thromb Haemost.* 2005; **93**: 1021- 1026.
- 38 Trope GE, Lowe GD, McArdle BM, Douglas JT, Forbes CD, Prentice CM, Foulds WS. Abnormal blood viscosity and haemostasis in longstanding retinal vein occlusion. *Br J Ophthalmol.* 1983; **67**: 137- 142.
- 39 Clouse LH, Comp PC. The regulation of hemostasis: The protein C system. *N Eng J Med.* 1986; **314**: 1298-1304.
- 40 McGrath MA, Wechsler F, Hunyor AB, Penny R. Systemic factors contributory to retinal vein occlusion. *Arch Intern Med.* 1978; **138**: 216-220.
- 41 Tekeli O, Gürsel E, Buyurgan H. Protein C, protein S and anti-thrombin III deficiencies in retinal vein occlusion. *Acta Ophthalmol Scand.* 1999; **77**: 628-630

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