

The Vascular Theory in Glaucoma

A focus on the endothelial cells.

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Glaucoma, a progressive optic neuropathy, is among the leading causes of blindness. IOP is widely recognized as the risk factor that can be modified to slow the progression of this disease. The importance of IOP in glaucoma has been confirmed in numerous well-controlled, multicentered, randomized trials.^{1,2} Nonetheless, despite pressure lowering, this neurodegenerative disease can still progress, producing structural and anatomical alterations along with functional loss.³ Documented structural changes, for example, occur within the lamina cribrosa, with a loss of retinal ganglion cells⁴ and changes in the ocular vasculature.^{5,6} The result of this progressive process is recognized as glaucomatous visual field loss.^{1,2}

Priestly Smith has been quoted as suggesting in the 19th century that the glaucomatous optic nerve is not purely a mechanical result but is at least in part “an atrophic condition which, though primarily due to intraocular pressure, includes vascular changes and impaired nutrition in the substance of the optic disc ... which may probably progress even though all excessive pressure is removed.”⁷ The vascular theory of glaucoma considers glaucomatous optic neuropathy to be a consequence of insufficient blood supply due to increased IOP and/or other risk factors reducing ocular blood flow. Over the last few years, there has been mounting evidence in the literature on the possible role in glaucoma played by the ocular vascular system, associated vascular cellular mediators, and factors other than IOP. The general consensus is that various contributing risk factors independent of and dependent on IOP are working to advance the damage occurring at the level of the optic nerve and the nerve fiber layer. These risk factors include diurnal fluctuations in IOP, age, arterial hypertension, low systolic perfusion pressure, low diastolic perfu-

sion pressure, a reduction of blood pressure in hypertensive patients, cardiovascular disease, migraines, smoking, and vasospastic disorders.^{3,8-11}

The Thessaloniki Eye Study established the relationship between treatment with antihypertensive medication in subjects without glaucoma and structural changes in the optic disc.¹² In this study, low perfusion pressure was found to be associated with increased cup area, decreased rim area, and a greater cup-to-disc ratio. Despite the data, there is no consensus on these IOP-independent factors. Nor is there agreement on how to regulate and influence these factors. Given the emerging data on blood flow, however, the ocular vasculature with associated vascular endothelial dysfunction has been implicated in the pathogenesis of glaucoma.¹³

Researchers have long reported that altered blood flow measurements exist in glaucoma patients, and glaucoma-like damage can be independent yet affected by IOP. A multitude of small prospective studies have demonstrated blood flow deficiencies in the retinal,¹⁴ choroidal,¹⁵ and retrobulbar^{16,17} circulation of patients with open-angle glaucoma (OAG). An alteration in the blood supply to the eye can be further correlated to vascular endothelial dysfunction.¹⁸ Researchers have suggested the paradigm that insults not

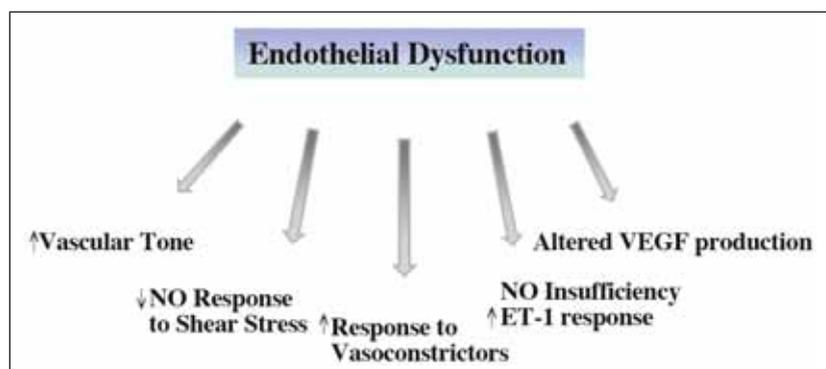


Figure 1. Endothelial cellular dysfunction can lead to alterations in the various secreted vascular mediators that may affect the overall vascular tone, contractility, and endothelial cellular repair. Abbreviations: ET-1, endothelin-1; NO, nitric oxide; VEGF, vascular endothelial growth factor.

related to IOP, such as those associated with endothelial cellular damage and atherosclerosis (eg, aging, inflammation, and reduced ocular blood flow), can damage the optic nerve head's connective tissue and axons.¹⁹ This idea helps substantiate the premise that reduced ocular blood flow and perhaps underlying vascular disease that increases with age are directly involved in the pathophysiology of glaucoma.

THE ENDOTHELIAL CELL AND ITS VASCULAR MEDIATORS

Primary endothelial dysfunction can influence the vessel's diameter and resistance. The narrowing of blood vessels will increase resistance to flow distally, thus leading to distal tissue hypoxia. Such narrowing can be induced by excessive endothelial damage resulting in vasoconstriction due to low levels of nitric oxide and can be seen in ocular pathologies with underlying vascular endothelial dysfunction.¹³ Evidence of retinal vascular narrowing was reported in Asians with glaucomatous eyes after adjusting for age,⁶ and these findings were consistent with two other population-based studies: the Blue Mountains Eye Study²⁰ and the Beijing Eye Study.²¹ The Beaver Dam Eye Study and the Rotterdam Study, however, have not supported this association.^{22,23}

The normal vascular endothelium regulates the microcirculation through the release of vasoactive factors, including the potent vasodilator nitric oxide,²⁴ the vasoconstrictor endothelin-1 (ET-1), and reparative and trophic proteins such as vascular endothelial growth factor (VEGF) and soluble VEGF receptor FLT-1.¹³

Vascular endothelial dysfunction is a common pathophysiological aspect of many disease states. Reduced levels of nitric oxide have been found to be associated with systemic vascular disease. Depressed levels of nitric oxide can result from a decrease in nitric oxide synthesis (ie, nitric oxide synthetase) as a result of dysfunctional endothelial cells. Low levels of nitric oxide will result in decreased vasodilatation and increased vasoconstriction, leading to reduced blood flow, which has been reported in glaucoma.²⁵ This decreased availability of nitric oxide can also result in elevated oxidative stress due to increased reactive oxygen species and the activation of proinflammatory mediators.

Giaconi et al pointed to the benefit of a diet high in fruit and vegetables (ie, antioxidants) in terms of a decreased risk of glaucoma.²⁶ The value of antioxidants for improving vascular function has been widely accepted in cardiovascular disease but has not been fully established in relation to glaucoma.

Compromised availability of nitric oxide as well as an imbalance between nitric oxide and ET-1 have been reported in glaucoma patients.¹³ Low aqueous levels of nitric oxide have also been reported in some individuals with glauco-

ma.²⁵ Furthermore, an abnormal response to a systemic nitric oxide synthetase inhibitor was found in ocular blood flow measurements among patients with OAG without a similar response in systemic blood pressure.²⁷ Researchers have reported increased plasma levels of ET-1 in patients with normal-tension glaucoma and elevated aqueous humor levels of ET-1 in OAG patients.¹³ If vasoconstriction indeed occurs through lower nitric oxide levels or increased reactivity to levels of ET-1, hypoxia will be present. With increased hypoxia, it is reasonable to suppose that VEGF may also get upregulated in glaucoma similar to the mechanism by which it is upregulated in ischemic retinal pathology (Figure 1).

Secreted from endothelial cells, VEGF is upregulated in hypoxic environments systemically. VEGF serves not only as a pro-angiogenic factor but also as a strong vascular trophic factor, thus encouraging vessel endothelial and basement membrane repair with a restoration of normal cellular function in both healthy and disease states.²⁸ Researchers have reported elevated aqueous levels of VEGF in glaucoma patients.²⁹ Underlying endothelial damage, if occurring in glaucoma, may lead to increased vascular inflammation, with further elevation of ischemically driven growth factors, inflammatory cytokines, and altered nitric oxide levels. The process is similar to what occurs in systemic age-related atherosclerotic vascular disease.

CONCLUSION

As research on glaucoma progresses, it may become worthwhile to look at the various cellular structures that compose the ocular system. If the disease is influenced by elements of ischemia and vascular insufficiency, and the endothelial cell is pivotal to a healthy vasculature and the normal function of vessels systemically, it seems reasonable to propose that endothelial dysfunction may play a role in glaucoma, particularly due to the presence of endothelial cells in the trabecular meshwork.¹³ It is intriguing to consider the endothelial cell as an additional target for pharmacologic mediators aimed at intervening in the glaucomatous process. □

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