Perfusion Pressure and Glaucoma

Work is ongoing toward understanding the participation of vascular phenomena in the pathophysiology of glaucoma.

BY ALON HARRIS, PHD

Glaucoma remains a multifactorial optic neuropathy of unknown etiology and sometimes inadequate treatment.[1] Several large-scale studies published during the past several years have provided substantial proof that reducing IOP benefits patients with glaucoma,[2-6] and, presently, the only definitive treatment for glaucoma is to lower IOP surgically and/or medically, thus slowing disease progression. This finding holds true for glaucoma patients with IOPs above and within the normal range.[7]

Research indicates that optic nerve ischemia may contribute to glaucomatous damage[8,9] and establishes links between glaucoma and microvascular disease, systemic vascular disease, and vasospasm.[10-12] According to evidence-based medicine, diastolic perfusion pressure is the only vascular parameter that meets the criteria necessary to be considered clinically. The relationship between perfusion pressure and glaucoma is not known, but the existence of a relationship begs the question, are vascular deficits and ischemia involved in the pathogenesis and progression of glaucoma? This article examines the current understanding of the role of vascular factors in glaucoma.

EVIDENCE-BASED STUDIES OF A VASCULAR ROLE IN GLAUCOMA

Population-based studies have found that vascular-related factors are also risk factors in glaucoma. In 1983, Framingham Eye Study participants with open-angle glaucoma (OAG) were reported to have significantly low blood pressure (BP)/IOP ratios.[13] In addition, persons with definite glaucomatous visual field defects had lower ratios than those with suspect defects or no defects. Low perfusion pressure was also an OAG risk factor in the Baltimore Eye Survey, Egna-Neumarkt, Proyecto VER, and, most recently, the Barbados Incidence Study of Eye Diseases.[14-17]

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The Baltimore Eye Survey found a diastolic perfusion pressure (diastolic perfusion pressure = diastolic BP - IOP) of less than 30 mm Hg to be strongly associated with OAG (risk ratio = 6), whereas systolic perfusion pressure (systolic perfusion pressure = systolic BP - IOP) and mean perfusion pressure (mean perfusion pressure = mean BP - IOP) were only mildly associated.[14] In the Egna-Neumarkt study, the OAG prevalence increased progressively with decreased diastolic perfusion pressure,[15] and the Proyecto VER study reported similar results at a low diastolic perfusion pressure.[16] The Barbados Incidence Study of Eye Diseases found all three factors (diastolic perfusion pressure, systolic perfusion pressure, and mean perfusion pressure) to be related to OAG, but a low diastolic perfusion pressure had the strongest correlation, approximately tripling subjects' risk ratio of developing OAG.[17]

CLINICAL EVIDENCE OF VASCULAR DEFICITS

Clinical studies have detected numerous ocular blood flow deficits in some patients with primary open-angle glaucoma (POAG). Several different methodologies have been used to assess blood flow. Fluorescein angiography has demonstrated reduced total retinal blood flow and dye leakage from optic nerve head (ONH) capillaries,[8] findings suggesting peripapillary ischemia in glaucoma.[9]

Scanning laser Doppler flowmetry combines laser flow-

metry over a defined area of points and creates a 2-D perfusion map. The penetration depth is approximately 400 µm and only measures the flow in the microcirculation. The velocity limit is 10 mm/second and is therefore inaccurate for large vessels. Researchers have used this technology to demonstrate reduced blood flow in a number of conditions, but the findings have been variable. Investigators have demonstrated (1) lower optic nerve blood flow in POAG compared to OHT subjects,[18] (2) an inverse relation between C/D ratio and ONH flow,[18,19] (3) reduced ONH flow in patients with normal-tension glaucoma (NTG),[19] and (4) decreased ONH flow with worsened mean defect or corrected pattern standard deviation.[20,21]

Studies have also shown that the choroidal circulation in glaucoma fails to vasodilate appropriately,[22] and delays in choroidal filling may be associated with a thinning of the entire choroid.[23] In addition, the retrobulbar vessels in both NTG and POAG patients exhibited increased resistance indices during color Doppler imaging.[10,24] Such imaging measures retrobulbar blood velocities and resistivity index in the ophthalmic artery, ciliary arteries, and central retinal artery. These vascular abnormalities may be among the earliest manifestations of glaucoma.[25-27]

Investigators including myself are evaluating the usefulness of retinal oximetry for assessing tissue ischemia. The measurement of blood oxygen saturation in the retinal vasculature may provide physicians with a better understanding of the relationship between vascular deficits, metabolic events, and glaucoma. The clinical measurement of oxygen saturation in humans is accomplished noninvasively by optical means. Via the different optical characteristics of oxygenated and deoxygenated hemoglobin, the wavelength-dependent transmission of light through perfused tissue allows us to calculate the ratio of oxygenated hemoglobin to total hemoglobin concentration.[28]

Reduced perfusion pressure to the eye (potentially nocturnal) may cause disease progression, regardless of an individual's well-controlled IOP.[11] Despite accumulating evidence that glaucoma patients suffer from inadequate ocular blood flow, the current clinical treatment of the illness involves neither documentation nor treatment of these deficits.[29]

CELLULAR EFFECTS OF ISCHEMIA

Recent evidence suggests that glaucoma characteristically damages the photoreceptors and the horizontal cells, as well as the retinal ganglion cells.[30,31] Retinal circulation nourishes the retinal ganglion cells, whereas the photoreceptors receive their blood supply from the underlying choroid. In order to define how enhanced blood flow improves visual function, therefore, it is essential to evaluate blood flow to the retina and choroid, for the retinal ganglion cells and photoreceptor cells, respectively. If specific damage to retinal ganglion cells indeed causes visual function deterioration in glaucoma,[31] then enhancing retinal blood flow should improve this deficit. If, instead, photoreceptor deterioration underlies the decline in visual function, then improving choroidal blood flow should mitigate this process. Finally, if a loss of both cell types occurs in glaucoma,[11,29-33] then improving retinal and choroidal blood flow may have a beneficial effect.

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In animal models of glaucoma, retinal ganglion cells die via apoptosis,[33,34] a process in which ischemia may play a role.[34] In vivo and in vitro models of retinal ischemic/reperfusion injury emphasize the impact of the loss of nutrient delivery, especially to the apparently highly sensitive retinal ganglion cells.[35,36] In this context, improving blood flow may deliver immediate neuroprotection to these cells. Also, relieving ischemia and increasing oxygen may be another route to providing immediate neuroprotection in glaucoma.

Clinical studies of glaucoma and diabetes have linked visual function to hemodynamics. Hyperoxia acutely improved contrast sensitivity in diabetic patients who possessed a substantial initial contrast sensitivity defect.[37] The acute enhancement of ocular perfusion may improve visual function in some patients with NTG.[12,38-41] In a series of experiments with NTG patients, breathing CO_2 for several minutes (sufficient to increase end-tidal PCO_2 by 15%) reduced resistance indices in their ophthalmic arteries to normal levels, a discovery suggesting the existence of a reversible ocular vasospasm.[42] Investigators have obtained findings similar to these short-term results with CO_2 breathing both acutely and over 6 months in NTG patients treated with calcium channel blockers.[39-41,43,44] These studies imply that improving ocular perfusion may simultaneously and immediately enhance glaucoma patients' visual function, but the mechanism for this action is not yet defined.

CONCLUSION

Today, the role of vascular factors in the management of glaucoma is as undetermined as the role of IOP was 10 years ago. The only vascular factor consistently meeting the criteria required for clinical consideration is diastolic perfusion pressure. Currently, no evidence supports the role of ischemia in the clinical management of the disease, despite numerous small, clinical findings supporting the role of vascular deficits and ischemia in glaucoma. Technology for the comprehensive assessment of vascular hemodynamics exists in the clinical research environment, and a large-scale, prospective, ocular hemodynamic study in glaucoma could yield useful findings. In the future, such technology and research may assist glaucoma management. ❑

Supported in part by an unrestricted grant from Research to Prevent Blindness.

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