Ocular blood flow in glaucoma: the need for further clinical evidence and patient outcomes research

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The benefit of reducing intraocular pressure to prevent progression of glaucoma is well documented.^{1,2} Despite decreased intraocular pressure some patients will, however, continue to suffer glaucomatous progression. Potentially, as yet undetermined risk factors may be present in those patients who portend progression despite seemingly adequate ocular hypotensive therapy.

Although the exact risk factors have yet to be elucidated, impaired ocular blood flow is commonly cited as a possible cause. However, conclusive evidence of its role in pathogenesis, or the benefit of improving ocular blood flow, and thereby improving patient outcomes, remains elusive.

The purpose of this review is twofold: to evaluate the data linking the pathogenesis of reduced ocular blood flow to glaucoma; and to review the benefits of improving ocular blood flow in glaucoma.

Two lines of evidence exist that potentially link impaired ocular blood flow to the pathogenesis of glaucoma: epidemiological and short-term ocular hemodynamic studies. Numerous published studies have found associations between various forms of cardiovascular disease and elevated intraocular pressure or glaucoma.³ These trials have generally linked two types of disease classes to glaucoma and ocular hypertension: chronic cardiovascular disease (i.e. systemic hypertension, diabetes or atherosclerotic heart disease) or vasospastic disorders (i.e. migraine and Raynaud's phenomenon). The common pathological effect of these disease states is presumed to be decreased ocular perfusion pressure.

Although the majority of published data suggest a link between atherosclerotic or vasospastic disease and glaucoma, the data are inconsistent. For example, the Ocular Hypertension Treatment Study did not confirm cardiovascular disease as a risk factor for glaucoma and suggested that diabetes might actually be protective.² Furthermore, epidemiological studies cannot determine whether cardiovascular disease is causal to, or only associated with, glaucoma.

In the early 1990s advances in technology led to several methods for directly measuring ocular and periocular hemodynamics, including pulsatile ocular blood flow (believed to measure peak choroidal blood flow), color Doppler imaging (retrobulbar red blood cell velocity and resistivity index), laser Doppler/Heidelberg retina flowmeter (superficial retinal blood flow), fluorescein angiography (retinal fill time), indocyanine green angiography (choroidal fill time) and the laser speckle technique (retinal red blood cell velocity).⁴

Despite these advances a number of problems exist with these techniques. First, the instruments are generally expensive and require considerable technical skill for accurate operation. Consequently, the accessibility of this technology for routine clinical use remains limited. Second, even if there were a confirmed link between the pathogenesis of glaucoma and reduced blood flow, its precise location within the ocular vasculature remains unknown.⁴ Therefore, it remains uncertain which of these instruments would be most able to identify or follow patients with glaucoma-related vascular disease. Third, whether any parameters assessed by these instruments, such as red blood cell velocity or resistivity index, adequately measure the altered ocular hemodynamics associated with the pathogenesis of glaucoma remains unclear. Finally, even if currently measured blood flow parameters are correct, it remains uncertain if these instruments are sufficiently sensitive to measure a clinically important hemodynamic change.

Nonetheless, studies evaluating ocular hemodynamics have indicated worsened ocular blood flow parameters in patients with ocular hypertension, normal tension or primary open-angle glaucoma compared with normal subjects. Furthermore, several investigators have suggested that patients with progressed glaucoma have worse ocular hemodynamics than non-progressed patients.^{5,6} In addition, several studies have also linked several cardiovascular-based diseases with normal tension or primary open-angle glaucoma,

including the presence of cerebral deep white matter lesions, Alzheimer's disease and poor carotid artery circulation.^{7,8}

Those studies, however, fail to confirm the pathogenic relationship of poor ocular hemodynamics with glaucoma. This is because it remains uncertain if the observed worsened ocular blood flow parameters were a primary insult from the glaucoma or secondary as a result of the glaucomatous process decreasing the amount of available optic nerve and its oxygen requirement. In addition, studies linking systemic vascular disease to glaucoma, such as epidemiological studies, cannot demonstrate if it is a casual or causal association.

Importantly, to demonstrate a pathogenic link between glaucoma and impaired ocular hemodynamics a long-term (five years) prospective study is needed that includes adequately populated patient groups that are similar in age, glaucomatous damage, ocular hypertensive treatments and intraocular pressure, but with dissimilar baseline ocular hemodynamics. The presence of more progressive disease over time in patients with worse baseline ocular blood flow parameters would demonstrate with more certainty a pathogenic link of ocular blood flow to glaucoma visual outcomes.

Currently, no medical therapy for glaucoma exists that was designed directly to improve ocular blood flow for ocular hypertension or glaucoma. A number of commercially available ocular hypotensive agents are, however, available that may improve blood flow. Betaxolol, a β -1 selective blocker, in animal and in-vitro models, has demonstrated a relative blood flow advantage over non-selective β -adrenergic blockers. Latanoprost may also improve ocular hemodynamics by pulsatile ocular blood flow and color Doppler techniques. It has, however, been thought that this finding is not a primary physiological response, but a consequence of the marked reduction in intraocular pressure associated with this medicine. Dorzolamide, as a single agent and in fixed combination with timolol, has been shown to increase red blood cell velocity with pulsatile ocular blood flow, color Doppler and laser Doppler techniques in normal individuals as well as low-tension and primary open-angle glaucoma patients. This positive effect on ocular hemodynamics has been greater than observed with betaxolol, latanoprost, bimatoprost or timolol even with similar or lesser intraocular pressure lowering.⁹

Despite these studies it is still unclear whether the animal and in-vitro models or the clinical data noted above are important for patients with glaucoma, a population that is usually older and often has coexistent atherosclerotic disease. Currently, no

definitive data show that improving ocular blood flow protects vision long term. Furthermore, even if improving ocular blood flow was determined to be of benefit the cost of an accurate measurement of ocular hemodynamics may be prohibitive. Therefore, the use of intraocular pressure-lowering agents for their potential ocular blood flow characteristics, apart from their hypotensive effect, remains speculative. Long-term prospective trials are needed to show that increasing ocular flow can prevent glaucomatous progression better than reducing intraocular pressure alone. It is possible that increased ocular blood flow may be harmful, lead to more optic nerve hemorrhages and resultant progression. In addition, reproducible and cost-efficient instrumentation should be developed to allow physicians to diagnose and follow the specific glaucomatous pathological change in ocular hemodynamics.

In summary, studies of epidemiology and short-term clinical trials suggest a potential association between altered ocular hemodynamics in the pathogenesis of glaucoma. There are, however, no long-term prospective data to support more than an association.

Although no specific ocular blood flow product exists to treat glaucoma, several ocular hypotensive agents are available that potentially improve clinical ocular blood flow parameters. Unfortunately, there is limited evidence to show that improving

ocular hemodynamics in patients with glaucoma improves patient outcomes. Furthermore, it remains difficult to measure the ocular blood flow effect clinically on a routine basis. Consequently, physicians who currently prescribe an ocular hypotensive product based on its ocular blood flow characteristics do so without confirmed knowledge of a positive long-term clinical effect on vision and the ability to measure any improvement in ocular hemodynamics to demonstrate to themselves or their patients the benefit gained from the product.

Hopefully, future research will clarify the relationship of glaucoma with reduced ocular blood flow and determine the effects of improving ocular hemodynamics. Once such data are available it may become both cost effective and vision saving to measure and manage ocular hemodynamics in the clinical setting.

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REFERENCES

- 1 **The AGIS Investigators**. The advanced glaucoma intervention study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. *Am J Ophthalmol* 2000;**130**:429–40.
- 2 **Gordon MO**, Beiser JA, Brandt JD, *et al*. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;**120**:714–20.
- 3 **Shields MB**. *Textbook of glaucoma*. Baltimore: Williams and Wilkins, 1987:45–70.
- 4 **Cioffi GA**, Alm A. Measurement of ocular blood flow. *J Glaucoma* 2001;**10**(5 Suppl 1):S62–4.
- 5 **Satilmis M**, Orgul S, Doubler B, *et al*. Rate of progression of glaucoma correlates with retrobulbar circulation and intraocular pressure. *Am J Ophthalmol* 2003;**135**:664–9.
- 6 **Galassi F**, Sodi A, Ucci F, *et al*. Ocular hemodynamics and glaucoma prognosis: a color Doppler imaging study. *Arch Ophthalmol* 2003;**121**:1711–15.
- 7 **Stroman GA**, Stewart WC, Golnik KC, *et al*. Magnetic resonance imaging in patients with low-tension glaucoma. *Arch Ophthalmol* 1995;**113**:168–72.
- 8 **Sugiyama T**, Utsunomiya K, Ota H, *et al*. Comparative study of cerebral blood flow in patients with normal-tension glaucoma and control subjects. *Am J Ophthalmol* 2006;**141**:394–6.
- 9 **Zeitz O**, Matthiessen ET, Reuss J, *et al*. Effects of glaucoma drugs on ocular hemodynamics in normal tension glaucoma: a randomized trial comparing bimatoprost and latanoprost with dorzolamide. *BMC Ophthalmol* 2005;**5**:6.