

Does Blood Flow Measurement Have a Role in Glaucoma Care?

Advanced imaging technologies and therapeutic options make blood flow measurement a prime consideration in glaucoma monitoring.

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Lowering the IOP remains the only proven method to prevent the development or slow the progression of glaucomatous optic neuropathy.¹ Interestingly, a significant proportion of the treatment groups in the Early Manifest Glaucoma Trial (EMGT),² the Collaborative Initial Glaucoma Treatment Study (CIGTS),³ and the Collaborative Normal-Tension Glaucoma Study (CNTGS)⁴ experienced glaucomatous progression despite achieving the targeted decrease in IOP.

Although the cause of disease progression despite seemingly adequate IOP lowering is likely multifactorial, abnormalities in ocular perfusion have become a prime consideration. Vascular risk factors for glaucomatous progression implicate abnormal or insufficient blood flow to the optic nerve as a likely contributor to the disease process.^{5,6} This article describes novel diagnostic techniques as well as potential therapies related to ocular blood flow and glaucoma care.

DIAGNOSING ABNORMAL BLOOD FLOW

Low ocular perfusion pressure (OPP) may be used to determine whether abnormal microvascular flow is likely to occur at the level of the optic nerve. OPP is defined as the mean arterial pressure minus the IOP. Epidemiologic studies have identified low OPP as an independent risk factor for the development and progression of glaucoma.^{7,8}

Investigators have studied the potential of several advanced imaging modalities to uncover an ocular blood flow abnormality related to glaucomatous disease. Color Doppler imaging uses Doppler ultrasound

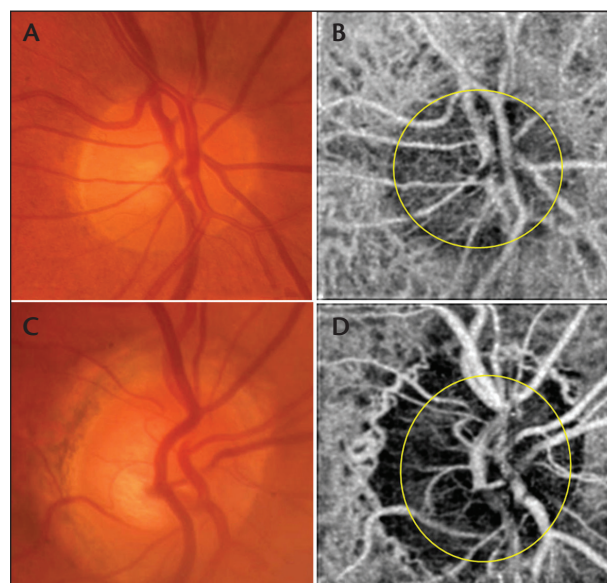


Figure. Disc photographs (A, C) and maximum projection of OCT angiograms (B, D) of the disc region (3×3 mm) in representative normal (A, B) and preperimetric glaucoma subjects (C, D). Both examples are from right eyes. The optic disc flow index is 0.178 in the normal subject and 0.150 in the preperimetric glaucoma subject.

to obtain quantitative measurements of the ophthalmic arterial circulation. This relatively noninvasive technique involves placing an ultrasound probe over a patient's closed eyelid. Based on diastolic flow velocities, ophthalmic arterial blood flow is measured in

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terms of ophthalmic arterial resistance (OA resistivity index). Galassi et al⁹ found that newly diagnosed glaucoma patients were six times more likely to suffer progressive disease when the OA resistivity index measured higher than 0.78 compared to patients with an OA index lower than 0.78 ($P < .001$). Laser Doppler flowmetry¹⁰ and laser speckle flowgraphy¹¹ have also been shown to be capable of detecting differences in optic nerve blood flow in glaucomatous and nonglaucomatous eyes. Unfortunately, the use of these methods for measuring the blood flow of small-caliber optic nerve vessels is limited by rather modest reliability indices.

Recently, Jia and colleagues reported on the use of optical coherence tomography (OCT) techniques to measure optic disc perfusion.¹² These techniques require the use of a high-speed OCT device (a repetition rate of 100-kHz axial scans) and a novel split-spectrum amplitude-decorrelation angiography algorithm to measure microvascular blood flow. This algorithm allows the detection of variable signal amplitudes returning from nonstatic tissues. Higher variability in signal amplitude leads to greater decorrelation of detected signals and occurs secondary to higher microvascular red blood cell flow rates. The degree of decorrelation may be quantified as the disc flow index, which is defined as the average decorrelation value within a three-dimensional volumetric scan of the optic disc. The investigators reported high intravisit repeatability and intervisit reproducibility indices with 100% sensitivity/specificity for differentiating normal optic discs from glaucomatous ones using a flow index cutoff of 0.1515. Importantly, disc flow index was found to correlate with visual field pattern standard deviation in patients with glaucoma ($R^2 = 0.752$, $P = .001$), indicating a relationship with functional deficit. The advantages of OCT angiography include its noninvasive nature and its ability to quantify microvascular flow in the optic nerve with high repeatability (Figure). The same investigators have also measured peripapillary retinal blood flow using a high-speed (70 kHz) commercial OCT device

(RTVue-XR Avanti; Optovue) with similarly favorable results (e-mail communication, August 4, 2014).

THERAPEUTIC OPTIONS

Considering the role of ocular blood flow in glaucoma care requires practical therapeutic options to allow for clinical decision making. Feke et al prospectively evaluated the effect of brimonidine 0.15% on retinal hemodynamics in glaucomatous eyes with retinal vascular dysregulation as determined by laser Doppler flowmetry.¹³ The group found that brimonidine significantly improved the impaired retinal vascular autoregulation in these patients, presumably through its interaction with the nitric oxide signaling cascade and modulation of retinal vascular tone. Using laser Doppler flowmetry, Kimura and colleagues investigated the effect of topical unoprostone on circulation in the optic nerve head of nonglaucomatous eyes and those with normal-tension glaucoma.¹⁴ The investigators found that, compared to baseline values, the mean blood flow and velocity values increased in both groups 2 hours after the topical instillation of unoprostone ($P < .05$).

In preliminary animal studies, Rho kinase inhibitors have also been shown to improve optic nerve blood flow, presumably via relaxation of the vascular endothelial smooth muscle.^{15,16} These agents are not yet commercially available but are in clinical trials for approval by the FDA.

Topical β -blocker therapy may diminish optic nerve head blood flow in susceptible individuals. Hayreh et

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1. Based on the information presented in this article, would you diagnose and treat blood flow abnormalities in the optic nerve to decrease the risk of glaucomatous progression in eyes with an acceptable IOP?

- ☐ Yes
☐ No
☐ Unsure

2. Do you currently use topical brimonidine, topical unoprostone, and/or trabeculectomy to treat blood flow abnormalities in the optic nerve?

- ☐ Yes
☐ No

al found that patients with normal-tension glaucoma who were treated with topical timolol twice daily were at increased risk of nocturnal arterial hypotension that potentially contributed to higher rates of visual field progression compared to subjects not treated with this agent ($P = .0003$).¹⁷ This potentially adverse effect of topical β -blockers may have contributed to the increased risk of visual field deterioration compared to subjects treated with brimonidine, as reported in the Low-Pressure Glaucoma Treatment Study (LoGTS).¹⁸

Januleviciene and colleagues reported on the beneficial effects of trabeculectomy surgery on ocular hemodynamic parameters in patients with pseudoexfoliative and open-angle glaucoma.¹⁹ In the study, a significant improvement in OPP and color Doppler imaging parameters was realized in the postoperative period compared to preoperatively.

CLINICAL CONSIDERATIONS

Advances in diagnostic imaging, particularly with novel OCT devices, promise to allow physicians to reliably measure optic nerve blood flow in the near future. Currently available therapeutic options such as topical brimonidine, topical unoprostone, and trabeculectomy appear to benefit optic nerve blood flow, whereas topical β -blockers may be disadvantageous in susceptible individuals. Topical Rho kinase inhibitors may also prove to be a therapeutic option. Clinicians' ability to diagnose and treat blood flow abnormalities in the optic nerve head may allow them to decrease the risk of glaucomatous progression in individuals with an IOP-independent component to their disease process. ■

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1. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol*. 1991;109(8):1090-1095.
2. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression. Results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol*. 2002;120(10):1268-1279.
3. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medication or surgery. *Ophthalmology*. 2001;108(11):1943-1953.
4. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. *Am J Ophthalmol*. 1998;126(4):487-497.
5. Drance S, Anderson DR, Schulzer M. Collaborative Normal-Tension Glaucoma Study Group. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. *Am J Ophthalmol*. 2001;131(6):699-708.
6. Bonomi L, Marchini G, Marraffa M, et al. Vascular risk factors for primary open-angle glaucoma: the Egna-Neumarkt Study. *Ophthalmology*. 2000;107(7):1287-1293.
7. Leske MC, Wu SY, Hennis A, et al. Risk factors for incident open-angle glaucoma: The Barbados Eye Studies. *Ophthalmology*. 2008;115(1):85-93.
8. Leske MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the Early Manifest Glaucoma Trial. *Ophthalmology*. 2007;114(11):1965-1972.
9. Galassi F, Sodi A, Ucci F, et al. Ocular hemodynamics and glaucoma prognosis: a color Doppler imaging study. *Arch Ophthalmol*. 2003;121(12):1711-1715.
10. Riva CE. Basic principles of laser Doppler flowmetry and application to the ocular circulation. *Int Ophthalmol*. 2001;23(4-6):183-189.
11. Piltz-Seymour JR, Grunwald JE, Hariprasad SM, Dupont J. Optic nerve blood flow is diminished in eyes of primary open-angle glaucoma suspects. *Am J Ophthalmol*. 2001;132(1):63-69.
12. Jia Y, Wei E, Wang X, et al. Optical coherence tomography angiography of optic disc perfusion in glaucoma. *Ophthalmology*. 2014;121(7):1322-1332.
13. Feke GT, Bex PJ, Taylor CP, et al. Effect of brimonidine on retinal vascular autoregulation and short-term visual function in normal tension glaucoma. *Am J Ophthalmol*. 2014;158(1):105-112.
14. Kimura I, Shinoda K, Tanino T, et al. Effect of topical unoprostone isopropyl on optic nerve head circulation in controls and in normal-tension glaucoma patients. *Jpn J Ophthalmol*. 2005;49(4):287-293.
15. Sugiyama T, Shibata M, Kajiura S, et al. Effects of fasudil, a Rho-associated protein kinase inhibitor, on optic nerve blood flow in rabbits. *Invest Ophthalmol Vis Sci*. 2011;52(1):64-69.
16. Tokushige H, Waki M, Takayama Y, Tanihara H. Effects of Y-39983, a selective Rho-associated protein kinase inhibitor, on blood flow in optic nerve head in rabbits and axonal regeneration of retinal ganglion cells in rats. *Curr Eye Res*. 2011;36(10):964-970.
17. Hayreh SS, Podhajsky P, Zimmerman MB. Beta-blocker eyedrops and nocturnal arterial hypotension. *Am J Ophthalmol*. 1999;128(3):301-309.
18. Krupin T, Liebmann JM, Greenfield DS, et al. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-Pressure Glaucoma Treatment Study. *Am J Ophthalmol*. 2011;151(4):671-681.
19. Januleviciene I, Siaudvytyte L, Diliene V, et al. Effect of trabeculectomy on ocular hemodynamic parameters in pseudoexfoliative and primary open-angle glaucoma patients [published online ahead of print May 19, 2014]. *J Glaucoma*. doi:10.1097/JIG.0000000000000055.

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