

Measuring Ocular Blood Flow

A surge in peer-reviewed publications examining the role of blood flow in glaucoma necessitates an understanding of the pros and cons of measuring ocular hemodynamic parameters.

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The reduction of IOP remains the only course of action for primary open-angle glaucoma (POAG), despite consistent observations of vascular risk factors such as low ocular perfusion pressure,¹⁻⁴ vascular narrowing,⁵ and a higher incidence of risk factors associated with cardiovascular disease.⁶ As interest grows in a possible vascular role in the development of glaucoma, the number of articles on blood flow and glaucoma has increased steadily (Figure 1). Clinicians therefore need to understand the nature of the measurements of ocular blood flow as well as their advantages and limitations. This article reviews the physical basis for these measurements and the pros and cons of the techniques currently most prevalent in the literature. Table 1 summarizes all of the measurements.

DOPPLER MEASUREMENTS

How They Work

Color Doppler Imaging

The determination of Doppler shifts is the basis of the vast majority of measurements of ocular blood flow. Color Doppler imaging (CDI) is the lone technology that measures Doppler shifts in sound waves, whereas the other techniques use laser light. With retrobulbar ocular structures serving as landmarks, the ophthalmic artery, central retinal artery and vein, and short posterior ciliary arteries can be located, and the velocity of blood and vascular resistance within each vessel can be measured over time. The peak systolic and end diastolic velocities are recorded, and the resistive index is calculated as (peak systolic velocity – end diastolic velocity)/peak systolic velocity. Color Doppler imaging is widely used in many research centers worldwide for the assessment of ocular blood flow. (Table 2 provides interpretations of measurements with color Doppler imaging.)

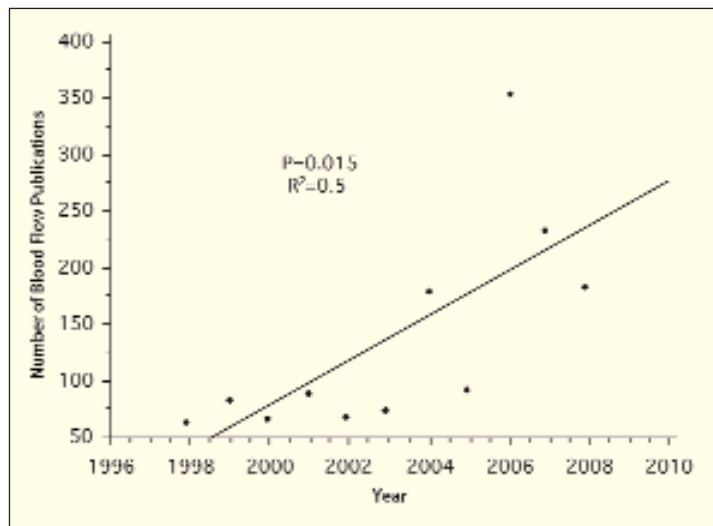


Figure 1. The annual number of publications including blood flow and glaucoma in the abstract has increased steadily at a rate of 20 additional publications per year.

Optical Doppler Measurements

Optical Doppler measurements can be broken into two broad categories: velocity and flow. Laser Doppler velocimetry measures the maximum Doppler shift at the location specified by the user. It computes maximum velocity and calculates real velocity over time. The Canon laser Doppler flowmeter combines laser Doppler velocimetry technology with vessel tracking and the use of a second laser to measure the vessel's diameter simultaneously. These two measurements allow the calculation of volumetric flow. Similarly, spectral domain optical coherence tomography combines the simultaneous measurement of the vessel's diameter and velocity over time to calculate volumetric flow, although limitations to lower velocities may make current devices unsuitable for measurements in larger retinal vessels.^{7,8}

TABLE 1. AN OVERVIEW OF THE MOST COMMON OCULAR BLOOD FLOW TECHNOLOGIES SEPARATED BY PHYSICAL BASIS OF MEASUREMENT

Basis	Technique	Source of Signal	Measurement	Meaning	Pros
Doppler measurements	Color Doppler imaging	Doppler shifts in ultrasound waves from retrobulbar blood	Blood velocity	Velocity measurements alone are difficult to interpret	Noninvasive Measurements in real units Measurements selectively from both retinal and choroidal sources of blood flow
	Canon laser blood flowmetry	Doppler shifts in laser light in isolated large retinal vessels	Blood velocity and blood column width	Calculated volumetric blood flow in selected arteries and veins	Measurement of blood velocity and vessel diameter in arbitrary units for calculation of volumetric blood flow
	Laser Doppler velocimetry	Doppler shifts in laser light in isolated large retinal vessels	Maximum velocity at a single position assumed to be 1.6 times larger than average	Velocity measurements alone are difficult to interpret	Noninvasive Velocity in real units
	Laser Doppler flowmetry	Doppler shifts in laser light scattered from vascularized retinal tissue	Capillary blood flow at a point in arbitrary units	Changes indicate changes in capillary volumetric blood flow, whatever the source of signal	Noninvasive Capillary blood Volumetric flow measurement
	Spectral domain Doppler optical coherence tomography	Doppler shifts in laser light scattered from moving blood in capillaries or large retinal vessels depending on image produced	Blood velocity, vessel cross-sectional area, and tissue volume	In the future, promises to provide only volumetric blood flow per unit tissue mass	Noninvasive A structure/metabolic function assessment in a single scan
	Heidelberg retinal flowmetry	Doppler shifts in laser light from vascularized retinal tissue	16,384 capillary blood flow measurements in a 2.7- X 0.7-mm area of tissue, in arbitrary units	Changes indicate changes in capillary volumetric blood flow Confocal optics aid in isolating source to the retina	Noninvasive
Observations of dye filling vessels	Fluorescein angiography	Fluorescence from blood entering the retinal vasculature	Filling rates and passage times of the retinal vasculature	Inverse indication of resistance of retinal vasculature to flow	Sensitive to very small changes in resistance
	Indocyanine green angiography	Fluorescence from blood entering the choroidal vasculature	Relative regional filling rates within the peripapillary and perimacular large choroidal vessels	Yet to be determined	Has demonstrated delayed peripapillary regional filling in glaucoma
Observations of blood vessels	Retinal vessel analyzer	Submicron-resolution observation of retinal vessel pulsation	Actual diameter of retinal artery or vein throughout the cardiac cycle	Indicates vascular compliance of diameter and pulsation response to perturbations or medications	Commercially available and FDA approved Noncontact Direct measurement
	Ophthalmodynamometry	Notation of elevated IOP at cessation of retinal vessel pulsation	Systolic and diastolic blood pressure in the central retinal artery and vein	Indicates perfusion pressure	Direct measurement of an observable phenomenon
IOP measurement	Pulsatile ocular blood flowmetry	Magnitude of IOP pulsation	Calculated change in ocular blood volume associated with the cardiac cycle	Indicates choroidal blood flow	Easy for technicians to learn Technique similar to Goldmann applanation tonometry

TABLE 2. INTERPRETATIONS OF MEASUREMENTS WITH COLOR DOPPLER IMAGING

CDI Index	Interpretation
When PSV and EDV move in parallel ⁹	Blood flow may increase as seen during in vitro modeling of CDI measurements
Velocity absent ¹⁰⁻¹²	Occlusive disease
Increased PSV ^{13,14}	Vessel narrow at measurement site
Resistance index ^{9,15-18}	Closely related to downstream vascular resistance
Reversal of flow ^{19,20}	Severe stenosis/ocular ischemic syndrome

Note: color Doppler imaging provides ocular hemodynamic information about the vasculature at the site of the measurement and the vascular beds distal to the measurement, depending on the observed measurements. Abbreviations: CDI, color Doppler imaging; PSV, peak systolic velocity; EDV, end diastolic velocity.

Laser Doppler flowmetry is a point measurement that integrates the area under the Doppler power spectrum to measure volumetric flow in arbitrary units. This approach measures all Doppler shifts from a single location specified by the user. The Heidelberg retina flowmeter (Heidelberg Engineering GmbH, Heidelberg, Germany) is a scanning confocal version of the laser Doppler flowmeter. The unit measures retinal capillary blood flow in arbitrary units from a 2.7- X 0.7-mm area of retinal tissue.

Pros and Cons

Color Doppler imaging has the advantages of being noninvasive, measuring velocity in real units, and providing independent hemodynamic measurements of both the retinal and uveal vascular beds. It also does not require clear optical media to obtain high-quality measurements.

The disadvantages of color Doppler imaging include the high cost of the device (although notebook computer-sized portable units cost considerably less) and the effects of examination-induced pressure on the eye. In addition, the examination is often performed while the subject is supine, and ocular conditions may differ from when the subject is seated. Because of their small size, the cross-sectional diameters of vessels cannot be accurately measured at this time, and therefore this technique is only capable of measuring the velocity at which blood is flowing. It is thus hard to interpret the meaning of the measurements, because unknown changes in a vessel's caliber make it difficult to determine the effect of changes in velocity on volumetric flow.

Like the laser Doppler flowmeter, the greatest disadvantage of the Heidelberg retina flowmeter is that its measurements of flow are in arbitrary units. The comparison of measurements between individuals is therefore difficult to interpret. Changes in measurements within a single eye, however, represent volumetric alterations in blood flow. It is unlikely that the current Heidelberg retina flowmeter will ever be able to produce absolute measurements of blood flow over time.

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ANGIOGRAPHIC MEASUREMENTS

How They Work

Scanning laser angiographic techniques allow the subjective visualization of the retinal (with fluorescein) or choroidal (with indocyanine green) vasculature as it fills with dye. Computer analysis of fluorescein dye coursing through blood vessels (30 frames per second in the United States, 25 frames per second in Europe) can be used to quantify the blood's velocity within the retinal arteries or, more commonly, the time between the dye's first appearance within a primary retinal artery and a corresponding vein (known as *arteriovenous passage time*). Prolonged arteriovenous passage times represent

increased resistance to retinal flow, and these protracted times are reduced with vasodilating perturbations. Computer analysis of indocyanine green dye permits the quantification of the dye's relative arrival times in the perimacular and peripapillary regions of the choroid. The meaning of regional delays in choroidal filling is less clear and remains to be determined.

Pros and Cons

Digital scanning laser ophthalmoscope angiography is the only current imaging technology that allows direct visualization of retinal and choroidal hemodynamics. Computer analysis quantifies retinal velocity and circulation times with fluorescein dye and relative delays in regional choroidal filling with indocyanine green dye.

The disadvantages of angiographic techniques include their minimally invasive nature and the time required for intensive computerized processing. The greatest disadvantage of each of these analyses is that they produce measurements in units of seconds, far from the milliliters/second/tissue volume units of blood flow measurement. Additionally, the parametric analysis of the angiograms is invasive and requires an expensive digital video analysis system and customized software.

VASCULAR MEASUREMENTS

How They Work

Indirect measurements of ocular phenomena with hemodynamic implications include the direct observation of blood vessels. Ophthalmodynamometry consists of the indirect ophthalmoscopic observation of retinal blood vessels while the IOP is slowly increased manually. The pressure at which pulsation begins represents the diastolic blood pressure in the observed vessel, and the IOP at which pulsation ceases and the vessel collapses represents systolic blood pressure within that vessel.

The other relevant observational form of measurement is the retinal vessel analyzer. Oversampling and averaging measurements of diameter provides the submicron-resolution diameter of retinal vessels throughout the cardiac cycle. The retinal vessel analyzer allows the measurement of retinal vessels' pulsation, and it is capable of measuring the small changes in absolute and pulsatile diameters that occur with perturbation.

Pros and Cons

The greatest advantage of ophthalmodynamometry is that the measured phenomenon is observed directly. The retinal vessel analyzer provides a reproducible assessment of retinal vessels' diameters of a specific size and, potentially, these vessels' reactivity to certain stimuli. The greatest disadvantage of ophthalmodynamome-

try is that the clinical meaning of vascular blood pressure remains unknown, but the arterial and venous blood pressures can be used to calculate ocular perfusion pressure. Also, the retinal vessel analyzer's measurement of these vessels in terms of retinal blood flow is uncertain.

REAL-TIME IOP MEASUREMENT

How It Works

The least direct measurement with any marginal implication for ocular hemodynamics is the calculation of real-time IOP. The IOP pulsates with the cardiac cycle. It is possible that the magnitude of this pulsation is associated with the level of volumetric flow in the choroid. If so, the association is stronger with the portion of choroidal blood flow that occurs during systole. Measurements may be obtained by a number of devices such as the Pascal Dynamic Contour Tonometer (Zeimer Ophthalmic Systems AG, Port, Switzerland) or the pulsatile ocular blood flow device, all operated similarly to a Goldmann applanation tonometer.

Pros and Cons

Optimistically named, pulsatile ocular blood flowmetry is a simple and inexpensive measurement to perform, which has led to its inclusion in numerous small clinical trials.

Unfortunately, the method risks corneal contact, and the precise clinical interpretation of these measurements is unknown. The greatest disadvantage of pulsatile ocular blood flowmetry is that it is not a direct measurement of blood flow but IOP. Assumptions about scleral rigidity and a universal IOP/eye-volume relationship introduce error into the calculation of pulsatile flow. Its relationship to ocular blood flow remains unproven.

CONCLUSION

An increasing number of articles in the peer-reviewed literature include findings of altered hemodynamics in ophthalmic disease. Combining these studies with future spectral measurements of metabolism may provide the next chapter in clinicians' understanding of the relationship between ocular hemodynamics and the pathogenesis and disease processes of glaucoma. For now, however, IOP remains the sine qua non in glaucoma, and measurements of ocular blood flow remain a surrogate for ocular tissue metabolism. □

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1. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment. *Arch Ophthalmol*. 1995;113:216-221.
2. Sommer A. Glaucoma risk factors observed in the Baltimore Eye Survey. *Curr Opin Ophthalmol*. 1996;7:93-98.
3. Hulsman CA, Vingerling JR, Hofman A, et al. Blood pressure, arterial stiffness, and open-angle glaucoma: the Rotterdam study. *Arch Ophthalmol*. 2007;125:805-812.
4. Leske MC, Wu SY, Hennis A, et al. Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. *Ophthalmology*. 2008;115:85-93.
5. Amerasinghe N, Aung T, Cheung N, et al. Evidence of retinal vascular narrowing in glaucomatous eyes in an Asian population. *Invest Ophthalmol Vis Sci*. 2008;49:5397-5402.
6. Orzalesi N, Rossetti L, Omboni S. Vascular risk factors in glaucoma: the results of a national survey. *Graefes Arch Clin Exp Ophthalmol*. 2007;245:795-802.
7. Kagemann L, Wollstein G, Ishikawa H, et al. Validation of spectral domain optical coherence tomographic Doppler shifts using an in vitro flow model [published online ahead of print September 29, 2008]. *Invest Ophthalmol Vis Sci*. 2009;50(2):702-706.
8. Wang Y, Lu A, Gil-Flamer JH, et al. Measurement of total blood flow in the normal human retina using Doppler Fourier-domain optical coherence tomography [published online ahead of print January 23, 2009]. *Br J Ophthalmol*. PMID:19168468.
9. Spencer JA, Giussani DA, Moore PJ, Hanson MA. In vitro validation of Doppler indices using blood and water. *J Ultrasound Med*. 1991;10(6):305-308.
10. Williamson TH, Baxter GM, Dutton GN. Color Doppler velocimetry of the optic nerve head in arterial occlusion. *Ophthalmology*. 1993;100(3):312-317.
11. Williamson TH, Baxter GM, Dutton GN. Colour Doppler velocimetry of the arterial vasculature of the optic nerve head and orbit. *Eye*. 1993;7(pt 1):74-79.
12. Sergott RC, Flaharty PM, Lieb WE Jr, et al. Color Doppler imaging identifies four syndromes of the retrobulbar circulation in patients with amaurosis fugax and central retinal artery occlusions. *Trans Am Ophthalmol Soc*. 1992;90:383-98; discussion 398-401.
13. Spencer MP, Reid JM. Quantitation of carotid stenosis with continuous-wave (C-W) Doppler ultrasound. *Stroke*. 1979;10(3):326-330.
14. Spencer MP, Whisler D. Transorbital Doppler diagnosis of intracranial arterial stenosis. *Stroke*. 1986;17(5):916-921.
15. Halpern EJ, Merton DA, Forsberg F. Effect of distal resistance on Doppler US flow patterns. *Radiology*. 1998;206:761-766.
16. Norris CS, Pfeiffer JS, Rittgers SE, Barnes RW. Noninvasive evaluation of renal artery stenosis and renovascular resistance. *J Vasc Surg*. 1984;1:192-201.
17. Norris CS, Barnes RW. Renal artery flow velocity analysis: a sensitive measure of experimental and clinical renovascular resistance. *J Surg Res*. 1984;36:230-236.
18. Adamson SL, Morrow RJ, Langille BL, et al. Site-dependent effects of increases in placental vascular resistance on the umbilical arterial velocity waveform in fetal sheep. *Ultrasound Med Biol*. 1990;16(1):19-27.
19. Lieb WE, Flaharty PM, Sergott RC, et al. Color Doppler imaging provides accurate assessment of orbital blood flow in occlusive carotid artery disease. *Ophthalmology*. 1991;98(4):548-552.
20. Ho AC, Lieb WE, Flaharty PM, et al. Color Doppler imaging of the ocular ischemic syndrome. *Ophthalmology*. 1992;99(9):1453-1462.