Ocular hemodynamics and glaucoma

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Abstract
Many factors are thought to contribute to glaucoma. One of these factors is ocular hemodynamics, or the state of vascular circulation in the eye. This article attempts to explain the effect of ocular hemodynamics on the normal eye and glaucomatous eye, as well as metabolic vascular mediators thought to be involved in the pathogenesis of glaucoma and external factors affecting ocular blood flow. A brief summary of current clinical ocular vascular testing devices and the effects of topical therapeutic medications on ocular blood flow will also be discussed.

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OCULAR HEMODYNAMICS AND GLAUCOMA

By

SCOTT SCHIRBER

and

JIM SCHRODER

A thesis submitted to the faculty of the
College of Optometry
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Ocular Hemodynamics and Glaucoma

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Pacific University College of Optometry

Abstract

Many factors are thought to contribute to glaucoma. One of these factors is ocular hemodynamics, or the state of vascular circulation in the eye. This article attempts to explain the effect of ocular hemodynamics on the normal eye and glaucomatous eye, as well as metabolic vascular mediators thought to be involved in the pathogenesis of glaucoma and external factors affecting ocular blood flow. A brief summary of current clinical ocular vascular testing devices and the effects of topical therapeutic medications on ocular blood flow will also be discussed.

Key Words:
autoregulation, choroid, circulation, Drance hemorrhage, glaucoma, intraocular pressure, normotensive glaucoma, ocular blood flow, ocular hemodynamics, optic nerve, vasospasm
Introduction

Glaucoma is well-known as a leading cause of blindness in the United States, afflicting more than 2 million Americans, of which approximately one million are not aware that they have it. Glaucoma has been classically defined as a group of ocular conditions characterized by progressive loss of visual field due to optic nerve damage and, in most cases, elevated intraocular pressure (IOP). Primary open angle glaucoma (POAG) is the most common presentation warranting continued research and discussion.

Historically, glaucoma was diagnosed based on elevated IOP alone, indicating increased pressure as the etiology. Glaucoma was viewed as a disorder of aqueous humor dynamics, with the optic nerve as an innocent but vulnerable bystander. In recent years, it is becoming more apparent that glaucoma is a multi-factorial condition characterized by progressive optic neuropathy leading to distinctive visual field loss. The most common theories pertaining to optic nerve damage purported are mechanical compression, ischemic vascular, excitotoxicity of ganglion cells, and genetically pre-programmed cell death (apoptosis). It is likely that a combination of mechanisms plays a role in optic nerve head (ONH) damage and not the result of one theory in particular.

Elevated intraocular pressure affects the nerve in several ways. First, elevated IOP causes mechanical stress at the lamina cribrosa through which the ganglion cell axons pass. The level of IOP that produces mechanical stress in any particular optic nerve is dependent on the structural integrity of the lamina. Second, high IOP restricts blood flow to the ONH in susceptible individuals who do not have adequate compensatory
autoregulatory mechanisms, causing increased tissue pressure within the optic nerve and increased extraluminal vascular pressure. Decreased optic nerve perfusion may mechanically weaken the connective tissue matrix supporting the lamina cribrosa, increasing its susceptibility to damage at any level of intraocular pressure. In addition, elevated IOP may ultimately physically block axonal transport of brain derived neurotrophic growth factor transported from the brain to the ganglion cells. When deprivation of a vital nutrient occurs, the cell loses the signal to “stay alive” and thus expresses the genetic potential for apoptosis (pre-programmed cell death). Apoptosis causes enzymes to be turned on, causing the ganglion cell to self-ingest its own DNA and initiate phagocytosis, leading to cellular “suicide”. The dead cells then release excess glutamate into the extracellular space which binds to receptors, propagating the opening of calcium channels on adjacent ganglion cells. From this, excess calcium floods into adjacent, healthy ganglion cells in a chain-reaction, causing them in turn to undergo apoptosis. Elevated IOP may also induce further release of glutamate intra-cellularly, eliciting accumulation of nitric oxide and destructive free radicals, which are toxic to healthy ganglion cells. Despite the interrelationship of these proposed mechanisms, this paper will focus on the vascular component related to glaucoma.

The eye is one of the best-perfused organs in the body. In humans, the eye has two separate systems of blood vessels that differ both anatomically and physiologically: the retinal vessels supplying the inner two-thirds of the eye, and the rest of the eye supplied by the uveal or ciliary vessels. However, in order to better understand ONH perfusion and the relationship to glaucoma, discussion of ocular blood vessel pathways,
beginning with the internal carotid arteries forward to the vasculature of the eye, is warranted.

Figure 1: Orbital blood supply
(Source: www.bartleby.com/107/Images/small/image514.jpg)

The right common carotid artery originates from the bifurcation of the brachiocephalic trunk, while the left common carotid originates directly from the aortic arch. Each common carotid artery bifurcates into an internal and external carotid artery in most individuals just below the angle of the jaw and approximately at the level of the thyroid cartilage. The internal carotid artery (ICA) then enters the skull through the foramen lacerum within the petrous portion of the temporal bone prior to reaching the cavernous sinus. The ICA ascends above the clinoid processes dividing into anterior and middle
cerebral arteries, sometimes referred to as the carotid siphon.\textsuperscript{8} Near the supraclinoid process, the ICA gives off its first important branches: ophthalmic, posterior communicating, and anterior choroidal arteries, which usually arise in this order.

The ophthalmic artery passes through the optic canal entering into the orbit.\textsuperscript{9} Throughout its course, many branches emerge: the central retinal artery (CRA), ciliary arteries, ethmoid arteries, supraorbital artery, muscular artery, medial palpebral arteries, supratrochlear arteries, and dorsonasal artery.\textsuperscript{9} Discussion will be provided on the arteries supplying the ONH - the CRA, ciliary arteries, and pial supply.

The CRA is the first branch to emerge from the ophthalmic artery and enters the dural sheath of the optic nerve approximately ten millimeters posterior to the globe. The CRA enters just nasal to the center of the optic nerve and gives rise to four branch retinal arteries, each supplying a quadrant of the retina and a portion of the anterior nerve head.\textsuperscript{10}

The short posterior ciliary arteries arise as one or two branches which further divides into ten to twenty branches entering the sclera around the optic nerve forming an arterial network within the choroidal stroma, the choroidal arteries.\textsuperscript{9} Some of the branches anastamose to form the circle of Zinn-Haller.\textsuperscript{9}

The ONH can be divided into four gross regions from anterior to posterior: the superficial nerve fiber layer (NFL), prelaminar region, lamina cribrosa region, and retrolaminar region.\textsuperscript{4} The first two anterior portions of the ONH display similar
Microvascular morphologies to the retina and its circulation. The vessels of the NFL and prelamina consist of tight junctions, capillary endothelial non-fenestrations, and a high number of intramural pericytes.\textsuperscript{11} In addition, autoregulation within the ONH capillary beds is similar to the retinal circulation. Autoregulation is the physiologic process an organ (in this case the eye) uses to maintain normal blood flow in the presence of varying perfusion pressures.

The superficial nerve fiber layer portion is principally supplied by the CRA arterioles which emanate from the peripapillary vessels. The prelaminar portion receives its blood supply from the vessels emanating from a ring (complete or incomplete) termed the \textit{circle of Zinn-Haller}. This ring gets its supply from branches of the short posterior ciliary arteries, ultimately derived from the ophthalmic artery.\textsuperscript{12} Other minor contributions may be from the pial vessels emerging from the CRA and small vessels of the superficial nerve fiber layer. The orbital portion of the optic nerve derives its blood
supply from the pial circulation and perhaps also to some extent from the ophthalmic artery and its branches, including the central retinal artery. That portion of the optic nerve lying in the optic canal derives its arterial blood supply from the ophthalmic artery, while the intra-cranial part of the optic nerve is supplied centripetally through the pial vessels. The blood is drained from the ONH via the central retinal vein.

**Hemodynamics and Glaucoma**

For many years, the development of glaucomatous atrophy of the optic nerve was thought to be secondary to raised intraocular pressure. However, at the time of diagnosis, up to 30% of those with glaucoma have normal intraocular pressure. This discrepancy points to additional mechanisms of glaucomatous damage. Several other theories have been proposed, as outlined in the introduction; however this paper will focus on the role of vascular perfusion in glaucoma. Before discussing the role of ocular hemodynamics in glaucoma, it is necessary to provide a background to the basic physiologic control mechanisms of blood flow to the retina.

**Physiology of Blood Flow in the Retina in Normals**

As previously mentioned, there are two separate blood supplies to the retina. The photoreceptors and retinal pigmented epithelium (RPE) cells receive their supply from the choroidal capillary bed, while the central retinal artery provides nutrition to the inner retinal layers. Two blood-retinal barriers are formed: one in the inner retinal supply between tight junctions formed by the endothelial cells of the capillaries and another in the choroidal supply by tight junctions between the RPE cells. Varying levels of flow
have been found between the retinal and choroidal supplies. Retinal blood flow has been described to be only 5% of total ocular flow. Laser Doppler flowimetry has shown the average rate of blood flow for the entire retina to be approximately 80 μl/min. Due to the high macular demand for oxygen and nutrients, blood flow to the temporal retina is three times higher than the nasal side. No difference between the superior and inferior supplies has been found. Blood flow through the choroidal supply has been difficult to accurately determine, due to the inaccessibility of the vasculature. If numerous studies on different species are averaged, it is estimated that the choroid receives 65-85% of total ocular blood flow. Based on available research data, it appears that there is an approximately 10:1 ratio of choroidal:retinal blood flow. The features and differences of the choroidal and retinal supplies are listed in the following table.

**Table 1: Salient features of the retinal and choroidal circulations** (Source: Roh S, Weiter J Anatomy and Physiology - Retinal and Choroidal Circulation In: Yanoff: Ophthalmology, 1st Ed. Mosby 1999. Section 8.3.3.)

<table>
<thead>
<tr>
<th>Choroidal blood flow</th>
<th>Total flow</th>
<th>800-1000 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal blood flow</td>
<td>Total flow</td>
<td>80 ml/min</td>
</tr>
<tr>
<td>Retinal regional blood flow</td>
<td>Temporal versus nasal ratio</td>
<td>3:1</td>
</tr>
<tr>
<td></td>
<td>Posterior pole and peripapillary versus remainder of retina ratio</td>
<td>4:1</td>
</tr>
<tr>
<td></td>
<td>Superior versus inferior ratio</td>
<td>1:1</td>
</tr>
<tr>
<td>Mean retinal circulation time</td>
<td></td>
<td>4-5 sec</td>
</tr>
<tr>
<td>Retinal vasculature diameters</td>
<td>Arteries at margin of optic nerve</td>
<td>110 μm</td>
</tr>
<tr>
<td></td>
<td>Veins at margin of optic nerve</td>
<td>150 μm</td>
</tr>
<tr>
<td></td>
<td>Capillaries</td>
<td>5-6 μm</td>
</tr>
<tr>
<td></td>
<td>Choriocapillaris</td>
<td>20-25 μm</td>
</tr>
</tbody>
</table>
Several factors play roles in controlling both blood supplies. Perfusion pressure and autoregulation play the most integral roles. Diastolic perfusion pressure (DPP), or systemic diastolic pressure minus intraocular pressure, is integral to controlling the rate of blood flow through vascular tissue. Obviously, a lower IOP facilitates entry of blood into the eye. This allows a lower diastolic pressure to overcome the pressure from within the eye. Perfusion pressure and blood flow are directly related. Accordingly, those with low DPP appear to be at risk for glaucomatous changes, because an increased IOP will more likely result in decreased ocular blood flow. The Baltimore Eye Study showed that patients with a DPP below 50 mm Hg were 6 times more likely to have glaucoma than those with a higher DPP.\textsuperscript{22}

Autoregulation, or the control of resistance to blood flow, is critical to controlling blood flow through the inner retinal supply. This is achieved through regulation of the vascular tone of the retinal vasculature.\textsuperscript{23} Autonomic control, endothelial factors, and metabolic factors such as oxygen and carbon dioxide all aid in determining vascular resistance. There are autoregulatory mechanisms that maintain normal perfusion pressure up to 30 mmHg changes in IOP.\textsuperscript{24} It has been hypothesized that these autoregulatory mechanisms may be defective in glaucoma and that elevated IOP may lead to anterior nerve head ischemia.\textsuperscript{25}

The choroidal blood supply is under direct nervous control.\textsuperscript{26} Conversely, the retinal blood supply, specifically the central retinal artery, is only innervated up to the lamina cribrosa.\textsuperscript{27} However, this innervation may play an important role. During times of
extreme stress, sympathetic activity increases resulting in increased blood pressure. Innervation to only the extraocular portion of the central retinal artery spares the changes in the vascular tonus of the intraocular portion, thereby acting to protect the fragile capillaries inside the eye by preventing the excessive filling of intraocular vascular beds. It is unclear how or if this nervous control affects blood flow to the optic nerve head.

Oxygen and carbon dioxide both affect vascular resistance in varying degrees. Oxygen reduces vessel size, reducing retinal blood flow significantly. Breathing pure oxygen for a small period of time has been found to constrict retinal vessels and reduce retinal blood flow by 55% to 60%. Carbon dioxide has the opposite effect. It acts more to negate oxygen’s vasoconstrictive effect than as a true vasodilator; however a slight increase in retinal vascular diameter is observed upon addition of 7% carbon dioxide during inhalation. This observation has fueled the controversial clinical technique of having patients breathe through a paper bag in hopes of expanding occluded retinal vessels enough to become un-occluded. There is questionable success with this treatment modality.

The vascular endothelium plays an integral role in controlling retinal blood flow resistance through its action of maintaining the blood retinal barrier and its release vasoactive agents. The acetylcholine-nitric oxide cascade is an example of this. When the endothelium’s muscarinic receptors are stimulated by acetylcholine, endothelial cells release nitric oxide, causing vasodilation and smooth muscle relaxation. Without the
endothelium, acetylcholine will not dilate vessels. Another role of the vascular endothelium is to release a family of short chain polypeptides known as endothelins that are extremely potent vasoconstrictors.\textsuperscript{34}

As just discussed, blood flow to the retina is maintained by several different physiologic mechanisms. It is thought that all of these mechanisms work in concert to control blood flow to the retina. They are all necessary, and inaction or dysfunction of any one mechanism may result in an ischemic situation.

Factors Affecting Ocular Blood Flow

Several factors such as age, gender, hormone levels, exercise, medication, dehydration, and vascular disease have been found to play a role in the physiology of blood flow to the eye. The following table presents a summary of various factors and their effect on blood flow:

Table 2: Various factors and their general effect on ocular blood flow

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>GENERAL EFFECT ON OCULAR BLOOD FLOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Reduction</td>
</tr>
<tr>
<td>Gender</td>
<td>Women (pre-menopausal) increased compared to men and post-menopausal women</td>
</tr>
<tr>
<td></td>
<td>Women (post-menopausal) decreased compared to pre-menopausal women and age equivalent men</td>
</tr>
<tr>
<td></td>
<td>Men decreased relative to age-matched pre-menopausal women, increased relative to age matched post menopausal women</td>
</tr>
<tr>
<td>Exercise</td>
<td>Increased</td>
</tr>
<tr>
<td>Medication</td>
<td>Varies—see following section on the effects of medication</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Reduction</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td>Reduction</td>
</tr>
<tr>
<td>Sleep Disorders</td>
<td>Reduction</td>
</tr>
</tbody>
</table>
It appears that age has a negative effect on blood flow to the optic nerve and surrounding tissue. Embleton and colleagues found that the retina, neuroretinal rim and lamina cribrosa all have decreased capillary blood flow with advancing age. Furthermore, it has been found that the velocity of flow surrounding the optic nerve head decreases more nasally than temporally. Further evidence suggests that both the choroidal supply and the central retina artery supply decrease with advancing age. The cause of this age-related reduction in blood flow is unclear; however several mechanisms have been proposed. It appears that aging results in an impaired ability of relaxation in the endothelium lining the capillaries. Increased attenuation of the choroid’s arterioles has been observed as one of the aging changes on histological slides. This, along with a decreased number of choroidal arterioles with aging, as seen on indocyanine green angiography, results in a decreased choroidal blood volume. Also, blood flow may be adversely affected by decreasing lumen diameter due to age-related atherosclerotic changes.

Gender plays a key role in ocular hemodynamics. Pre-menopausal women show a significant increase in blood flow compared to age-equivalent men. However, this changes after menopause. Post-menopausal women show a decrease in blood flow relative to age-equivalent men and pre-menopausal women. This may be due in part to increased resistance in the posterior ciliary arteries as well as reduced levels of estrogen. It is thought that estrogen is protective in coronary heart disease and glaucomatous changes in pregnant women. At present, the effects of hormone replacement, specifically estrogen, on ocular hemodynamics have yet to be studied; however the underlying
mechanism that estrogen plays in prevention of cardiovascular disease is thought to be similar to its role in enhancing ocular blood flow. Unlike women, men don't appear to undergo any significant blood flow transformations other than normal aging changes.\textsuperscript{44}

Dehydration can affect vascular blood flow and resistance, which could play a role in blood flow to the optic nerve. Dehydration increases blood viscosity, and unless compensated by vessel dilation, it could potentially slow the flow rate of blood through both the arterial and venous circulation. It appears that mild dehydration reduces the peak velocity and affects resistance levels in the ophthalmic artery. In the central retinal artery, dehydration appears to slow the peak velocity but does not affect the resistance index.\textsuperscript{45}

Sleep disorders also seem to play a role in glaucomatous changes, especially in normotensive glaucoma (NTG). The mechanism for NTG remains unknown; however it has been widely proposed that reduced ocular blood flow caused by vasospasm or systemic hypotension plays an integral role in the pathogenesis of NTG. Sleep disorders, such as sleep apnea, result in significant nocturnal hypoxia and increased vascular resistance. This may compromise the blood flow to the optic nerve head region.\textsuperscript{46}

**Ocular Blood Flow in Glaucoma**

Understanding how vascular changes affect those with glaucoma has been a difficult process. Many individuals with glaucoma also have other vascular diseases. Cardiac disease, systemic hypertension and hypotension, atherosclerosis, diabetes
mellitus and cerebrovascular disease are the more common diseases that may be associated with glaucoma and can also influence ocular blood flow. Unfortunately, no universal standard in measurement of ocular hemodynamics has been established at this time. Many techniques have been employed and standardization of conclusions has been difficult. Possibly, the underlying problem is the difficulty in imaging the orbital vessels, namely the ophthalmic, central retinal, and short ciliary arteries. Regardless, it is the intent of the following sections to present a comprehensive view of ocular hemodynamics as it relates to glaucoma.

**Autoregulation**

Blood flow is affected by glaucoma and ocular hypertension. By using flow-associated parameters, Duijm et al. found that there were differences in both choroidal and retinal circulation in those with glaucoma versus normal subjects. Also, the type of glaucoma also affected blood flow. The primary open angle glaucoma (POAG) group showed especially slowed retinal circulation, whereas the NTG group showed delayed choroidal circulation. Glaucoma vascular hemodynamics are delayed when compared to normal patients and the type of glaucoma impacts the type of delay. Since the retinal circulation is under autoregulation control, there are indications that in POAG, autoregulation is impaired because of possible mechanical damage from a chronic increase in intraocular pressure. The breakdown of autoregulation may also play a critical role in NTG.
Control of metabolites, such as endothelins and nitric oxide, to influence vessel diameter (resistance to flow), is the key mechanism of autoregulation control. It has been suggested that dysfunction in regulation of endothelins may be one of the mechanisms contributing to the vascular component of glaucoma. Endothelins are a class of vasoactive peptides that appear to have an autoregulatory role in the eye. At the ciliary body, they act to decrease IOP by decreasing aqueous production and increasing outflow facility. In contrast to their beneficial role at the ciliary body, endothelins appear to have a damaging effect to the retinal ganglion cells (RGC) at the level of the optic nerve head. The following diagram illustrates presents their dual role within the eye, illustrating their IOP lowering effects in the anterior chamber, and their damaging processes at the optic nerve head:\(^{52}\)

![Diagram](image_url)

Figure 3: The autoregulatory role of endothelin-1 (ET-1) on retinal ganglion cell (RGC) death leading to glaucoma and other neuropathies. IOP – intraocular pressure; RPE/ONA – retinal pigmented epithelium/optic nerve arteries; NPE = non-pigmented epithelium (Source: Krishnamoorthy R, Prasanna G, Yorio T. Endothelin: Is It a Contributor to Glaucoma Pathophysiology? Journal of Glaucoma 2002, 11(3): 259-270.)
Abnormally high systemic levels of endothelin-1 (ET-1) were found in normal tension glaucoma, where ET-1 has been found to reduce blood flow to the posterior ciliary arteries supplying the optic nerve.\textsuperscript{53,54} Interestingly, ET-1 may also play a role in POAG. Compared to non-glaucomatous individuals, those with POAG were found to have abnormally high levels of ET-1.\textsuperscript{55}

Nitric oxide has several roles within the eye. It acts to influence blood flow, sodium transport, IOP, and neuronal viability by acting as a vasodilator, vasorelaxant and neurotransmitter.\textsuperscript{56} Nitric oxide appears to play a strong role in the pathophysiology of glaucomatous optic neuropathy. Specifically, excessive amounts of nitric oxide react with free radicals to form toxic compounds (called peroxynitrites and hydroxyl radicals) that bind to neuronal organelles. Ultimately, this binding results in destruction and subsequent loss of structure and function of the retinal ganglion cells.\textsuperscript{57} Excessive amounts of nitric oxide appear to result from two factors. First, elevated IOP has been linked to the overproduction of nitric oxide. Second, elevated levels of the endothelins appear to result in increased levels of nitric oxide synthase 2 and nitric oxide concentrations in ocular tissues.\textsuperscript{58}

A second key autoregulatory mechanism is known as myogenic regulation. Arteriolar blood vessels respond to increased intralumenar pressure by contracting. Thus, by decreasing flow this process (myogenic regulation) allows blood circulation to remain normal in the presence of increased perfusion pressure.\textsuperscript{59} This mechanism tends to act when blood flow is above normal; however the mechanism of this control within the eye
is unknown and additional work is required to discover its role in glaucoma.\textsuperscript{60} It is thought that choroidal flow, versus retinal flow, is more affected by myogenic processes than metabolite processes.\textsuperscript{61}

\textbf{Vasospasm}

The apparent link between NTG and vasospasm is evident through the association of NTG with migraine headache\textsuperscript{62} and excessive peripheral vasoconstriction to cold.\textsuperscript{63} It is thought that NTG is primarily a vascular disease, this assumption suggests that vasospasm results in decreased blood flow to the optic nerve. Specifically, vasospasm results in poor perfusion, ischemia, and ganglion cell death.\textsuperscript{64} Defective autoregulatory mechanisms may be the underlying cause of a vasospastic event. The link between vasospasm and autoregulation may be due to endothelial cell dysfunction, which could be attributed to an imbalance between the levels of nitric oxide and ET-1.\textsuperscript{65} Several vascular conditions, such as Raynaud’s Syndrome,\textsuperscript{66} recurring migraine headache,\textsuperscript{67} and variant angina,\textsuperscript{68} have been found to be associated with increased plasma levels of ET-1. In addition, as previously mentioned, those with NTG also have elevated systemic levels of ET-1. Interestingly, they also have decreased ET-1 response to postural changes. The vasospastic phenomenon is more readily understood and accepted in the NTG group, however, it may play a role in POAG as well. Vasospasm may happen as frequently in the POAG group as the NTG group. In POAG patients, there appears to be a direct positive relationship between the level of vasoconstriction (or elevation of IOP) and the amount of neurotrophic damage.\textsuperscript{69} Vasospasm may also play a key role in decreasing choroidal flow. In normals, it appears that choroidal blood flow is independent of
perfusion pressure. However, those with NTG often have peripheral vasospasm and blood flow isn't maintained with varying perfusion pressures.\textsuperscript{70} Along with the inability to maintain blood flow through varying perfusion pressures, those with NTG may have elevated basal resistance levels that contribute to reduced blood flow.\textsuperscript{71,72}

**NTG and Reduced Ocular Blood Flow**

Along with vasospasm, NTG patients typically present other interesting findings that may provide clues into how ocular perfusion and glaucoma are related. Events of nocturnal hypotension (reduced blood pressure during sleep) may be related to progression of the neuropathy and those with NTG have been found to have more frequent episodes of nocturnal hypotension than normals.\textsuperscript{73} Also, those with progressive glaucoma show significant variances in nocturnal hypotension. Another interesting phenomenon is the link between vasospasm and cold temperatures. In those with NTG, it has been shown in one study that immersion of one hand in cold water leads to worsening of the visual field in some patients.\textsuperscript{74}

Another sign that NTG has a vascular component is the prevalence of Drance hemorrhage (also known as a splinter hemorrhage), typically presenting on the inferior temporal rim of the nerve head. These characteristic hemorrhages in NTG appear to be more common than in POAG. Varying percentages of frequency of this hemorrhage in NTG have been reported. One study reports the frequency to be as high as 43\%.\textsuperscript{75} The Blue Mountain Eye Study found that hemorrhage was three times more likely in NTG than POAG.\textsuperscript{76} The exact cause of hemorrhage is unknown, but different theories have
been proposed. It is unclear if the hemorrhages represent glaucoma damage, or if the damage present in glaucoma causes the hemorrhage. One theory purports that mechanical damage at the lamina cribrosa causes microvascular damage. Another theory argues that the hemorrhages occur as a result from a microvascular event such as vasospasm. POAG is thought to limit the amount of visible hemorrhage because the elevated IOP limits the amount of fluid leaving the vessel.

Figure 4: Drance hemorrhage at the inferior temporal rim
(Source: http://www.opt.pacificu.edu/ce/catalog/Glaucoma_Kirstein/KirstGlauc.html)

Recent advances in technology have allowed specific measurements to be made showing that NTG does involve reduced blood flow. A recent study using the Heidelberg retinal flowmetry (HRF) technology found that those with NTG have reduced blood flow in the peripapillary retina. A further indication of blood flow in those with NTG is reduced pulsatile blood flow (POBF). POBF is a derived measurement of ocular blood flow to the eye based on continuous recording of the change of intraocular pressure as the ocular volume of blood changes. POBF has been found to be decreased in both NTG
Specifically, Ravalico et al found that mean POBF was 32.32% lower in NTG patients than normals. This deficit was found to be lower when the patients with NTG were in a supine position. This correlates with previous information about the increase of nocturnal hypotension in NTG.

Ocular Blood Flow Measurement

Various techniques have been implemented in imaging and measuring the ocular blood circulation. New technologies, such as the scanning laser ophthalmoscope and confocal scanning laser Doppler flowmetry offer exciting possibilities, while traditional methods, such as fluorescein and indocyanine green angiography, still provide valuable information.

Angiography

Angiography has been the traditional method of imaging and measuring blood flow. It provides information about the retinal, choroidal, and optic nerve circulation. Two types of angiography exist: fluorescein angiography and indocyanine green angiography. Both types of angiography are semi-quantitative and semi-invasive in nature.

Fluorescein angiography is used to visualize retinal vasculature and can be used to calculate capillary blood velocity by observing distance of movement of dye through individual capillaries in relation to time.
Figure 5: Topcon retinal camera and sample fluorescein angiography. (Source: http://www.topcon.co.jp/iyou/iyou_e_ima2000.html)

Figure 6: Peak fluorescence approximately 25 seconds after fluorescein injection. Both arterial and venous circulations are shown in detail. (Source: Guyer D, Mandava N, Yannuzzi. Ancillary Tests – Fluorescein Angiography In: Yanoff: Ophthalmology, 1st Ed. Mosby 1999. Section 8. 8.1.)
The following defects have been found with angiography in glaucomatous patients: filling defects in the superficial optic nerve and choroid, delayed retinal artery and venous filling times, prolonged arteriovenous passage time and reduced velocity in the retinal circulation.\textsuperscript{82,83}

Indocyanine green angiography is used to image the choroidal vasculature, specifically cases of choroidal neovascularization (CNV). Indocyanine green, unlike fluorescein, which fluoresces under visible light, is viewable only under infrared light. It is primarily used in those with macular degeneration or other causes of occult CNV.\textsuperscript{84} The drawbacks of both angiography techniques are their semi-invasive nature and lack of absolute flow measurement.

Both techniques have traditionally utilized photography and video to allow interpretation. Recent introduction of the scanning laser ophthalmoscope (SLO) has increased the capabilities of angiography. The SLO operates on the principle of confocal light. Light is reflected off of the area of interest, and passes through an aperture before reaching the solid-state detector. This detector determines the voltage level, based on the energy level of the incoming light. The voltage level is measured in real time, and is used to create a video signal. This video signal is similar to those obtained with traditional video angiography, however, since scattered light and light from sources outside the focal plane cannot enter the aperture, the resolution and contrast of the image is improved.\textsuperscript{85} The SLO offers better penetration of corneal and lens opacities. It also allows for decreased retinal illumination and improved contrast since the laser beam
illuminates only a single spot at time. As with traditional angiographic techniques, SLO is invasive and data analysis is time consuming.

Color Doppler Imaging

Instruments that utilize the Doppler effect can measure blood-flow velocities in the major ocular vessels. Light waves undergo a Doppler shift when they are reflected off moving objects, such as red blood cells. This shift is proportional to the velocity of the moving object. This data is then analyzed and superimposed, in color, on a standard image and is termed color Doppler imaging (CDI). CDI is used to image the ophthalmic artery, the central retinal artery, and the short posterior ciliary artery. CDI is limited to determining blood-flow velocities. In order to calculate absolute volume flow, vessel diameter is needed, and at present, there is no feasible means of determining retrobulbar vessel diameter. CDI has been used to show reduced velocity and increased resistance to flow in both POAG and NTG, and eyes having lower velocities have more damage than eyes with high velocities. CDI is also limited because it can not image the short posterior ciliary arteries because of their lack of size and the resolution limit of CDI.
Figure 7: Color Doppler Imaging of the ophthalmic artery. The peak systolic velocity is indicated by the sharp rise. The end diastolic velocity is indicated by the gradual tail-off of each pulse wave. (Source: Harris A, O'Brien C. Optic Nerve Blood Flow Measurement. In: Yanoff: Ophthalmology, 1st Ed. Mosby 1999. Section 12.9.1.)

Confocal Scanning Laser Doppler Flowmetry

The Heidelberg Retinal Flowmeter (HRF) combines a confocal scanning laser with a laser Doppler flowmeter. The scanning system of the HRF maps a retinal area of 10 degrees by 2.5 degrees. This area is initially scanned with a resolution of 256 points by 64 lines. It is then scanned another 128 times to create an intensity matrix. Each point within this matrix is then assigned a power spectrum based on fast Fourier transformation to extract the Doppler frequency shift of the reflected light. This analysis is completed on each of the approximately 16,000 points within the imaged area, allowing for a two-dimensional map of retinal perfusion for each 10 degree by 2.5 degree area. This technology allows the HRF to obtain measurements of flow, volume and velocity. In glaucoma, laser Doppler flowmetry has shown reduced blood-flow velocities
in the lamina cribrosa and in the nasal and temporal neural rim and retina. The HRF has also shown that NTG patients present with significantly lower blood flow than age-matched norms. The HRF is limited in the current expense of the instrument. Also, image acquisition requires 2 seconds, which requires reasonably good vision (20/40 or better) for stable fixation. Finally, the accuracy of the HRF has been shown to have coefficients of reliability close to 0.85 for acute measurements of volume, velocity and flow. This value decreases when measured over a four-week period. To overcome this limitation, the Glaucoma Research and Diagnostic Center of Indiana University has developed a pixel-by-pixel analysis method that overcomes some of the short-falls of the 10 by 10 pixel area method traditionally used and reduces the coefficient of variability to 15% for increased accuracy and repeatability over longer periods of time.

Figure 8: Heidelberg Retinal Flowmeter
(Source: http://www.heidelbergengineering.com/hrtf/hrf.html)
Ocular Blood Flow Analyzer

Another means of determining ocular blood flow is to measure the pulsatile ocular blood flow (POBF). POBF is believed to be a measurement of choroidal flow. Dicon's Ocular Blood Flow Analyzer does this by measuring IOP 200 times continuously throughout the cardiac cycle. In other words, the POBF tracks changes in IOP at a frequency of 200 Hz. IOP rises with the systole and falls with diastole. The change in IOP is termed the pulse amplitude. From the measured pulse amplitude, the Ocular Blood Flow Analyzer's software calculates the ocular blood flow by essentially measuring the entire orbital pulse. Along with previously mentioned POBF deficits in NTG, the Ocular Blood Flow Analyzer has shown reduced pulse amplitude and POBF in POAG and NTG. Despite its ease of use, the Ocular Blood Flow Analyzer's calculated
Ocular blood flow is not a direct measurement of blood flow. Rather, it is a mathematic estimate based on several assumptions, including scleral rigidity and a model of the cardiac cycle. Therefore, POBF measurements are influenced by individual differences in scleral rigidity, ocular volume, heart rate, systemic blood pressure, and IOP. 107

Figure 10: Paradigm's Dicon Ocular Blood Flow Analyzer
(Source: http://www.paradigm-medical.com/pages/eq_bfa.html)

Figure 11: IOP variation over time via Ocular Blood Flow Analyzer pneumotonometry
(Source: http://www.opt.pacificu.edu/ce/catalog/Glaucoma_Kirstein/KirstGlauc.html.)
Topical Medications and Blood Flow

The role of hemodynamics in glaucoma has sparked considerable interest regarding the impact of topical medications on blood flow. Of particular promise is the possibility of tailoring topical therapy to those with identified vascular insufficiency.

Carbonic Anhydrase Inhibitors

The carbonic anhydrase inhibitors (CAI) appear to favorably affect ocular hemodynamics in virtually all vascular beds of the posterior segment.\textsuperscript{108} CAI’s act to lower IOP by decreasing aqueous production, inhibiting the inter-conversion of bicarbonate and carbon dioxide. In the ciliary body, carbonic anhydrase acts in the production of bicarbonate ions, which creates the osmotic gradient necessary for aqueous production.\textsuperscript{109}
Using SLO angiography, it was shown that 2% dorzolamide significantly improved arteriovenous passage time of fluorescein in the retina.\textsuperscript{110} Other studies, using POBF, HRF and CDI, have shown an increase in ocular hemodynamics after using dorzolamide.\textsuperscript{111, 112, 113} CAI's enhancement of ocular blood flow is due to their ability to act as a vasodilator by inhibiting the vasoconstrictive effects of endothelin-1.\textsuperscript{114, 115} Another remarkable finding was the improvement in visual function following administration of topical CAI. Contrast sensitivity and visual field perimetry both showed significant improvement following administration of dorzolamide.\textsuperscript{116, 117} Trusopt, which is dorzolamide 2%, and Cosopt, which is a fixed combination of dorzolamide 2%-timolol 0.5%, are two forms of topical dorzolamide manufactured by Merck & Co.

Prostaglandin Analogues

The effects of prostaglandin analogues on ocular hemodynamics have been favorable, but only for choroidal blood flow. Latanoprost (Xalatan) was the first prostaglandin analogue introduced to the ophthalmic market. It works to lower IOP by enhancing uveoscleral aqueous outflow. POBF measurement has shown an increase in choroidal flow after administration of Xalatan in normal, NTG and POAG eyes.\textsuperscript{118, 119, 120, 121}

While acting on choroidal flow as measured by POBF, Xalatan appears to have no effect on retrobulbar hemodynamics as viewed by CDI.\textsuperscript{122} The only other prostaglandin analogue/docosanoid studied thus far, unoprostone (Rescula), has also been shown to have a favorable effect on ocular blood flow by decreasing vascular resistance.\textsuperscript{123} Unfortunately, unlike the CAI's, the prostaglandin analogues do not appear to improve contrast sensitivity.\textsuperscript{124}

Figure 14: Xalatan (latanoprost 0.005%)
(Source: http://www.bartletteye.com/xalatan.jpg)
Beta Blockers

Non-selective topical beta blockers have the theoretical possibility of decreasing ocular blood flow by increasing vascular resistance. Increased vascular resistance is likely due to their sympathetic action to cause vasoconstriction via beta receptor blockade.\(^{125}\) Beta receptors have been shown to exist in the human choroid, anterior optic nerve, optic nerve head and retina.\(^{126, 127, 128}\) However, thus far the research has not been conclusive on their effect on ocular hemodynamics. Beta blockers work to reduce IOP by reducing aqueous production.

Some evidence has shown that timolol (generic, Timoptic, Timoptic XE), a non-selective beta blocker, actually acts to increase blood flow in those with POAG by reducing flow resistance in the short posterior ciliary arteries.\(^{129}\) Another study on POAG patients, using the HRF, showed increased blood flow to the ONH following administration of timolol after 4 weeks.\(^{130}\) Other studies, using laser Doppler flowmetry and CDI, have also shown increased blood flow following timolol administration.\(^{131, 132}\)\(^{133}\) In contrast, several studies have shown a decrease in ocular blood flow following the use of timolol. Carennini and associates found a significant decrease in POBF in timolol treated patients.\(^{134}\) This result was confirmed in other studies of normals and those with POAG.\(^{135, 136}\) Further complicating evidence comes from research that indicates timolol may have no effect on ocular blood flow.\(^{137, 138, 139, 140}\)

While the results of timolol on blood flow are somewhat inconclusive, betaxalol (Betoptic-S) appears to have a favorable impact on blood flow. Betaxalol, unlike timolol, is a beta-1 selective blocker. In those with NTG, it has been shown to increase
retrobulbar blood flow.\textsuperscript{141, 142} Whereas timolol was shown to possibly decrease choroidal flow, POBF remained stable in those treated with betaxolol.\textsuperscript{143, 144}

![Beta blocker examples](http://www.revoptom.com/drugguide.asp?show=view&articleid=3)

**Figure 15:** Beta blocker examples (from left to right): Timoptic, Timoptic-XE, Betoptic S.
(Source: http://www.revoptom.com/drugguide.asp?show=view&articleid=3)

**Alpha Agonists**

Alpha agonists are a group of drugs with potential vasoactive effects. These drugs, specifically brimonidine tartrate (generic, Alphagan-P), alter IOP by suppression of aqueous humor production and uveoscleral outflow and may exhibit a neuroprotective effect.

The classic alpha agonist is apraclonidine (Iopidine). There has been no data to support that either apraclonidine, or the newer alpha agonist brimonidine (Alphagan P), significantly alters ocular blood flow. Using CDI, it was shown that brimonidine did not alter the hemodynamics of the retina.\textsuperscript{145} Another study conducted by Jonescu-Cuypers and associates examined the effect of brimonidine using CDI and SLO, and found no changes in either retrobulbar or retinal perfusion.\textsuperscript{146} Two other studies confirm previous results: alpha agonists appear to have no effect on ocular blood flow.\textsuperscript{147, 148} The literature
demonstrates a non-existent effect which may be attributed to the minimal penetration of this class of drug into the posterior pole, the absence of alpha-2 adrenergic receptors in the posterior ciliary arteries, or the release of endothelial-derived relaxing factors.144

Figure 16: Alphagan P
(Source: http://www.revoptom.com/drugguide.asp?show=view&articleid=3)

Non-topical Drugs

From a clinical standpoint, the eye care practitioner should maintain awareness of the effect of systemic medications on ocular health. Steroids such as prednisolone have been known to cause elevated intraocular pressure in a select percentage of individuals; however the exact mechanism of this is unclear. The effect of beta blockers, of which the orally-ingested form is typically used for the treatment of systemic vascular problems, may or may not have ocular vascular sequelae, as mentioned prior.

A group of drugs showing important impact on blood flow are the calcium channel blockers, which were initially used for angina pectoris patients.149 By interfering with calcium intracellular uptake and release, they also affect blood vessels. Studies on animals have proven to show benefit regarding ONH and retinal blood flow150,151. Although visual field function stability has not been shown with these drugs on all types
of glaucoma, calcium-channel blockers are eventually helpful in low tension glaucoma patients. Few studies have shown that topically applied calcium channel blockers improve consistency of lowering IOP than systemically administered ones. Topically applied calcium channel blockers are a rarity. Systemically administered calcium channel blockers have shown positive vascular effects on the CRA and ONH.

\[ \text{(152, 153)} \]

**Conclusion**

Traditionally, it has been accepted that medicinal therapy for glaucoma should be initiated when repeatable visual field loss appears or several risk factors in addition to obvious ONH changes occur. However, detecting and managing glaucoma prior to obvious nerve or visual field changes is paramount. Pulsatile ocular blood flow analysis, along with other various tools for analysis, now allow clinicians to more fully understand an individual’s risk for developing glaucoma. The goal of current glaucoma management is to catch and treat glaucoma as early as possible without first waiting for damage to occur.

Ocular hemodynamics is a relatively new field of study regarding glaucoma and its progression. Clinical observations and studies show that various vascular factors may influence the pathogenesis of glaucomatous damage, either through reduced blood flow to the optic nerve head, or by malfunction in ocular autoregulation. Future research is needed to provide more concrete answers to the role vascular insufficiency plays in glaucoma. New research will also provide a more rational approach to the use of topical and systemic medications in the treatment of glaucoma.
References


27. Ehinger B. Adrenergic nerves to the eye and to related structures in man and the cynomolgus monkey. Invest Ophthal 1966; 5:42.


142. Evans DW, Harris A, Cantor LB. Primary open-angle glaucoma patients characterized by ocular vasospasm demonstrate a different ocular vascular response to timolol versus betaxolol. J Ocul Pharmacol Ther 1999; 15:479-487.


