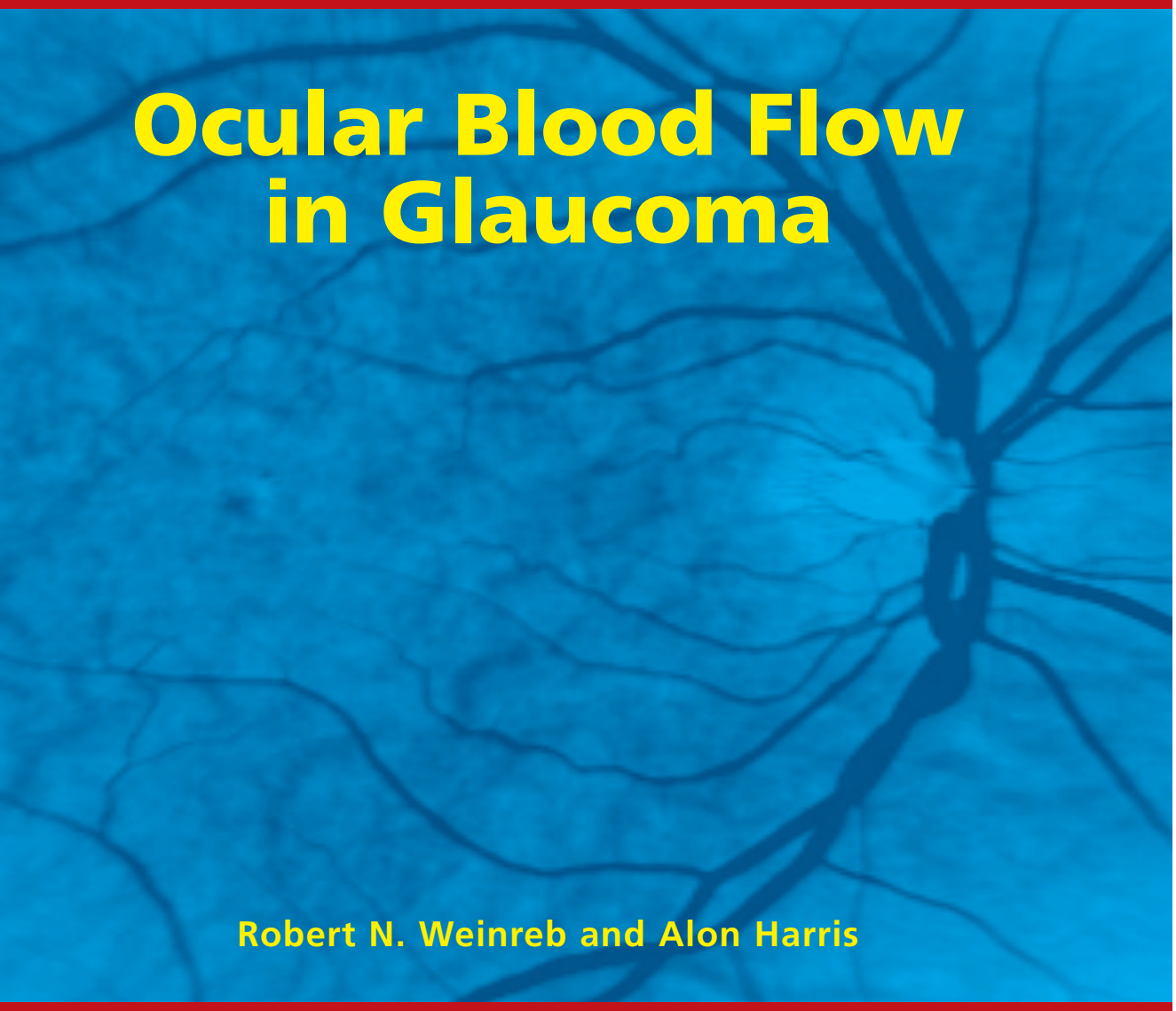
World Glaucoma Association

Ocular Blood Flow in Glaucoma



Robert N. Weinreb and Alon Harris

Consensus Series - 6

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OCULAR BLOOD FLOW IN GLAUCOMA

Robert N. Weinreb

Alon Harris

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The 6th Consensus Report of the

World Glaucoma Association

Editors

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and
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Consensus meetings in Glaucoma
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World Glaucoma Association

Blood Flow Consensus Meeting participants, Fort Lauderdale, May 2, 2009.

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The more that you read,
the more things you will know.
The more that you learn,
the more places you'll go.

Dr. Seuss, *I Can Read With My Eyes Shut!*

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PREFACE

This is the sixth World Glaucoma Association Consensus. The relationship between ocular blood flow and glaucoma has been discussed for more than a century, and still it uniformly fuels debates at glaucoma meetings throughout the world. Clearly, the results of this report will have broad and significant impact on glaucoma research and clinical practice. The global faculty, consisting of leading authorities on the scientific and clinical aspects of ocular blood flow, will met in Fort Lauderdale on May 2, 2009 to discuss the reports and refine the consensus statements.

Obtaining consensus on the relationship of blood flow to glaucoma was a daunting task. So much has been studied and written, but how much do we really know? As with the previous WGA consensuses, the Glaucoma Blood Flow consensus is based on the published literature and expert opinion. Although consensus does not replace and is not a surrogate for scientific investigation, it does provide considerable value, especially when the desired evidence is lacking. The goal of this consensus was to establish a foundation for ocular blood flow research of glaucoma and the best practice for its testing in clinical practice. Identification of those areas for which we have little evidence and, therefore, need additional research was a high priority. We hope that this consensus will serve as a benchmark of our understanding, and that it will be revised and improved with the emergence of new evidence.

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Ingrida Januleviciene, Lou Pasquale, Alon Harris (co-Chair) and Robert N. Weinreb (Consensus Chair)

Jonathan Crowston

WELCOME

For the World Glaucoma Association Consensus VI, our topic was Blood Flow in Glaucoma. Global experts were assembled beginning in November 2008 to participate in the Project Forum E-Room, a unique aspect to facilitate discussion of each of the consensus meetings.

With each of the prior meetings, arriving at the consensus was circuitous and filled with compromises, and this meeting had a similar path. Nevertheless, this was an excellent opportunity to critically assess the evidence relating to the relationship between glaucoma and ocular blood flow and develop consensus statements. The meeting, as with previous ones, was stimulating, educational, thought-provoking, and enjoyable for all participants and attendees.

Robert N. Weinreb
Alon Harris

The only real voyage of discovery consists not in seeking new landscapes, but in having new eyes.

Marcel Proust

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ANATOMY AND PHYSIOLOGY

Louis Pasquale, Jost Jonas, Douglas Anderson

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Consensus points

- Blood supply to the retinal nerve fiber layer invariably comes from the central retinal artery and, when present, from the cilioretinal artery(ies).
  Comment: There are no anastomotic connections between the arteries, which function as end-vessels even though the capillaries are a continuous bed.
- Blood supply to the prelaminar and laminar portion of the optic nerve head comes from branches of the short posterior ciliary arteries.
  Comment: These often form an incomplete vascular ring around the optic nerve head ('Vascular ring of Zinn and Haller'), before giving off branches into the tissue of the optic nerve head located inside of the peripapillary scleral ring of Elschnig. These vessels feature an anastomotic blood supply.
- Retinal vessels are not fenestrated and are not innervated. Since they lack a continuous tunica musculosa, the retinal 'arteries', except for the main central retinal vessel trunk, are anatomically arterioles.
  Comment: These anatomical features may have implications for understanding how blood flow is regulated in this vascular bed.
- It is unclear whether the branches of the posterior ciliary artery that feed the intrascleral portion of the optic nerve are innervated and/or fenestrated.
  Comment: Such knowledge is essential to understand how the intrascleral papillary tissue responds to various insults, including abnormally high IOP.
- Branches of the short posterior ciliary arteries supply the choroidal vasculature. The majority of total ocular blood volume and flow (~80-90%) is derived from the choroidal vascular. The capillaries are among the largest in the body and are fenestrated. The arteries that feed them are innervated.
  Comment: These features have important implications for how the choroidal vasculature is regulated. It has remained unclear whether there is a clinically relevant anastomotic blood exchange between the choroidal vasculature bed and the vascular system of the ciliary body, which is fed by the two long posterior ciliary arteries and the 7 anterior ciliary arteries.

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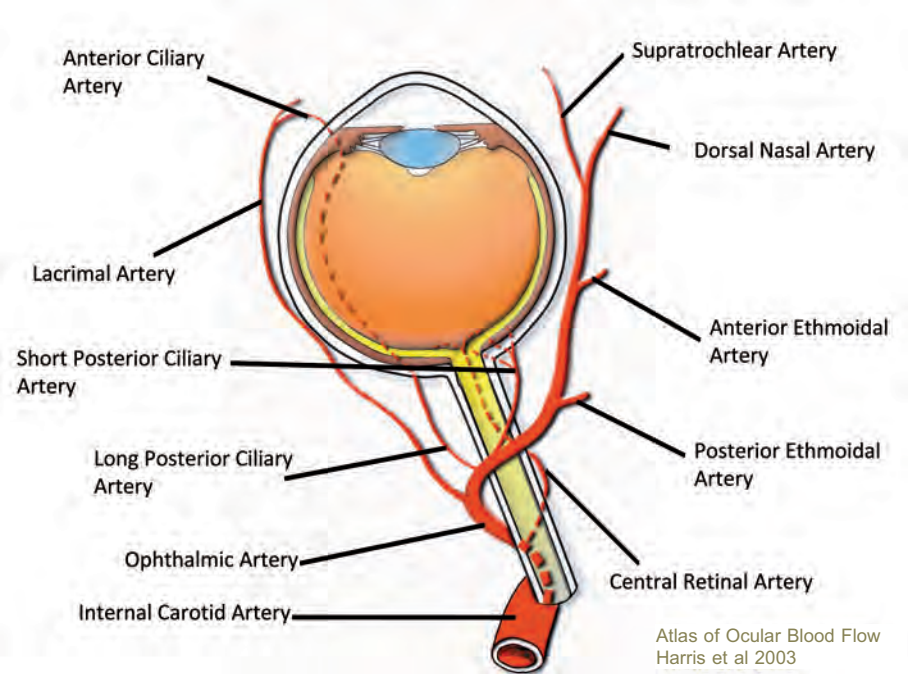
- The central retinal vein drains all blood from the entire retina and the optic nerve head.
  Comment: Upon contact-free ophthalmoscopy, a spontaneous pulsation of the central retinal vein can be detected in ~80 to 90% of normal eyes. Since the central retinal vein passes through the optic nerve and then through the cerebrospinal fluid space before piercing through the optic nerve meninges in the orbit, the blood pressure in the central retinal vein should be at least as high as the cerebrospinal fluid pressure within the optic nerve meninges in the orbit plus a (hypothetical) trans-lamina cribrosa outflow resistance.
- Blood flow to the optic nerve and retina is dominated primarily by myogenic and metabolic regulation. The blood flow to the choroid is believed to be primarily regulated mainly by hormonal and neuronal mechanisms. The extent of autoregulation in the choroid is not known.
  Comment: Ocular vascular autoregulation maintains adequate blood flow that provides nutrients and oxygen, as well as adequate tissue turgor, to ocular structures in the face of changing metabolic needs and altered ocular perfusion pressure. Such functions are all designed to allow sharp vision at all times.



Vasculature of the eye. (From: Harris, A. *et al.*, Atlas of Ocular Blood Flow. 2003. Butterworth Heinemann. Reprinted with permission of the publisher.)

Anatomy

Anatomy of blood from the heart to the eye

The vascular supply to the eye proceeds from the heart to the internal carotid artery to the ophthalmic artery. The ophthalmic artery branches to the short posterior ciliary vessels, the long posterior ciliary vessels and the central retinal artery (CRA).[1] There are important clinical implications for this blood supply. True ophthalmic artery occlusion produces no light perception vision and ocular hypotony. Further, there is the conspicuous abssence of a cherry-red spot.[2] In contrast, CRA occlusion typically produces count fingers-type vision, normal ocular tension and a cherry-red spot. The histologic appearance of a CRA occlusion is somewhat similar to the appearance of the retina in end-stage glaucoma with some minor differences. In glaucoma, the ganglion cells and some of the inner plexiform layer are lost. In retinal artery occlusion, in contrast, the damage and tissue loss goes deeper into the inner nuclear layer, because that layer depends on the retinal artery for nutrition and is not adequately nourished by the choroid.[3]

Blood supply of the optic nerve

When considering the blood supply to the optic nerve, the site of degeneration in all the glaucomas, it is important to remember that the optic nerve is a white fiber tract that includes the nerve fiber layer (NFL) plus 5 segments that course over a length of 45 to 50 mm:[4]

- prelaminar segment/laminar segment
- orbital segment – this is the longest portion of the optic nerve
- canalicular segment
- intracranial segment

The blood supply to the optic nerve is complex and varies by optic nerve segment. Using vascular cast corrosion techniques in postmortem human eyes, Onda *et al.* found that the central retinal artery supplies the NFL.[5] Presumably, cilioretinal arterial branches also contribute in eyes with such vessels. Some eyes have more than one cilioretinal artery, the number of which correlates with the size of the optic disc. The cilioretinal artery(ies) arise(s) directly from short posterior ciliary arteries (or potentially from large choroidal arteries). The retinal arteries and the cilioretinal arteries are functionally end arteries, *i.e.*, there is no anastomotic blood exchange at all in the case of an artery occlusion, invariably leading to an ischemic infarct in the whole area supplied by the artery or its branch.

Blood supply to the prelaminar and laminar portion of the optic nerve head comes from branches of the short posterior ciliary arteries. These vessels often

form an often incomplete vascular ring around the optic nerve head ('Vascular ring of Zinn and Haller') before giving off branches into the tissue of the optic nerve head located inside of the peripapillary scleral ring of Elschnig. Clinically, this vascular ring can be appreciated using indocynanine green videoangiography in highly myopic eyes.[6] These vessels do have an anastomotic blood exchange,[7] but critical questions remain unanswered. It is unclear whether the anastomotic blood exchange in the vascular ring of Zinn Haller can compensate for an insufficiency of a single posterior ciliary artery. It has also remained unclear whether there are anatomoses between the capillary or pre-capillary bed of the intra-laminar region, the pre-laminar region and the retinal nerve fiber layer region. If these anastomoses do exist, it is unclear if they are (partially) functional in the case of a sudden (or slowly progressive) vascular occlusion on the pre-capillary or intra-capillary level.

Curiously, the central retinal artery within the intraorbital optic nerve is innervated, but the retinal vascular branches are devoid of innervation once they emerge onto the retinal surface.[8] Yet, retinal vessels do retain receptors for various neurotransmitters on their surface.[9,10] Ye *et al.*[8] postulate that retinal tissue itself, namely the inner plexiform layer, may be the source of mediators that interact with these retinal vascular receptors. In addition, normal retinal vessels lack fenestrations, as supported by absence of dye leakage from even the smallest retinal capillaries on fluorescein angiography. Only pathological retinal neovascular tufts, like those that appear in global retinal ischemia, demonstrate such fenestrations.[11] The absence of fenestrations in endothelial cell cytoplasm and the lack of retinal vascular innervation influence how blood flow is regulated in the retina. When fenestrations are absent, large vasoactive hormones in the vascular lumen do not leak from the capillaries to gain access to the muscular coat of nearby feeding arterioles where they may exert some influence on blood flow. The lack of fenestrations in retinal arterioles also prevents unwanted fluid accumulation within the neurosensory retina.

Except for the main central retinal vessel trunk, the retinal 'arteries' are arterioles from an anatomical perspective, since they lack a continuous smooth muscle coat. Rather than a continuous smooth muscle coat, these vessels have isolated smooth muscle fibers that wrap around the vessel in a spiral fashion. This anatomical attribute has clinical implications in giant cell arteritis, which attacks only arteries with continuous smooth muscle coats and, therefore, spares arterioles within the retina. Of course, giant cell artertitis can produce central artery occlusion by targeting more proximal portions of the retinal vascular tree, such as the main retinal vascular trunk or the intraorbital portion of the central retinal artery. Furthermore, the ciliary branches of the ophthalmic artery have a continuous smooth muscle coat and are susceptible to involvement by giant cell arteritis.[12] Interestingly, cupping without enlargement of parapapillary atrophy is a common occurrence in the wake of anterior ischemic optic neuropathy related to giant cell arteritis.[13]

It is unclear whether the branches of the posterior ciliary artery that feed the intrascleral portion of the optic nerve are innervated and/or fenestrated. Such

knowledge is essential to understand how the intrascleral papillary tissue responds to various insults, including abnormally high intraocular pressure (IOP).

Branches of the short posterior ciliary arteries supply the choroidal vasculature in a lobular pattern.[1] The choroidal vascular bed dominates the ocular hemodynamic profile and large capillaries lie flattened against the retinal pigment epithelium to enhance metabolic exchange.[14] These vessels are fenestrated[15] and innervated[16] and these features have important implications for how the choroidal vasculature is regulated. It has remained unclear whether there is a clinically relevant anastomotic blood exchange between the choroidal vascular bed and the vascular system of the ciliary body, which is fed by the two long posterior ciliary arteries and the 7 anterior ciliary arteries. Since the description of the existence of choroidal ganglion cells a few years ago, some research has focused on the physiological and pathophysiological role that these cells may play for the regulation of choroidal (and optic nerve head) blood circulation.[17]

The central retinal artery is always located nasal to the central retinal vein in the lamina cribrosa. The central retinal vessel trunk passes through the lamina cribrosa slightly decentered into the nasal upper quadrant, with a large interindividual variability. Taking into account the usual slight, vertical orientation of the oval shape of the optic disc, the temporal inferior disc region is the one with longest distance to the central retinal vessel trunk, and the nasal superior disc quadrant is the one with the shortest distance to the vessel trunk.[18-20] This vascular arrangement may have implications for the local glaucoma susceptibility inside of the optic disc.

The central retinal vein collects blood from all retinal regions. Upon performance of contact-free ophthalmoscopy, spontaneous pulsation of the central retinal vein can be detected in 80 to 90% of normal eyes. Since the central retinal vein passes through the optic nerve and then through the cerebrospinal fluid space before piercing through the optic nerve meninges in the orbit, the blood pressure in the central retinal vein should be at least as high as the cerebrospinal fluid pressure within the optic nerve meninges in the orbit plus a (hypothetical) trans lamina cribrosa outflow resistance. A blood pressure measurement of the central retinal vein may, therefore, give some information about the orbital cerebrospinal fluid pressure. In the case of a central retinal vein occlusion, small veins may dilate for by-passing the intraluminal thrombus, leading to ‘venous optic disc collaterals’.[21-25]

Physiology

Overview of blood flow regulation in general

Blood flow in all tissues is regulated. Blood flow regulation includes control by hormonal and neural influences, which may be for systemic needs (skin vasoconstriction or vasodilation to control body temperature) or correlated needs (such as adrenergic stimulation when alertness is needed during the classical

'fight or flight' response affecting many body systems or widespread cholinergic stimulation when sleepy or while digesting a large meal).[26]
In the microvasculature, vascular tone refines not only the volume of blood flow, but also the intraluminal vascular hydrostatic pressure, which is important to maintain tissue hydration and protein movement while avoiding edema. To accomplish both requires an appropriate, delicate balance between vascular smooth muscle and pericyte tone in the arterioles, capillaries, and veins given the systemically controlled pressure in the arteries feeding the tissue.

The mediators of autoregulation

The notion of 'autoregulation' is that flow to a particular tissue with the property of 'autoregulation' is refined and, in the end, controlled by events within the local tissue. Thus local flow is 'auto'-regulated rather than regulated from afar. There are several mechanisms that participate in the complex process of local regulation or refinement of regulation. Among these are some that have been called '**metabolic autoregulation**'. The implication here is that the local tissue nutritional needs are met, but not exceeded, by virtue of the influence of local conditions, such as carbon dioxide levels (mediated by pH), local oxygen levels (which affect nitric oxide catabolism), adenosine levels (which build up when ATP is not being produced because of hypoxia), and perhaps other chemical signs of the local metabolic state.[27] An example of this at play occurs when the eye views a flickering light. The number of action potentials, and, therefore, the need for re-polarization of the axon membrane is increased because these signals are sent with each 'on' and 'off' of the light. In response to high metabolic demand, the blood flow in the optic nerve head needs to increase.[28]

A second class of autoregulation is seemingly more dependent on **mechanical influences**. Hence, with high arterial pressure, the resistance arterioles (those under 50 microns in diameter) react with constriction. This both reduces flow and perhaps protects the smaller vessels from harm that might result from high intraluminal pressure within vessels with thin walls. As another contributing mechanism, sheer or rapidly moving blood along the endothelium through a narrowed segment of the vessel results in local vasodilation.[29] The complexities of the physiologic control of the blood flow in the microvasculature have not all been discovered and understood.

The anatomic underpinning of ocular blood flow control

The physiology of the vascular system may be best understood by first reviewing the micro-anatomy. In general, the structures that control blood flow to a particular tissue are the resistance arterioles (arterial branches smaller than 50 microns or so), which provide the major resistance between the larger arteries and the veins. They determine how much of the pressure in the larger arteries reach the entrance to the capillary beds of a region. The capillaries individually have narrow lumina and have the highest resistance per unit length, but

they are so numerous that the total cross-sectional area of the capillaries is much higher than the total of all the arterioles. Thus, the capillary channels as a whole, being in parallel, do not produce much net resistance between arteries and veins. In addition to control by the resistance arterioles for a region, entrance to a local capillary net is often controlled by a pre-capillary sphincter, a ring of vascular smooth muscle located where the capillaries branch off from small arterioles. Finally, the capillaries themselves may have contractile tone in the walls by virtue of the contractile properties of pericytes. It is the balance between arteriolar tone, pre-capillary sphincters, capillary pericyte tone, and vascular smooth muscle in veins that permit a balance between flow and intraluminal pressure within each segment, particularly the capillaries. Capillary pericytes may substitute for the usual role of pre-capillary sphincters where they are absent.[30]

In addition to the nature of the contractile elements of vascular segments, the nature of the endothelium is another important anatomical feature to consider. Broadly, capillaries may be classified for our purposes as fenestrated or non-fenestrated. Fenestrated capillaries are found in most organs which lack a blood-tissue barrier to the entrance of large molecules, particularly proteins. In other tissues, such as the retina, the endothelial cells not only lack fenestrations, but also are joined by tight junctions which prohibit diffusion of substances within the plasma into the surrounding tissue.

The ocular vasculature and its role in regulating blood flow to the optic nerve and retina

Turning our attention to these anatomic features in the optic disc (and surrounding tissues), the retinal and optic nerve capillaries lack pre-capillary sphincters, but pericytes are conspicuously numerous in these vessels. There is evidence that pericytes respond in an appropriate manner to carbon dioxide concentrations (mediated by pH), oxygen levels (mediated by modification of nitric oxide levels) and adenosine concentration. This response is similar to the reactions of vascular smooth muscle.[31-33] Thus, they are thus equipped to participate in local control of blood flow in the optic nerve head through metabolic autoregulation. In contrast, the capillary bed of the choroid (the choroiocapillaris) consists of fenestrated capillaries and sparse pericytes. The retinal tissue, part of the central nervous system, has a preserved blood-brain barrier by virtue of the tight junctions between the retinal pigment epithelial cells. Of possible relevance is that no such cellular layer separates the choroid from the optic nerve head.

The contrast between the choroidal capillaries and those of the optic nerve head, with regard to the blood-tissue barrier, illustrates a fundamental aspect of vascular physiology. Circulating vasoconstrictive hormones (angiotensin II, epinephrine, etc.) act by elevating intracellular calcium when they occupy receptors. In vascular smooth muscle (and pericytes), entrance of calcium into the cell induces contraction of the cell. Endothelial cells react by increasing production of nitric oxide, which causes local relaxation of vascular smooth

muscle and pericytes. In this way, during an adrenergic response of some sort, the circulating hormones leak through fenestrated vessels to reach the muscular coat of vessels in the region, causing vasoconstriction in the skin and many visceral organs. In contrast, central nervous vessels, where hormones can only affect the endothelial cells and are prevented from reaching the contractile coat of the vessels, respond with vasodilation. As a rule of thumb, this combination of vascular responses well serves the whole body under various circumstances of life. Tissues with vital functions are helped by local regulation that may overcome maldistribution of blood flow during extreme systemic reactions. Fundamental differences between the choroidal and retinal vasculature are summarized in Table 1.

Both the capillaries, and the arterioles differ between the choroid and the neural tissues of the retina and optic nerve. The choroidal blood vessels are innervated and under the influence of the autonomic nervous system, while the central retinal vessels are not innervated, at least anterior to the lamina cribrosa. The posterior ciliary arteries are of particular interest, and they must make provision for much of the intraocular circulation, especially the choroid. To our knowledge, the innervation of the arteriolar branches that feed the optic nerve head has not been studied. It would seem that as long as the feeding arterioles provide sufficient pressure and capability for total flow for all the tissues it supplies, the distribution of flow will be under the control of the smallest arterioles, pre-capillary sphincters (where they exist), and seemingly the capillary beds themselves. Of note, the retinal arterioles illustrate the presence of mechanical autoregulation. With hypertension, the retinal arterioles become narrow, and at least if the hypertension is short-lived (as in eclampsia), the vessels dilate again when the arterial hypertension is relieved.

Turning our attention now to glaucoma, it may be noted that it is necessarily defined at present according to clinical manifestations, with various etiologies for determination of the level of intraocular pressure, and varying degrees of (or absence of) optic nerve damage and loss of visual function. If glaucoma were to be defined as a pathogenic entity, we might decide that glaucoma is an abnormal pathophysiology within the optic nerve, the severity of which is affected by the level of intraocular pressure. More concretely, we are considering the fact that, among other things, whenever the intraocular pressure is higher than venous pressure in the orbit, blood flow within intraocular structures is challenged by a reduced arterio-venous pressure difference. The resulting pathophysiology results from an inadequacy of the vascular physiology to maintain flow in face of that challenge. In other words, we are considering the manner in which ischemia might play a role in the pathogenesis of this disease.

There is considerable evidence that blood flow to both the retinal and optic nerve is autoregulated.[34-37] Several perturbations have been employed to assess autoregulation in various ocular beds including light flicker,[38] CO_2 breathing,[39] alterations in IOP,[40-43] exercise,[44-46] positional change[47-49] and changes in blood pressure.[50-51] It is unclear which, if any of these assays should be used to assess ocular vascular autoregulation in the future. Consensus around a clinical defini-

tion of ocular vascular autoregulation and how best to assess it, is essential to provide insight into how this critical physiologic feature might be impaired in glaucoma. Care should be taken in assessing autoregulation clinically. A problem may be that the regulation mechanisms may seem adequate on a particular clinic day, but may become inadequate when the person is tired, dehydrated, or his/her cardiovascular system is in some way dealing with other stresses, reducing the ability of the optic nerve vascular bed to be as responsive as at other times. Protocols can be developed to overcome these problems. However, physiologic limitations to some stress tests may also exist. The problem with breathing carbon dioxide as a stress test is that it affects the whole body, causing changes in the entire cardiovascular physiology, thereby altering cardiac output, blood pressure, vasoconstriction or vasodilation in other organs and tissues, etc., which may impact the measured blood flow in the optic nerve.

Table 1. Retinal vs. Coroidal circulation: A comparison of attributes

Retinal circulation	Choroidal circulation
15% of total ocular blood flow	85% of total ocular blood flow
Low flow system	High flow system
High pressure system	Low pressure system
Autoregulated	Unknown extent of autoregulation

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Vital Costa, Claude Burgoyne, Alon Harris and Robert N. Weinreb

Paul Healey, Daniel Grigera and Lou Pasquale

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David Huang

Mark Lesk and Leopold Schmettere

CLINICAL MEASUREMENT OF OCULAR BLOOD FLOW

Alon Harris

Ingrida Januleviciene

CLINICAL MEASUREMENT OF OCULAR BLOOD FLOW

Alon Harris, Ingrida Januleviciene, Brent Siesky, Leo Schmetterer, Larry Kageman, Ingeborg Stalmans, Ali Hafez, Makoto Araie, Chris Hudson, John Flanagan, Subha Venkataraman, Edward Gilmore, Gilbert Feke, David Huang, Einar Stefánsson

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Consensus points

- Color Doppler imaging of the ophthalmic artery, central retinal artery and posterior ciliary arteries measures blood flow velocity noninvasively and calculates resistive index.
  Comment: Color Doppler imaging does not measure flow.
  Comment: With careful interpretation, color Doppler imaging measures blood flow velocity and vascular resistivity in the retrobulbar blood vessels. The exact relationship between vascular resistivity index and resistance is not fully understood.
  Comment: The measurements with one color Doppler instrument are not necessarily compatible with those of another.
- Scanning laser Doppler flowmetry measures velocity, volume and flow limited to the retinal microcirculation and the optic nerve head.
  Comment: There is a lack of standardization for analysis, and flow is limited to arbitrary units of measure.
  Comment: The depth of the measurements is not known and may not be comparable among subjects.
- The retinal vessel analyzer provides a dynamic assessment of retinal vessel diameters of branch retinal arterioles and venules.

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Comment: The retinal vessel analyzer does not evaluate either velocity or blood flow.

Comment: At the current time, vessels with a diameter of 90 micrometers or larger are measured.

- The relationship between ocular pulse amplitude and total blood flow to the eye and, specifically, to the optic nerve is uncertain.
- Laser speckle flowgraphy provides 2-dimensional *in vivo* measurements of blood velocity in the optic nerve head and subfoveal choroid.

  Comment: Measurements in human eyes of the retina and iris have been problematic.

  Comment: Measurement with laser speckle flowgraphy is not clearly understood.
- Digital scanning laser ophthalmoscope angiography allows direct visualization of retinal and choroidal microvasculature.

  Comment: Various aspects of observed blood flow parameters and filling characteristics can be quantified, including retinal velocity and circulation times with fluorescein dye, and relative regional choroidal filling delays with indocyanine green dye.

  Comment: At the current time, scanning laser ophthalmoscope angiography requires an intravenous dye injection.
- By combining bidirectional laser Doppler velocimetry with simultaneous measures of retinal vessel diameter and centerline blood velocity, it is possible to calculate retinal blood flow in absolute units.

  Comment: These measurements require clear optical media and pupil dilation.

  Comment: The method is limited to vessels greater than 60 micrometers.
- Doppler Fourier Domain Optical Coherence Tomography provides rapid measurements of volumetric flow rate, velocity, and cross-sectional area in branch retinal vessels.

  Comment: At the current time, the method is limited to vessels greater than 60 micrometers and there are limited data.
- Retinal oximetry is a non-invasive measurement of oxygen saturation.

  Comment: At the current time, there are limited data. The method is limited to retinal vessels greater than 60 micrometers. It may be applicable also to the optic nerve head..
- At the present time, there is no single method for measuring all aspects of ocular blood flow and its regulation in glaucoma.

  Comment: A comprehensive approach, ideally implemented in a single device, may be required to assess the relevant pathophysiology of glaucoma.

Color Doppler Imaging

Alon Harris, Brent Siesky

Description

Color Doppler imaging (CDI), or ultrasound, is a common imaging technology used extensively in radiology, cardiology, and obstetrics. The use of CDI to measure blood flow parameters in the blood vessels supplying ocular tissues (retrobulbar) has become increasingly more common. Depending on the specific device, CDI uses pulse-Doppler measurements or Doppler-shifted frequencies with b-scan grayscale images. During CDI, various scanners and transducers (from approximately 5-14 MHz) have been utilized to assess ocular tissues depending on desired tissue depth and specific CDI methodologies.[1] The relative phase changes of the pulses are used to obtain the frequency shift which allows for estimation of distance.

Within the eye, CDI can evaluate the ophthalmic artery, central retinal artery and short posterior ciliary arteries (often as temporal and nasal groupings) to provide blood flow velocities and estimates of downstream vascular resistance.

Analysis

During CDI examination of the eye, the operator identifies the desired vessel based on anatomical location and places a sampling window for pulsed-Doppler measurements on the vessel. The frequency of sound waves striking moving reflective sources is Doppler shifted allowing for quantification of blood flow velocities.[2] The peak and trough of the velocity waveform are then identified by the computer/operator. Most commonly, CDI is used to measure the end diastolic velocity (EDV), peak systolic velocity (PSV), pulsatility index (PSV-EDV)/Tmax[3] and a calculated (PSV-EDV/PSV) vascular resistivity index originally described by Pourcelot.[4-6]

Reproducible procedure is vital for accurate CDI assessment. When using CDI on the eye, the technician rests the base of his/her hand on the subject's forehead to take the weight of the probe off of his/her arm to avoid fatigue, as well as to reduce pressure on the globe. This is essential for accurate assessment of vessels with diameters between 80 and 200 μm as excessive pressure may acutely alter IOP, changing the velocities being measured.[7] Appropriate angle correction is required for vessel tracking especially when measuring the ophthalmic artery.[1] Further, it is important to ensure exact duplication of vessel location and angle correction for an individual undergoing consecutive measurements. The examiner may view pervious CDI vessel acquisitions for an individual patient while remaining blind to parameter values to assist in ensuring identical measurement location placements.

Advantages and limitations

The CDI has several advantages and limitations compared to other hemodynamic assessment technologies. CDI is non-invasive, allowing hemodynamic data to be obtained in eyes with poor optical media and regardless of pupil size. Additionally CDI is vessel selective, has acceptable reproducibility, and is capable of detecting resistance of vascular beds distal to point of measurement,[8-12] although not all studies are in agreement.[13] A recent paper by Sato *et al*.[14] has suggested increasing pulsatility in the central retinal artery is affected by the compliance of the arterial system proximal to the measurement site as well as increases in vascular resistance distal to the measurement site.[14]

Among CDI limitations, the devices are expensive, and reproducible data requires an experienced technician. Reliance on automated computer generated PSV, EDV, PI and RI measurements is not recommended. Further, in its current state CDI measures blood flow velocities and not net flow due to a lack of vessel diameter measurement. Also, it is the only ocular hemodynamic measurement that is normally performed with the subject in a supine position; although CDI can also be performed with good reproducibility in seated subjects.[15] In younger patients it is often difficult to locate a separate posterior ciliary artery signal, because the strong activity of the ophthalmic artery can mask their individual appearance to the probe. Certain variables such as age and carotid artery status may also influence CDI measurements.[16]

Clinical utility

Numerous prospective investigations report CDI to be a valid measure of blood flow disturbances in various ocular disorders especially glaucomatous optic neuropathy.[17-54] Vascular abnormalities measured by CDI have been associated with the presence of glaucoma, IOP levels, structural changes in the optic disc and glaucomatous visual field progression.[17-54] A multitude of studies have reported lower PSV and EDV levels in the ophthalmic artery, central retinal artery and short posterior ciliary arteries and increases in downstream vascular resistance of the vessels of glaucoma patients compared to healthy controls (often age and sex matched). Although each specific study varies slightly in their findings,[17-54] a consistent theme of lower blood flow velocities and higher calculated vascular resistance in the retrobulbar blood vessels measured utilizing CDI has been reported in patients with glaucomatous optic neuropathy.

Questions to be addressed include:

- Which retrobulbar blood vessel has been shown to be most related to the presence, incidence and progression of glaucoma?
- Do different studies utilizing different CDI machines produce different mean values?
- Can a normative database of CDI parameters be established taking into account the various patient demographics, IOP, blood pressure, etc. of

participants in previous published studies which may affect the reported mean values?

Laser Doppler Flowmetry and Scanning Laser Flowmetry

Brent Siesky, Larry Kagemann

Description

The Laser Doppler Flowmeter (LDF) is a laser Doppler device consisting of a modified fundus camera and computer system. The most established method utilizing LDF principles is the Heidelberg retinal flowmeter (HRF, Heidelberg Engineering GmbH, Dossenheim, Germany) which provides noninvasive confocal scanning laser Doppler flowmetry measurements of retinal capillary blood flow.[55] Unlike the stationary laser points of the older LDF system, the HRF laser quickly scans the fundus and each scan line is divided into 256 individual points. Doppler shifts from each point are considered independently while scattered light from each point is quantified as with LDF, however, only scattered light from the point of illumination is analyzed by the HRF. Since separation of the incident beam and detection point, as used in the LDF increases penetration of the measurement, HRF measurements tend to be concentrated on surface vasculature (retinal capillaries). The system is confocal, with a focal plane thickness of 400 μm, further acting to eliminate the contribution of deeper tissue to the measurement. Every point is illuminated and sampled 128 times at a frequency of 4 kHz.[55]

Analysis

The HRF provides noninvasive measurements of retinal capillary blood flow and vascular density. Several methods of analyzing raw HRF data are currently available for academic and clinical application, each with inherent advantages and limitations. Default software utilizes the 10x10 pixel box to determine mean values of velocity, volume, and flow. Studies have demonstrated a coefficient of reproducibility between 0.7 and 0.95 for flow measurements with this technique.[56-61]

Another method, automatic full field perfusion image analysis (AFFPIA), was developed to analyze blood flow more specifically and automatically. This software program calculates the Doppler frequency shift and the hemodynamic variables flow, volume and velocity of each pixel according to the theory of Bonner and Nossal.[58-60] An interobserver coefficient of variation less than 6% in both nasal and temporal fields using this software has been reported.[62]

A third method, developed by Alon Harris and co-workers,[63-64] utilizes manual pixel-by- pixel analysis to collect individual pixel measurement points of sufficient quality and displays them by histogram and cumulative percentages. The distribution of pixels is described by identifying 0, 10, 25, 50, 75 and 90th

percentile flow values.[61,63-64] In a study using pixel-by-pixel analysis, Jonescu-Cuypers *et al.* found no statistically significant interobserver differences between two observers analyzing HRF images of a predetermined area of the peripapillary retina.[65] A more recent study incorporating pixel-by-pixel HRF images from the Thessaloniki Eye Study found no statistically significant differences of any parameters when identical images of a predetermined area were analyzed on three separate occasions by two masked observers. The authors reported an intraclass correlation of > 0.75 for all percentiles of blood flow.[66]

Advantages and limitations

To its advantage, the HRF measures volumetric retinal capillary blood flow, though in arbitrary units. Further, the HRF represents an important advance in hemodynamic analysis by providing sub-capillary resolution. While a complete understanding of HRF blood flow measurements remains unclear, it has been demonstrated through the use of *in vitro* models that the HRF is sensitive to small changes in blood flow. Numerous studies have shown HRF measurements to differentiate blood flow deficits in glaucoma patients compared to controls and reduced HRF blood flow measurements have been shown to correspond to visual field defects in several studies.

The greatest disadvantage of the HRF is that flow measurements are in arbitrary units. The gold standard of ml/min/gm has not been met, and it is unlikely that the current instrument will ever be able to produce absolute measurements of blood flow. In studies with an *in vitro* model, and in a follow-up study in humans, it has been demonstrated that the instrument is also susceptible to errors due to improper sensitivity settings. When considering data from studies utilizing HRF images, high-quality HRF images are required for data to be reliable, which are not often obtained in all patients as clear optical media and good fixation are required.

Clinical utility

Numerous studies have found HRF measured retinal capillary blood flow measurements to be reduced in glaucoma patients compared to healthy subjects (often age and sex-matched). Specifically, HRF-measured reductions have been reported within the neuroretinal rim[67-68] and peripapillary retina.[69-70] HRF measurements have also been used to indicate faulty autoregulation in glaucoma patients' response to IOP reductions.[71] Reduced retinal capillary flow has also been found to correspond to the visual field defects.[72-74] HRF measured reductions in retinal capillaries have additionally been linked to pathological structural parameters in glaucoma.[67,75]

Questions to be addressed include:

- With differing HRF analysis software, each with inherent limitations, what can be done to standardize HRF measurements?

- Can retinal capillary blood flow produced by HRF in arbitrary units be used to establish a normal value for retinal blood flow in healthy vs. glaucoma patients?
- Since HRF is no longer commercially available, what imaging technology may best be utilized to examine the retinal capillaries in research centers that cannot acquire a new HRF imaging device?

Retinal Vessel Analyzer

Ingrida Januleviciene, Brent Siesky, Alon Harris

Description

The retinal vessel analyzer is comprised of a fundus camera, a video camera, a real-time monitor and a computer with vessel diameter analysis software. It allows continuous and on-line measurements of the diameter of a segment of a retinal blood vessel with a temporal resolution of 25 readings/second in relation to time.[76] Retinal vessel diameters are analyzed in real-time with a maximum frequency of 50 Hz. The consecutive fundus images are digitized using a frame grabber. Because of the absorbing properties of hemoglobin, each blood vessel has a specific transmittance profile. Measurement of retinal vessel diameters is based on adaptive algorithms using these specific profiles.[76-77]

Analysis

The RVA program initiates analysis of vessel diameter over the length of the vessel within a rectangular cursor. This window can either include a retinal artery or vein for the measurement of vessel diameters.[76-77] The main outcome variable of the RVA is the vessel width measurement of the selected vessel(s), expressed in units of measurement (UM). In a normal Gullstrand eye, 1 UM is equivalent to 1 μm. For the stimulation with flicker light, the outcome is defined as percent change to baseline.

The RVA reproducibility coefficients have been shown to vary between 1.3-2.6% and 4.4-5.2%, respectively. Reproducibility is reported to be slightly higher for retinal veins than for retinal arteries.[76] Regarding the resolution of the instrument, it is generally recommended not to measure vessels with a diameter smaller than 90 μm.[77]

Advantages and limitations

RVA enables continuous monitoring of the vessel diameter. Different vessel segments, as well as different retinal vessels, can be investigated simultaneously. Sections of recordings compromised by eye movements or blinks can be eliminated from the analysis. Fundus images are stored on a videotape recorder for off-line measurement of other vessels within the captured field of view.

RVA measurement quality is strongly dependent on clear optical media. Good fixation abilities are required, otherwise variability is greatly increased. Further, RVA requires dilating the pupil which may affect local blood flow itself. RVA does not allow absolute retinal vessel size measurements which may limit its use in cross-sectional studies. It is important to note that this technique measures the reaction of retinal vessel diameters and does not provide a true measure of blood flow. The relationship of retinal vessel diameter measurements to blood flow in the retinal tissues is unknown.

Clinical utility

This technique for studying the retinal vascular reactivity has primarily been applied in patients with diabetes. For instance, it has been reported that the vasoconstrictor response decreases with increasing stage of the disease and improves after pan-retinal photocoagulation.[78] Stimulation with flicker light has been used as a physiological provocation method to investigate increases in retinal vessel diameter, retinal blood flow, and optic nerve head blood flow in regulation of vascular tone. For instance, the technique has been shown to have sensitivity to pharmacologic interventions and reflects changes in vessel caliber consistent with physiological provocation after breathing 100% oxygen.[79-82] Specifically, a vasoconstrictive effect on retinal vessels was fully established after 6 minutes and remained stable over a period of at least 30 minutes.[83] The mechanism underlying the vasoconstrictor response to hyperoxia is largely unknown as is the reason for reduced responses in diabetic patients.

Few studies have utilized RVA in glaucoma assessment. One study found a local vessel wall difference in glaucoma patients compared with age-matched controls using RVA.[84] Another investigation found that a short-term rise in IOP leads to less retinal vessel reaction in glaucoma patients than in healthy volunteers and ocular hypertensives. The authors suggested this might be due to impaired autoregulation to ocular perfusion changes in glaucoma patients.[85]

Questions to be addressed include:

- What is the relationship of RVA measurements of retinal arteries to blood flow in the retina?
- Is there research which examines vascular compliance (*i.e.*, blood vessels are more rigid / have a loss of compliance) using RVA?
- What evidence is available that suggests that vascular deficits of glaucoma patients can be detected using RVA images?

Blue Field Entoptic Stimulation
Ali Hafez

Description

Blue field entoptic techniques are based on the blue field entoptic phenomenon, which consists of the perception of leukocytes flowing through the subject's own retinal macular vasculature. This non-invasive method was described in detail by Riva and Petrig in 1980 for the subjective evaluation of perimacular hemodynamic parameters.[86] Subjects can note the presence of leukocytes in the capillaries around the macula when looking at diffuse blue light of a wavelength of approximately 430 nm. The leukocytes can be seen moving in an area of 10-15 degrees surrounding fixation. The phenomenon can be explained by the different absorption properties of erythrocytes and leukocytes when the retina is illuminated with blue light. Moving leukocytes do not absorb the short wavelength light, whereas the erythrocytes do. Leukocytes are thus perceived as moving corpuscles. Similar patterns are created by computer simulation on a screen and subjects are then asked to match the number and speed of the computer-generated particles seen by the fellow eye with those seen by the study eye in the blue field. These parameters are adjusted in standardized intervals until a close match is achieved.

Analysis

The pattern match between actual velocity and actual density of leukocytes in the study eye and the same variables viewed on the simulation screen by the fellow eye can be used to draw conclusions about perifoveal capillary perfusion. Retinal leukocyte flux is deduced from leukocyte velocity (mm/sec) and leukocyte density (cells per 10-15 degrees radius of the central entoptic field).

The intensity of the blue light is adjusted according to the clarity of the ocular media. Eyes with cataract should be tested with higher intensity and maximum mydriasis to avoid false negative responses. Correction for ametropia as well as alignment with the visual axis should also be performed before the test. For accurate results, simulation velocity and density should be randomized for at least five matches. An average and a standard deviation of the five matches are calculated. An intra-subject variability of less than 15% is required for an accurate test.

Advantages and limitations

The technique is non-invasive, relatively inexpensive, and simple to perform. Data is acquired rapidly and requires minimal analysis.

The data that can be drawn from the technique, however, depends on the patient's cooperation and perception. Large variations between patients exist and data is limited to the perifoveal anatomical region.[87] Furthermore, the accuracy

of the data may be affected by the physiologic and pathologic state of the retina. The technique is also based on the assumption that macular capillaries have a fixed diameter. It is not clear whether leukocyte flux is proportional to retinal blood flow under all clinical conditions.[88]

Clinical utility

Blue field entoptic stimulation technique has been used in various physiologic and pharmacologic studies.[89-94] Using this method, studies have demonstrated autoregulation of macular circulation in response to acute elevations of IOP in normal subjects.[95] Such autoregulation was shown to be abnormal in glaucoma patients.[96] Studies also showed significant positive correlation between loss of visual function and reduced leukocyte velocity.[97] Through blue-field entoptic stimulation, the relative effects of oxygen and carbon dioxide on perimacular circulation have been shown.[98] The technique also revealed that Endothelin-1 contributes to hyperoxia-induced retinal vasoconstriction.[99] Such vasoconstriction was shown to differentially affect erythrocytes and leukocytes in the human retina.[100]

Questions to be addressed include:

- How accurate are blue field hemodynamic parameters?
- Does leukocyte flux represent total retinal blood flow or a singular event?
- What evidence is available that suggests glaucoma patients' vascular deficits can be detected using blue field technologies?
- How might the technology be improved upon to develop more meaningful data?

Laser Interferometric Measurement of Fundus Pulsation
Leo Schmetterer

Description

Laser interferometric measurements of fundus pulsation are based on the measurement of heartbeat-related distance changes between the front surface of the cornea and the retina. This non-invasive method was previously described in detail[101-103] and aims to assess the pulsatile component of ocular blood flow. When the eye is illuminated with laser light of high spatial and temporal coherence, the light is reflected at each optical interface. The reflections from the front surface of the cornea and the retina form non-localized concentric interference changes. Any distance change between cornea and retina, as it occurs for instance due to the rhythmic filling of blood vessels during the cardiac cycle, is seen as a change in interference order. During systole the distance between cornea and retina decreases because the blood volume entering the eye via the

arteries exceeds the blood volume leaving the eye through the veins. When the interference pattern is imaged to a CCD camera or a linear CCD array, the distance changes between retina and cornea can be evaluated with high temporal resolution. Measurements can be done at the fovea, by asking the subject to fixate on the laser beam, or at pre-selected fundus locations when the instrument is mounted on a fundus camera.

Analysis

The maximum distance change between cornea and retina is called fundus pulsation amplitude (FPA) and contains information on the pulsatile component of ocular blood flow.

The reproducibility of the method is high.[104,105] Schmetterer and co-workers reported intraclass correlation coefficients between 0.95 and 0.97 in healthy subjects. It has been shown that there is a high degree of association between intraocular pressure and pulse amplitude as measured with pneumotonometry and FPA.[104,106,107] Based on a mathematical model of the eye an estimation of pulsatile ocular blood flow has been provided based on FPA measurements.[108]

Advantages and limitations

The technique is non-invasive, simple to perform and can be measured in almost all patients unless the optic media is opaque to a degree that the retinal reflection can no longer be seen. Data is acquired rapidly, but requires analysis of the interferograms, which can be time consuming.

The technique has a number of significant limitations. Most importantly only the pulsatile component of blood flow can be accessed with this technique. The ratio of pulsatile to total ocular blood flow is, however, unknown, and ocular disease as well as administration of vasoactive drugs may change the ratio of pulsatile to total ocular blood flow. In addition, the relative contributions of different vascular beds to the FPA is unknown, although the choroidal circulation has the largest impact.[104] Because of these limitations the technique has never been commercialized.

Clinical utility

Laser interferometric measurement of fundus pulsation has been used to characterize ocular perfusion abnormalities in a variety of ocular pathologies including glaucoma,[109] age-related macular degeneration,[110] diabetic retinopathy[111] and central serous chorioretinopathy.[112] Only recently it has been suggested that one may get insight into ocular rigidity by comparing FPA measurements with pneumotonometric measurements, but this needs to be further elucidated.[113]

Questions to be addressed include:

- What does the pulsatile component of blood flow accessed with laser interferometric measurement mean in terms of the ocular circulation?
- Is there any significant evidence which shows laser interferometric measurement of fundus pulsations reveals differences in ocular circulation between patients with glaucoma and healthy controls?

Dynamic Contour Tonometry and Ocular Pulse Amplitude

Ingeborg Stalmans

Description

The dynamic contour tonometer represents a device for non-invasive and direct measurement of intraocular pressure (IOP). The concave contact surface of the measuring tip creates a distribution of forces between the central area of the tip and the cornea that equals the forces generated by the internal pressure of the eye.[114-115] A piezoresistive pressure sensor records the IOP without deformation of the cornea. Because of the absence of applanation, the values obtained with this device are unaffected by differences in the central corneal thickness or changes in corneal topography.[116]

By measuring IOP continuously, a sinusoidal variation of IOP, synchronous to the heart rate, is determined. The difference between the highest and the lowest IOP level is called ocular pulse amplitude (OPA).[114]

Analysis

The pulsatile variations in IOP are thought to be caused by the blood volume that is pumped into the eye during each cardiac cycle. Therefore, OPA might reflect volumetric changes that are dependent on ocular blood flow, mainly choroidal, or even better, the pulsatile component. Indeed, IOP pulsation measured with pneumotonometry correlated well with choroidal excursions during pulsatile blood flow.[117] OPA measurements within and between observers have a high amount of agreement.[118] OPA readings are not influenced by the structure of the anterior segment of the eye (central corneal thickness, corneal curvature, anterior chamber depth). However, they are positively correlated with the IOP and negatively correlated with the axial length.[118-120]

Advantages and limitations

Although OPA has been correlated to glaucoma and its severity, its relationship to ocular blood flow remains uncertain. The exact relationship of OPA with ocular hemodynamics remains poorly understood and an algorithm to convert OPA into blood flow is not yet available. Therefore, OPA should not be used as a surrogate for ocular blood flow measurement.

Clinical utility

OPA has controversial significance in the diagnosis and management of glaucoma. OPA is reduced in patients with NTG or POAG as compared to healthy individuals,[120] and higher in ocular hypertension.[121] In patients with glaucoma, higher OPA seems to correlate with less severe glaucoma.[122] Conversely, a small ocular pulse amplitude is correlated with moderate to severe glaucomatous visual field loss and might be a risk factor for the development of glaucomatous visual field defects.[123] OPA has been correlated with the resistive index in the retrobulbar vessels, as measured by color Doppler imaging. (Stalmans *et al.,* EJO 2009; 19, in press) Further, a significant correlation exists between the OPA and the presence of spontaneous venous pulsations.[124] OPA readings are related to left ventricular ejection time, but not to blood pressure levels and amplitude. It seems that the OPA strongly depends on the time-course of the cardiac contraction, but that the resulting blood pressure variations are dampened between the heart and the eye and/or within the eye, and therefore are not reflected in the OPA.[125]

Questions to be addressed include:

- Do OPA or POBF measurements actually represent any aspect of the ocular circulation?
- All current vascular theories are based upon multiple assumptions which have never been proven. If OPA measurements are indeed linked to glaucoma, might it not be a better IOP measurement device than a blood flow device?
- Does OPA more strongly represent glaucomatous risk than singular IOP readings?

Pulsatile Ocular Blood Flow (POBF) Analyzer
Ingrida Januleviciene

Description

POBF analyzer is a modified pneumatonometer interfaced with a microcomputer, which records the ocular pulse. The OBF examination consists of the placement of the tonometer on the cornea for several seconds and measuring the air pressure required to indent the cornea. The pneumotonometer sends an analog signal to the computer, where it is digitized and recorded. The arterial blood flow to the eye varies with the heart cycle, and IOP and ocular blood volume vary accordingly, resulting in a peak during systole and a dip during diastole. The pulse wave is the rhythmic change in IOP exhibiting an almost sinusoidal pattern.

Advantages and limitations

The advantages of the POBF are that the analyzer is relatively inexpensive, simple to operate, data acquired immediately, requires no special training for anyone able to perform applanation tonometry, minimally invasive for the patient.

The disadvantages are that the analyzer measures IOP rather then blood flow, and the rate of venous flow is not known. POBF determinations are influenced by the pulsatile components of both choroidal and retinal perfusion.[139] Coefficient of reliability is high – about 0.92.[126] The coefficient of variation was found to be greater than the manufacturer's claim of within 10%. An average of three consecutive measurements were found to be adequate to detect the minimum reported difference in POBF between glaucoma and normal patients.[143] If IOP measurements have to be repeated using the POBF, they are best done after an interval of at least 2 minutes and preferably after 15 minutes. Use of the POBF Tonograph had no significant immediate effect on the IOP or POBF values obtained from a fellow eye.[144]

The POBF device measures rhythmic change in IOP. Acquiring approximately 200 measurements per second, real-time fluctuations in IOP during the cardiac cycle are quantified. The amplitude of the IOP pulse wave is used to calculate the change in ocular volume. A detailed POBF report contains the IOP fluctuations and average IOP, amplitude of the pulse wave from which the changes in ocular pulse volume are calculated, ST and DT demonstrate the duration of pulse systole and diastole cycles, pulsatile component of ocular blood flow is calculated in µl/s, MNI is proportional to the maximum speed of blood flowing to the eye, PEQ is a pulsatility index equivalent (steepness of the pulses), IDR quantifies the proportion of systole in the cardiac cycle. Reliability coefficient for POBF values ranging from 290 microliters/min to 2.196 microliters/min have been reported at 0.92.[126]

Clinical utility

POBF values are significantly influenced by gender, mean blood pressure, pulse rate, and axial length.[127,128] Practitioners should measure the axial length in POBF assessment.[129] The reduction in POBF with age is significant.[130] Although aging affects scleral rigidity and systemic blood pressure, multiple regression analysis indicates that the most influential factor affecting POBF is aging. The peak systolic velocity in the ophthalmic artery also decreased with age, indicating reduced ocular blood supply.[131] The wide range of normal values and the low discriminating power of POBF between normal and glaucomatous eyes limits the clinical use of the device for glaucoma patients.[132]

The absence of change in the POBF during transient mild systemic hypoxia indicated that the global pulsatile choroidal blood flow was not vulnerable to the effects of the transient mild systemic hypoxic stress in the healthy young adult.[133] The clinical usefulness of measuring POBF in tumor patients is limited.[134] POBF is not different between fellow eyes of Caucasian patients with asym-

metric AMD.[135] A single measurement of POBF does not distinguish between subjects with and without mild/moderate non-proliferative DR.[136] POBF assessment is not a good diagnostic tool for screening for ICA stenosis.[137] Following treatment with systemic steroid a significant improvement in POBF in patients with Grave‘s ophthalmopathy has been demonstrated.[138]

POBF was found to be associated with systolic and pulsatile components of blood flow velocities in both the central retinal artery and the temporal short posterior ciliary arteries. These results suggest that POBF determinations are influenced by the pulsatile components of both choroidal and retinal perfusion, but this does not confirm what POBF actually measures.[139] POBF was found to be insensitive to mild systemic hypoxia.[140] POBF was not altered by systemic hyperoxia although a mild increase was seen during carbogen breathing.[141] POBF was uninfluenced by systemic hypercapnia despite significant blood flow changes measured using both CDI and SLDF.[142] POBF was found not be an adequate measure of ‘total ocular blood flow’.[143]

Questions to be addressed include:

- No study to date has identified what POBF signals specifically identify in terms of the ocular circulation. Despite numerous inferences in the commentary of articles on the topic, the original assumptions that suggested POBF may be related to ocular blood flow have not been confirmed.[145]

Laser Speckle Method (Laser Speckle Flowgraphy)
Makoto Araie

Description

Laser speckle method (laser speckle flowgraphy, LSFG) assesses circulation in ocular tissues using the interference phenomenon. A fundus camera is equipped with a diode laser (wavelength 808 nm), image sensor, infrared charge-coupled device (CCD) camera, and a high-resolution digital CCD camera. The area of the fundus where the laser beam is focused is observed by an infrared CCD camera, while a high-resolution digital CCD camera is used for the measurement of the retinal vessel diameter and recording of fundus photographs. The scattered laser light is imaged on an image sensor, on which a speckle pattern appears and is scanned at 512 scans per second in the current model. A diode laser and an image sensor are used for the laser speckle measurements.

The interference phenomenon is observed when coherent light sources, such as lasers, are scattered by a diffusing surface. The speckle pattern which appears under illumination of laser irradiation can only be described statistically. In accordance with movement of blood cells in the tissue, the structure of the pattern varies rapidly, depending on the blood flow velocity. Fercher and Briers[146] first presented pictures of velocity distribution of red blood cells in the retina by means of laser speckle photography. Later, Tamaki *et al.* developed an apparatus

for non-contact, two-dimensional, and quantitative analysis of ocular blood flow in living eyes utilizing the laser speckle phenomenon.[147-149]

Analysis

One of the most useful speckle-method outcomes is the standard deviation of the intensity distribution of the speckle pattern. The fundamental statistical properties of these time-varying speckles can be studied by analyzing the space-time correlation function of the speckle intensity fluctuation. These specifics are described in detail elsewhere.[146,150-152] The outcome variables of this method are the Square blur ratio (SBR) or Normalized blur (NB) values of the selected region in arbitrary units. Both variables are originally quantitative indices of blood velocity, but the NB values were also shown to correlate significantly with blood flow data simultaneously determined with the hydrogen gas clearance method, colored microspheres technique, and other methods in the ONH, iris, choroid and retina.[147,148,153-161]

The application of this system to humans in certain situations is difficult because the argon illumination causes too much glare to allow for adequate steady fixation during the measurements, even when an area outside the vascular arcade is measured. Comparison of the results to those obtained by indocyanine green angiography was carried out in subjects with choroidal diseases to confirm that LSFG may be used to evaluate aspects of choroidal hemodynamics.[162] Although the current system has been used primarily in vascular beds with low blood velocity, such as capillary beds, SBR values can be theoretically applied in higher velocity vascular beds such as major retinal vessels.[163] Reproducibility of the measurements has been commented on previously.[157,158,164]

Advantages and limitations

Laser speckle method follows time change in the tissue velocity at the same site of the same eye at various intervals. It has been applied in multiple tissue beds in animal models and in humans. These values are suited to monitor the time course of change in the tissue blood velocity at the same site of the same eye at various intervals.

Conversely, the meaning of normalized blur measurement is not clearly understood in terms of blood flow. The technique is also not capable of inter-eye or inter-individual comparisons and should not be used for velocity comparison between different sites of an eye since the result depends on not only velocity of blood cells but also reflectivity of the laser light of measured tissues.

Clinical utility

The LSFG is reported to be a useful tool for the assessment of certain aspects of circulation changes in the iris, ONH, choroid and potentially retina. Care must be taken in interpreting the results of studies in which inter-eye or

intra-eye differences in NB values are compared or in which blood flow indexes as measured by LSFG are correlated with those obtained by scanning laser Doppler flowmetry. Correlations of the ONH rim circulation and the damage in corresponding visual fields in glaucoma patients must also be carefully interpreted.[165-167]

Questions to be addressed include:

- What exactly do LSFG readings represent in terms of the ocular circulation?
- How subjective are the measurements which involve patient participation for elderly or diseased individuals?
- Due to the multiple limitations of these devices in humans, what can be done to further develop this technology in its application for glaucoma?

Digital Scanning Laser Ophthalmoscope Angiography
Larry Kagemann, Alon Harris

Description

Digital scanning laser ophthalmoscope angiography (SLOA) is a set of techniques that quantify various aspects of blood filling the retinal and choroidal vasculature. Fluorescein dye is used to examine retinal hemodynamics, and indocyanine green (ICG) allows visualization of the filling of both retinal and choroidal vessels. The approximately 6:1 volumetric predominance of choroidal to retinal flow, coupled with the numerous and overlapping vessels of the choroid in contrast to the structured vascular tree of the retina, allow the assumption that ICG angiograms primarily represent choroidal hemodynamics. The exceptional optics and pure laser light sources of the SLO are currently most often used in spectral retinal analysis and microperimetry. Detailed descriptions of SLO imaging are available.[168-179]

In brief, SLOA technology consists of a scanning laser which illuminates the retina in a raster scan pattern. Backscattered light is quantified by a photo detector and a time-based stream of measured intensities is used to construct a video signal. This signal is displayed on a monitor at the time of examination, and is also stored, either in analog fashion on a video tape or digitally. The disadvantage of digital storage is the high data volume produced, especially if compression is limited to ‘loss-less’ strategies. After a baseline image of the retina is obtained, an angiography high-pass filter is placed between the reflected light and the photo detector. This filter blocks all incident laser light reflected from the retina. A fluorescent compound (ICG or fluorescein) is injected into a vein and observed as it fills the vasculature of interest. These compounds become excited by the laser light and produce light of longer wavelengths than those of the stimulation light. The high-pass filter, as previously mentioned, is selected so that excitation light is blocked by the filter but emission light (light

of a longer wavelength) is able to pass through. The result is a video image of moving blood on a nearly black background. Autofluorescence contributes light to the signal (especially in fluorescein angiography). When the filter is introduced (in a good system), the image consists of inner-retinal vessels casting shadows across the fluorescing pigmented tissues of the outer retina.[168-179]

Analysis

All parameters utilize graphs of fluorescence within retinal arteries and veins against time. A number of groups have developed quantitative parameters to characterize retinal hemodynamics with fluorescein angiography. The simplest is mean dye velocity, which represents the speed of blood moving through the large retinal branch arteries. It is determined by measuring the delay (usually in video frames) between the first appearances of dye in two locations on a retinal artery. However, this may be an insensitive parameter. Usually, at a video rate of 30 frames per second, dye appears at two points in any retinal artery in two sequential frames. This makes the velocity calculation completely dependent on the distance between the points measured, as the time component of velocity is always 0.03 seconds (1 frame). Changes in dye velocity may represent hastened flow through the retina, or merely a localized arterial constriction, resulting in increased velocity.

Arterio-venous passage time (AVP) is the amount of time between first appearance of dye in a retinal artery and the associated vein. Measurements are taken adjacent to the optic nerve head, and are usually measured in frames and translated to seconds. This parameter has proven to be very sensitive to small changes. At NTSC frame rates of 30 per second, a normal AVP time of 2.5 seconds is actually quantified as a measurement of 70 video frames. This small unit of measurement (increments of 0.03 seconds) provides the opportunity for very small real changes in the rapidity of dye passage through the retina to be observed with statistical significance. Hastened AVP times represent hastened flow through the retinal vascular bed. Selection of the artery/vein pair of interest allows localization of measurements to quadrants.

Mean transit time (MTT) represents the mean retinal circulation time, or amount of time that blood spends in the retinal vasculature. Unlike AVP and velocity measurements, which require identification of only the first appearance of dye, MTT is calculated from an analysis of complete dye dilution curve, limiting its use to examinations in which a subject can remain still with eyes open for at least 5 seconds. MTT is the difference in time coordinates of the centers of gravity of the extrapolated arterial and venous curves. Specifically, the curves are ‘extrapolated’ to zero fluorescence based on the stable downward slope as dye passes the measurement region. This avoids error due to dye recirculation.

Capillary transit velocity is quantified in high magnification fluorescein angiograms of the perimacular capillary bed. It is the velocity of micro-boluses of dye (or possibly Rouleaux formations) observed as they rapidly move through the single layer of retinal capillaries adjacent to the foveal avascular region. Due

to the small distances involved, the sensitivity of the measurement to change is less than that of AVP times. The unit of measurement of time is 0.03 seconds, as with AVP; however, the distances are limited to capillaries free of branch points in the macula.

ICG angiography has produced a number of parameters describing choroidal hemodynamics,[168-179] all of which describe some aspect of relative regional filling rates. Unlike fluorescein, in which measurements from individual vessels have meaning, the overlapping and redundant arteries of the veins of the choroid limit quantification of fluorescence of ICG dye within groups of vessels. Originally, these groups of vessels were selected to correspond with the regions assessed by automated visual field. No correspondence between hemodynamics and function has been observed, but the use of four perimacular and two temporal peripapillary regions persists. The most useful of these has been quantification of delayed peripapillary dye arrival compared to the dye arrival in the macular regions of the choroid.

Advantages and limitations

SLOA data are able to be obtained at the point of interest by observing moving blood, as represented by the dye it carries directly in high resolution. SLO AVP is very sensitive to change in retinal hemodynamics while SLO with ICG provides the only source for assessment of regional choroidal hemodynamics viewed directly. SLOA provides hemodynamic data obtained directly from moving blood, flowing precisely in a broad selection of areas of interest.

Conversely, SLO is invasive, with rarely but potentially deadly reactions to dye injection. Analysis is not commercially available and is both time and labor intensive. SLOA equipment is expensive and requires skilled operators utilizing customized image processing software.

Clinical utility

SLO/SLOA provides great detail about retinal and choroidal hemodynamics producing direct visualization of retinal and choroidal vasculature and circulation in real-time. Utilizing SLO video technology, evidence of reduced retinal hemodynamics have been observed in patients with glaucoma,[180] as evidenced by prolonged AVP times.[181] It has also been demonstrated that areas corresponding to more severe visual field damage have prolonged AVP time compared to areas of less damage.[182] Initial studies utilizing this technique suggest that some glaucomatous eyes present with select regions of slow choroidal filling and sluggish movement of blood into and out of the choroid.[183]

Questions to be addressed include:

- While clearly providing precise directly viewed circulation parameters in glaucoma patients, how can the invasive nature of the device be minimized?

- Since no commercial software is available for SLO analysis, what can be done to develop standardized SLO images?

Bi-directional Laser Doppler Velocimetry and Simultaneous Vessel Densitometry

Chris Hudson, John Flanagan, Subha T. Venkataraman, Edward D. Gilmore, Gilbert Feke

Description

Bi-directional laser Doppler velocimetry (LDV) to quantify blood velocity in the large retinal vessels and simultaneous densitometry to measure diameter, are two techniques incorporated into the Canon Laser Blood Flowmeter (CLBF). The CLBF also utilizes an image stabilization system to minimize the impact of eye movement.[184] Absolute centerline blood velocity is calculated by using two distinct photodetectors separated from each other by a known constant angle, irrespective of the angle between the moving particle and reflected beam (generated from a 675 nm diode laser).[185-186] The resulting Doppler signal is analyzed by determining the frequency at which there is an abrupt reduction in the amplitude of the fluctuations in the Doppler-shift power spectrum and therefore it does not depend on any presumed shape of the average power spectral density curve.[187] Velocity measurements are acquired automatically every 0.02 seconds throughout the 2-second measurement window, resulting in a velocity-time trace.

Retinal vessel diameter is determined by projecting a green (543 nm) rectangular laser perpendicular to the vessel segment of interest. Densitometry analysis of the cross-sectional vessel image on the CLBF array sensor is used to calculate vessel diameter.[188-189] Diameter measurements are acquired every 4 milliseconds during the first and last 60 milliseconds of the 2-second velocity acquisition window. The CLBF stabilizes the optical system on the selected vessel segment by detecting any lateral motion of the green laser on the array sensor which, via a negative feedback loop, controls a steering system to rapidly adjust the position of the optics[184,,190-191] This system also permits the identification and post-acquisition rejection of velocity measurements impacted by significant eye movements.

Analysis

The CLBF instrument has been used extensively by a limited number of research centers to investigate aspects of blood flow physiology and patho-physiology of the major retinal vessels. Two sequential measurements of blood velocity and of vessel diameter are taken to ensure consistency of each parameter. Measurements of velocity (V, mm/sec) and diameter (D, μm) are used to calculate retinal blood flow (F, μL/min) using the formula:

$$F = \tfrac{1}{2} (\pi \cdot {}^{D2}/_{4}) (V_{maximum} \cdot 60)$$

The CLBF calculates the average blood velocity, Vmean, as:

$$Vmean = {}^{Vmaximum}/_{2}$$

which is theoretically correct for a parabolic velocity profile consistent with Poiseuille flow conditions.[192] An earlier LDV instrument, developed by Charles Riva and co-workers[193] in the early 1980s, calculated Vmean using the formula:

$$Vmean = {}^{Vmaximum}/_{1.6}$$

where 1.6 is a constant of proportionality between centerline blood velocity, $V_{maximum}$, and mean blood velocity, V_{mean}.

The different methodologies should result in velocity values being approximately 20% lower with the CLBF. However, measured velocity and flow values in healthy individuals were actually found to be lower with the Riva developed LDV instrument. The absence of a stabilization, or eye-tracking, system in the Riva developed LDV may have resulted in the acquisition of non-centerline velocity data and thereby lower flow values.[194] Furthermore, since the CLBF measures centerline blood velocity, direct comparison of flow magnitudes with techniques based upon fundus fluorescein angiography (FFA) that measure the speed of the advancing fluorescein dye front is invalid.[195] Such FFA based techniques in effect assess flow closer to the vessel wall, probably because of limited light penetration into the center of the vessel, where velocity is slower than the centerline value.

Retinal blood flow measurements using an earlier LDV instrument as well as the CLBF have been found to agree with microsphere results in animal models.[195] The CLBF instrument has also been shown to give consistent and repeatable measurements of blood flow.[196-203]

Advantages and limitations

Combining bi-directional LDV instruments with simultaneous measures of vessel diameter and centerline blood velocity make it possible to derive blood flow in absolute units. In this respect, this improved technology is unique amongst blood flow measuring devices.

The CLBF can only be used to measure blood flow in inner retinal (but not optic nerve) vessels of 60 μm in diameter or larger. Any given measurement is limited to a single point on the selected vessel segment and applies only to the 2-second measurement window. Additionally, clear optical media and pupil dilation are required, and it has not been as thoroughly researched as other established imaging technologies. In addition, the calculation of flow assumes that the vessel has a circular cross section and that the flow characteristics obey Poiseuille's law.[204] The densitometry measurement can be influenced by light scatter, such that an artifactual increase in vessel diameter occurs with increas-

ing light scatter.[205] Finally, the CLBF instrument is no longer commercially available.

Clinical utility

The CLBF instrument has been used in clinical settings to investigate retinal, systemic, and vascular diseases, especially retinal vein occlusion and diabetes. It has also been used to investigate disturbances of retinal blood flow and vascular regulation in age-related maculopathy and glaucoma, and changes in blood flow following various interventions including ocular and systemic pharmacological agents. [194]

Questions to be addressed include:

- Do CLBF measurements of single vessels represent total retinal blood flow?
- Since CLBF is no longer commercially available, what future does CLBF have in the assessment and research of glaucoma?
- CLBF has unique abilities to measure blood flow in standard units, but can another device be designed which incorporates CLBF features for the future?

Doppler Optical Coherence Tomography
David Huang

Description

Doppler optical coherence tomography (OCT) is based on the principle that moving particles, such as red blood cells inside blood vessels cause a Doppler frequency shift (Δf) to the back scattered light. Given the angle θ between the scanning beam and the flow direction, the Doppler shift is simplified to:

$$\Delta f = -2Vn \cos\theta / \lambda_0$$

where λ_0 is the center wavelength of the light source, n is the refractive index of the medium. In OCT,[206] this frequency shift Δf will introduce a phase shift in the interference pattern that could be obtained by analyzing the spectrum within an axial scan (A-scan),[207-209] the phase difference between sequential A-scans, [210-213] or phase difference between sequential B-scans (cross-sectional images).[214] With the recent improvement in scan speed using Fourier-domain optical coherence tomography (FD-OCT) technology, it has become possible to capture Doppler information from retinal blood vessels in 3 dimensions in a time spanning a fraction of the cardiac cycle.[215,216] With current FD-OCT technology, the phase difference between sequential A-scans provide the appropriate velocity detection range to measure flow in major branch retinal vessels.

It can be seen that the detection of the relative angle θ between the probe beam and flow direction is required to determine the total velocity of blood flow in a blood vessel. The minimum scanning required to determine both retinal vessel orientation and volume flow measurement was achieved with dual parallel scan planes spaced a small distance along the vessel.[217] Other approaches scan retinal vessels with many parallel sections in 3-dimensional (3D) imaging to calculate vessel orientation and blood volume.[215,216,218] To measure total retinal blood flow in the minimum amount of time, Wang and Huang recently developed a double circular scanning pattern (DCSP) that scans across all retinal vessels around the optic nerve head 4 times per second.[219] The average total retinal venous blood flow could be calculated with the data sampled within 2 seconds.

Analysis

Doppler OCT can be used to measure blood velocity and volumetric flow rate in retinal branch vessels. Since the cross-sectional velocity profile of the blood vessel is captured, both peak and average velocity could be analyzed as a function of time along the cardiac cycle. Vessel diameter could be directly measured from the cross-sectional velocity profile (OCT phase image) or from the more familiar reflectivity image (OCT amplitude image). Volumetric blood flow rate (µl/min) in each vessel is calculated by integrating the velocity over the vessel cross-section and includes steps to account for background motion, beam incidence angle, sampling step size, and pulsation. Although both retinal branch arteries and veins could be measured, the faster arterial flow is more difficult to measure accurately with current FD-OCT speed of 17-26 kHz due to phase-wrapping (Doppler shift of greater than 2π radians).[219] By combining the measurements from branch retinal veins, hemispheric and overall averages of retinal blood flow, combined venous cross-sectional area, and average venous flow speed could be obtained.[219]

Doppler OCT measurement in an experimental setting where the flow was controlled by a calibrated pump showed that the difference between the measured flow and the flow setting was less than 10%.[220,221] The coefficients of variation of total blood flow measurement were 10.5% and 12.7% for normal and glaucoma subjects, respectively.[220-221]

Advantages and limitations

Doppler OCT is able to measure flows in branch retinal vessels in absolute units of µl/min. Total retinal flow could be measured several times per second and the flow could be averaged over time to obtain a repeatable value. Vessel dimensions could also be directly measured from cross-sectional velocity profile.

Quantitative measurement of retinal blood flow with Doppler OCT is relatively new and there is limited information from clinical studies. So far quantitative measurements have been limited to major retinal branch vessels and measurement in capillary beds has not yet been demonstrated. Automated quantitative retinal

blood flow measurement and commercial instrumentation (RTVue, Optovue Inc., Fremont, CA) are still under development. The current primary limitation to measurement precision is the error in vessel orientation determination due to eye movement. This error is greater in vessels that have near normal incidence angles. This limitation can be reduced with greater imaging speed, which would increase the upper range of detectable flow speeds, allow finer sampling in both time and space, and reduce motion-induced error in vessel orientation measurement. With the continual improvement in the speed of line cameras that make up the heart of FD-OCT system, we can expect the speed limitation to become less important over time. Another limitation is the increased scan time required. The system requires further validation.

Clinical utility

The Doppler OCT instrument has been investigated in clinical settings to evaluate retinal blood flow in normal subjects and subjects with optic nerve and retinal diseases. Eyes with glaucoma, diabetic retinopathy, retinal vein occlusion and anterior ischemic optic neuropathy were found to have reduced total and hemispheric retinal blood flow. One study indicated that the reduction of total retinal blood flow was correlated with glaucoma severity. The total retinal blood flow in glaucomatous eyes (N = 12) were found to be well correlated with visual field parameters.[220]

Questions to be addressed include:

- Will Doppler OCT data be shown to be relevant to glaucoma?
- What software can be designed to best utilize Doppler OCT's abilities to provide meaningful hemodynamic data?
- How might retinal and optic nerve head structure and blood flow be evaluated together using Doppler OCT?
- With further developments in analysis using Doppler OCT, will blood flow be able to be measured in the laminar region?

Retinal Oximetry
Einar Stefansson

Description

Retinal oximetry is a method for noninvasive measurement of hemoglobin oxygen saturation (SO_2) in retinal structures by digital imaging. The techniques involved are described in detail elsewhere.[222-225] In brief, depending on the specific device, standard clinical digital fundus photography is performed coupled with a beam splitter to a digital camera with the image data filtered into discrete bandwidths. Images of vessels are recorded at oxygen sensitive and insensitive wavelengths. In each channel, there is a different narrow band-pass filter, through which only

light of specific wavelengths can pass. The center wavelengths of the filters are 542, 558, 586, and 605 nm and the half-bandwidth is 5 nm, except for the 542-nm filter, which has a 9-nm half-bandwidth. Images are then examined digitally using specialized analysis software.

Analysis

Optical densities (ODs) of vascular segments are determined using a computer algorithm to track the path of reflected light intensity along vessels. With a specialized computer program, OD can be calculated for every retinal vessel observed at each of the four wavelengths. OD is a measure of the blood's light absorbance and is calculated as:

$$OD=\log(\frac{I_o}{I}),$$

where I and I_o are the brightness levels inside and just outside a vessel, respectively. It can be shown that the ratio of ODs at certain wavelengths (OD ratio, ODR) has an inverse and approximately linear relationship to hemoglobin oxygenation:[222-225]

$$SO_2=a+k\cdot(\frac{OD_x}{OD_y})=a+k\cdot ODR.$$

In equation 2, SO_2 is the percentage of hemoglobin oxygen saturation; a and k are constants; OD_X and OD_Y are ODs (no unit) at wavelengths X and Y, respectively; and ODR is the optical density ratio. Thus, in theory, hemoglobin oxygenation can be calculated using brightness inside and outside vessels at two wavelengths of light.[3] Oxygen delivery (FO_2) can be approximated by FO_2 = RBF X $\Delta SO_{2(av)}$ where RBF is retinal blood flow and $\Delta SO_{2(av)}$ is the arteriovenous oxygen saturation difference.[226]

Advantages and limitations

Retinal oximetry is non-invasive and may provide valuable information regarding the metabolic link in glaucoma pathology. It represents an important step forward in attempting to assess the metabolism of ocular tissues directly. Conversely, retinal oximety is new and not sufficiently validated to date. Additionally, clear optical media is required for high quality images.

Clinical utility

Ocular blood flow remains a surrogate for tissue oxygenation and metabolism.[227] It is therefore important to consider the oxygen saturation of the delivered

blood. While increased retinal blood flow is suggestive of potentially increased oxygen supply to local tissue, oxygen saturation is not directly assessed when measuring blood flow with current technologies.[227] Blood flow is inherently biologically unstable[228] and the body readily changes blood flow to keep the chemical environment constant. For example in the heart we readily increase blood flow 5-fold during exercise, and in the retina, light will reduce blood flow by almost half. The variable results in blood flow measurements are not only methodological and technical; they also represent this biological variability. However, the chemical environment in the CNS and eye is more stable allowing for more reliable measurements and interpretation. Retinal oxymetry may be a step in this direction.

We need to turn our attention to the metabolic link in glaucoma assessment. Oxymetry measures oxygen saturation in retinal vessels and gives an indication of oxygen tension in the retina and the possible presence of hypoxia. However, in order to measure the delivery of oxygen to the retina it is necessary to combine measurements of retinal vessel oxygen saturation and blood flow. The ideal approach is to combine blood flow and oxygen saturation measurements.

In the limited pilot research currently available, eyes with normal tension glaucoma showed significantly decreased arteriolar oxygen saturation but these changes were not seen in POAG patients.[229]

Questions to be addressed include:

- Knowing the limitations of human clinic research, how can retinal oximetry measurements be further validated in clinical trials?
- What is the best approach to standardize retinal oxyimetry measurements?
- With a multitude of useful information available in a non-invasive technique, what information can be further elucidated from retinal oximetry images?

Future research on ocular blood flow imaging and glaucoma

- Standardization of blood flow imaging techniques is required before meaningful comparisons can be made between various studies.
- A normative database of blood flow values of the various parameters from each technology should be established to help screen patients who may have vascular risk. These values should be corrected for age, gender, blood pressure and intraocular pressure.
- Imaging of retinal and optic nerve structure and blood flow may provide insight into vascular contributions to glaucoma pathophysiology.
- Effective imaging of vascular autoregulation under various physiological conditions should be further explored in glaucoma patients. This may reveal susceptibilities of certain patients who have lost normal vascular autoregulation abilities.

- Effective ways to directly measure the blood flow in the optic nerve head, laminar capillaries and from the circle of Zinn Haller need to be developed.
- There is a need to develop a non-invasive imaging device capable of accurately assessing all vascular beds relevant in glaucoma, namely blood flow within the optic nerve, retina and choroid which have all be implicated in various investigations.
- Ocular blood flow remains a surrogate for tissue metabolism. Future imaging devices should attempt to measure metabolic changes in ocular tissues, namely oxygen saturation, redox potential, glucose uptake, carbon dioxide levels and oxygen utilization.

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CLINICAL RELEVANCE OF OCULAR BLOOD FLOW (OBF) MEASUREMENTS INCLUDING EFFECTS OF GENERAL MEDICATIONS OR SPECIFIC GLAUCOMA TREATMENT

Makoto Araie

Jonathan Crowston

CLINICAL RELEVANCE OF OCULAR BLOOD FLOW (OBF) MEASUREMENTS INCLUDING EFFECTS OF GENERAL MEDICATIONS OR SPECIFIC GLAUCOMA TREATMENT

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Consensus points

- Blood pressure (BP) is positively correlated with IOP.
- It is unclear whether the level of BP is a risk factor for having or progressing open-angle glaucoma (OAG) in an individual patient.
  Comment: It has been hypothesized that low blood pressure is a risk factor for patients with abnormal autoregulation.
- Lower ocular perfusion pressure (OPP = BP – IOP) is a risk factor for primary OAG.
- OBF parameters measured with various methods are impaired in OAG, especially in NTG, compared with healthy subjects.
  Comment: Reduction of OBF with aging has been confirmed by various methods.
  Comment: The optic nerve head blood flow may be reduced during the nocturnal period.
- Vascular dysregulation may contribute to the pathogenesis of glaucoma, more likely in people with lower intraocular pressure.
- Certain drugs, even when formulated in an eye drop, may have an impact on ocular blood flow and its regulation.
  Comment: The impact of eye drop related changes in ocular blood flow on the development and progression of glaucoma is unknown.

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Comment: Some data support increased blood flow and the enhancement of ocular blood flow regulation with carbonic anhydrase inhibitors. These appear to exceed what one would expect from their ocular hypotensive effect alone.

- Some systemic medications may have an impact on ocular blood flow and its regulation.
  Comment: The impact of systemic medications altering ocular blood flow on the development of glaucoma and the progression of glaucoma is unknown.
  Comment: Classes of systemic medications with agents that have been reported to increase ocular blood flow include calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor inhibitors, carbonic-anhydrase inhibitors, phospodiesterase-5 inhibitors.
- The association between diabetes and cardiovascular diseases with OAG still remains unclear.

1.A What is the evidence supporting a role for ocular blood flow in glaucoma patients?

Aiko Iwase, Atsuo Tomidokoro

1.A.1 Population data

Epidemiologic factors

- There are no available data on ocular blood flow itself in population-based studies.
- Numerous population-based studies have confirmed significant positive correlation of intraocular pressure (IOP) with systemic blood pressure (BP)[1-11] and/or diastolic BP[1,3,5,7,8,11] mainly in elderly populations.
- Higher BP was significantly associated with higher prevalence of open-angle glaucoma (OAG) in the Baltimore Eye Survey[12] and the Blue Mountains Eye Study.[13] In the Egna-Neumarkt Study, hypertension was a significant risk for high-tension OAG, but not for normal-tension OAG.[3] To the contrary, baseline hypertension decreased risk of OAG in the Barbados Eye Study[14] and the Oman Eye Study[15] In the Tajimi Study, hypertension was not a significant risk for OAG in a multivariate analysis.[16] In the Thessaloniki Eye Study, low diastolic blood pressure was significantly correlated with a large cup-to-disk ratio and narrow rim in non-glaucoma subjects.[17]
- Lower ocular perfusion pressure (OPP, = BP – IOP), especially diastolic OPP, was a significant risk factor for POAG in the Baltimore Eye Survey,[12] the Barbados Eye Study,[14] the Egna-Neumarkt Study,[3] Proyecto VER,[18] In the Rotterdam Study, in persons treated for systemic hypertension, low diastolic OPP was inversely associated with normal-tension POAG and

positively associated with high tension POAG.[19] On the other hand, in the Beijing Eye Study, OPP was not significantly associated with OAG.[20]
- Narrowing of the retinal vessels was associated with OAG in the Blue Mountains Eye Study,[21] the Singapore Malay Eye Study,[22] and the Beijing Eye Study,[23] but not in the Beaver Dam Study[24] and the Rotterdam Study.[25]

1.A.2 Physiologic factors

Aging changes

Reduction of ocular circulation with aging in normal subjects has been confirmed with various measurement methods.
- Using color Doppler imaging (CDI), correlation between older age and decreased blood flow parameters was reported in ophthalmic artery[26,27] and central retinal artery.[26]
- An age-associated decrease in microcirculation as determined by the blue field simulation technique was also reported.[28,29]
- Using the measurement of pulsatile ocular blood flow (POBF), POBF decreased with age and the decrease was more evident in subjects older than 50 years.[30] This same trend was confirmed by other investigators after adjusting for scleral rigidity and systemic blood pressure.[27]
- Capillary blood flow in the retina, neuroretinal rim and lamina cribrosa evaluated with scanning laser Doppler flowmeter was reduced in elderly subjects (mean age, 65.2 years) compared with young subjects (27.9 years).[31]
- A menstrual cycle in women may influence ocular blood flow, but there was no statistical difference in CDI parameters in ophthalmic, central retinal and posterior ciliary arteries during the regular menstrual cycle in healthy women.[32]

Postural changes

- When the posture is changed from sitting (or standing) to supine, ocular perfusion pressure (OPP, calculated as ophthalmic arterial pressure minus intraocular pressure [IOP]) is usually increased mainly due to the decrease in height differences between the heart and the eyes in spite of an increase in IOP.
- If the blood vessels in the ocular tissues are passive vascular beds, the blood flow is almost linearly correlated with OPP. This phenomenon was found in macular choroidal flow evaluated with laser Doppler flowmetry in healthy subjects.[33,34]
- As for the retinal artery circulation evaluated by a laser Doppler instrument, arterial diameter decreased and blood speed increased resulting in stable

blood rate which was unchanged when the position shifted from sitting to supine in normal subjects.[35]

- Using CDI, autoregulatory response in the ophthalmic and central retinal arteries was observed in normal subjects, but glaucoma patients demonstrated no such changes in the central retinal artery, suggesting possibility of faulty autoregulation of the retinal circulation in glaucoma.[36]
- Decrease in the POBF in the supine position has been reported in normal subjects,[37-39] as well as ocular hypertension,[38] normal-tension glaucoma,[37] and treated and untreated primary open angle glaucoma patients.[39] The postural response of the POBF did not differ significantly between eyes with glaucoma and ocular hypertension.[39]

Circadian changes

- Nocturnal decrease (or dip) in systemic blood pressure is commonly seen in healthy subjects. Nocturnal dip by more than 10% compared with the daytime mean pressure is observed in roughly two-thirds of healthy individuals.[40]
- In normal eyes, IOP often shows, a nocturnal increase, with peak IOP occurring at the end of the night just before awakening.[41,42] However, peak OPP usually occurred in the nighttime probably because an increase in ophthalmic arterial pressure due to the supine position outweighs the increase in IOP.[43]
- Circadian changes in ocular blood flow were studied with several methods. Using CDI, Harris *et al.* found nocturnal decrease in blood velocity only in the short posterior ciliary artery,[44] but no significant changes in the ophthalmic artery.[45] Galambos *et al.* found no nocturnal changes in any CDI index in the central retinal artery and the ophthalmic artery.[46] Between normal subjects and glaucoma patients, no apparent differences in nocturnal changes in most CDI indexes were found in their studies.[44-46]
- The POBF showed no significant diurnal variation in any of the patient groups including normal, primary open-angle, and ocular hypertension patients.[47]
- A laser Doppler flowmetry study found significant nocturnal decrease in optic nerve head blood flow in normal subjects.[48]

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1.B Clinical evidence derived from different measurement parameters

Chris Leung, Oliver Zeitz

1.B.1 Retinal vascular diameter

Five population-based studies have been performed investigating the association between retinal vessel diameter and glaucoma – two from Chinese and three from Caucasians. Three of the five studies suggest an association between retinal vessel caliber and glaucoma. Differences in subjects' characteristics (*e.g.*, age, ethnicity) and definition of glaucoma may explain the disparities.

- The Blue Mountains Eye Study[1]
  Generalized retinal arteriolar narrowing is significantly associated with open-angle glaucoma (odds ratio, 2.7; 95% confidence interval, 1.5-4.8).
- The Beijing eye study[2]
  Eyes with glaucoma showed significantly ($P < 0.001$) thinner retinal arteries while the retinal vein diameters were not different from normal subjects.
- The Singapore Malay Eye Study[3]
  An association of narrower retinal arteriolar and venular diameter with glaucoma was found (odds ratio [OR], 1.29; 95% confidence interval [CI], 1.07-1.56 and OR, 1.49; 95% CI, 1.24-1.79, for each SD reduction in arteriolar and venular caliber, respectively).
- The Beaver Dam eye study[4]
  No association was found between retinal vessel diameter and glaucoma.
- The Rotterdam study[5]
  Baseline retinal vessel diameters did not influence the risk of incident glaucoma. No evidence was found for a retinal vascular role in the pathogenesis of OAG.

1.B.2 Ocular perfusion pressure

Most population-based studies showed that a lower diastolic perfusion pressure (diastolic blood pressure – IOP) is associated with a higher prevalence of open-angle glaucoma, although the association between systolic perfusion pressure and glaucoma is less certain. There is evidence from case series and case-control studies suggesting that circadian mean ocular perfusion pressure fluctuation is related to glaucoma severity in patients with NTG.

Population-based studies

- Baltimore Eye Survey[6]
  Lower diastolic perfusion pressure (< 50 mmHg) was associated with an increased prevalence of POAG.
- The Egna-Neumarkt Study[7]
  Reduced diastolic perfusion pressure (< 70 mmHg) is an important risk factor for primary open-angle glaucoma.
- Barbados Eye Study[8,9]
  Lower PP at baseline increased risk of POAG (systolic PP < 101 mmHg, 2.6 [95% CI, 1.3-4.9]; diastolic PP < 55 mmHg, 3.2 [95% CI, 1.6-6.6]; mean PP < 42 mmHg, 3.1 [95% CI, 1.6-6.0]).
  Lower ocular perfusion pressures, doubled the risk of glaucoma (RR, 2.6; 95% CI, 1.4-4.6 for low mean perfusion pressure [< 40 mmHg]).
- The Rotterdam study[10]
  Low diastolic perfusion pressure (< 50 mmHg) was inversely associated with ntOAG (OR, 0.25; 95% CI, 0.10-0.63) and positively associated with htOAG (OR, 4.68; 95% CI, 1.29-17.01).

Case series and case-control studies

- Circadian mean ocular perfusion pressure fluctuation was the most consistent clinical risk factor for glaucoma severity in eyes with NTG.[11]
- Circadian MOPP fluctuation showed positive associations with visual field indices at initial diagnosis of NTG.[11]
- Patients with POAG had the higher IOP ($P < 0.001$) and lower MOPP ($P = 0.025$).[12]

1.B.3 Blood flow velocities

Blood flow velocities were not the subject of large epidemiologic trials. However, there is a notably number of small and mid-size single center trials addressing this issue. The trials differ in terms of methodology. Dependent on methodology, the studies investigate different sections of the ocular vasculature (methods compared in[13] and reviewed, *e.g.*, in[14]).

Blood flow velocity may be measured either by color Doppler imaging (CDI), by laser Doppler flowmetry (LDF) or fluorescein angiography (FA). CDI assesses the blood flow velocities in retrobulbar vessels,[15,16] while LDF measures perfusion in funduscopically visible vessels.[17] There exist several commercial derivatives of the LDF method e.g. the Heidelberg Retina Flowmeter or the Canon Laser Bloodflowmeter.[18,19] In FA, the arm-retina time is evaluated. This is the time the fluorescence dye needs to travel through the lung and the heart to the retina.

LDF measures average velocity in the sample volume. It has to be mentioned that simple velocity measurements are not the domain of LDF, since the method

is much more powerful and allows to estimate blood flow in the sample volume. LDF-based studies address either retinal or choroidal perfusion.

Readouts of CDI studies are usually peak-systolic and end-diastolic velocity (PSV and EDV resp.).[13] From these primary measures, derived indices may be calculated. Resistivity index (RI) is frequently used in literature and is defined as RI=(PSV-EDV)/PSV. Although not definitely proven, a concomitant change in PSV and EDV is thought to reflect a proportional change in blood flow.[20] RI should be a measure for downstream vascular resistance, but its value in ophthalmology is extremely controversial.[21,22] For glaucoma the central retinal artery and the paraoptic short posterior ciliary arteries are of particular interest, but the ophthalmic artery and the long posterior ciliary artery may also be investigated.

In general, most reports find a more or less pronounced decrease of blood flow velocities in glaucoma patients when comparing with healthy controls or subjects with ocular hypertension.[23-27] LDF-based studies also reveal decreased blood flow velocities and decreased blood flow.[19,28] Results in literature are controversial if disturbed ocular hemodynamics are a special feature of normal tension glaucoma or if all patients with the classic primary open angle glaucoma are also affected.[29-31] There are indications that reduced blood flow velocities and/or altered resistivity index are a predictor for glaucoma progression,[32-35] although it has to be emphasized that the degree of evidence of those studies is much lower than that of large epidemiologic trials like AGIS.

1.B.4 Dynamic measurements

The hemodynamic disorder in glaucoma patients is more a disorder of regulation of blood flow than a primary disruption of baseline perfusion as it occurs e.g. in occlusive vascular diseases, for example.[7,36,37] This has to be taken in account when choosing a method to assess ocular perfusion for clinical or scientific purposes in glaucoma patients.

Several methods have been reported combining a challenge of hemodynamic regulation of the eye and an estimative measurement of perfusion. In these settings, regulation is challenged by peripheral cold-provocation,[38] hand-grip stress,[39] variation of intraocular pressure,[40,41] exercise,[42] posture change,[30,43] or by flicker light.[44,45] Laser Doppler flowmetry (LDF)[46] or color Doppler imaging[13] are usually used for the concomitant perfusion measurements.

Summarizing the results of the mentioned reports comparing glaucoma patients and healthy volunteers, most authors show a clear statistical difference between healthy volunteers and a glaucoma population; however, the overlap of individual measures of both groups is too large to allow for a clear diagnostic separation between ‘healthy’ and ‘glaucoma’. This would limit the introduction of such method into clinical routine.

The majority of the mentioned methods are based on investigator-designed set-ups. The main purpose of these set-ups is experimental. The only method available commercially is the dynamic Retinal Vessel Analyzer (dRVA) by

IMEDOS, Jena, Germany. This device combines a digital fundus camera with a flicker light stimulation of the retina. It allows for the vessel diameter response to flicker light stimulation to be followed. Therefore, the dRVA does not assess hemodynamics. In addition, only the central retinal artery and their branches may be assessed by the dRVA. This might limit the use of the device in glaucoma patients, where it is assumed that hemodynamics particularly in the funduscopically invisible circuit of Zinn-Haller are affected.

1.B.5 Systemic measurement – blood pressure

A positive correlation between intraocular pressure and blood pressure has been consistently reported in population-based studies across different ethnic groups.[6,7,47-49] Longitudinal data from the Beaver Dam Eye Study shows that there was a 0.21- (95% CI: 0.16 to 0.27) mmHg increase in IOP for a 10-mmHg increase in systolic blood pressure (SBP) and 0.43- (0.35 to 0.52) mmHg increase in IOP for a 10 mmHg increase in diastolic blood pressure (DBP) over 5 years.[50] In general, the change in IOP for each 10-mmHg change in SBP or DBP is less than 0.5 mmHg and the association between BP and development of open-angle glaucoma (OAG) is weak. In the Blue Mountains Eye Study, hypertension (defined as a history of hypertension currently receiving treatment, or a systolic BP of 160 mmHg and/or a diastolic BP of 95 mmHg at the examination) was associated with OAG (OR: 1.56 (95% CI 1.01-2.40)) after adjustment of glaucoma risk factors including IOP.[51] In the Rotterdam study, the odds ratios for OAG per standard deviation increase of SBP and DBP were 1.12 (95% CI 0.98-1.29) and 1.09 (95% CI 0.96-1.25), respectively.[48] These findings, however, are not supported by the results from longitudinal studies. In the Barbados Eye Studies (BISED II), lower baseline systolic BP (RR, 0.91; 95% CI, 0.84-1.00 per 10 mmHg) was found to be a risk factor for incident OAG over 9 years' follow-up.[9] In the Early Manifest Glaucoma Trial, low SBP was found to be a predictor for glaucoma progression.[52] Nocturnal reduction in BP was found in glaucoma patients with progressive visual field loss.[53,54] Although there is evidence suggesting that nocturnal variations in BP is a potential risk factor of glaucoma,[53-56] this finding is not universally observed.[57,58] The relationship among blood pressure, intraocular pressure, and development of OAG is complex and requires further investigation.

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1.C Evidence from experimental animal studies

Algis Vingris, Jonathan Crowston

1.C.1 Vascular autoregulation

- Geijer and Bill showed that healthy monkeys are able to maintain ONH autoregulation for elevations in IOP up to 40 mmH_2O.[1]
- Systemic BP plays an important role in maintaining the normal autoregulation of the ONH. Autoregulation may breakdown when systemic BP is altered. Recent evidence from the rhesus monkey showed ONH autoregu-

lation was shown to become deficient in rhesus monkeys when BP was lowered.[2]

1.C.2 Perfusion pressure

- Many past studies have manipulated perfusion pressure by elevating intraocular pressure and keeping blood pressure constant. These methods find that low ocular perfusion pressure selectively attenuates ganglion cell function.[3]
- The role of vascular supply was considered indirectly in rats by introducing glucose into the vitreous: this sustained retinal function with IOP challenge implies a vascular deficiency during elevated IOP.[4]
- What is unclear from IOP-elevation is whether ganglion cell dysfunction is impaired due to direct mechanical compression (of axons or ganglion cell soma) or whether the defect is secondary to the vascular insufficiency caused by the reduced perfusion pressure.
- Studies that consider the effect of manipulating blood pressure to lower ocular perfusion pressure, report conflicting outcomes. Several show that retinal[5] and optic nerve function[6,7] is compromised with low blood pressure.[7] Others found little effect of low blood pressure on retinal function.[8,9]
- Such discrepant findings may reflect a non-linear relationship between perfusion pressure and function due to autoregulatory mechanisms in the vascular beds.[10]

1.C.3 Vascular insufficiency and axonal loss

- Chronic ischemia of the primate and rabbit anterior optic nerve induced with endothelin-1 infusion results in diffuse loss of axons and optic cup enlargment (rabbits) without a change in the intraocular pressure.[11,12]

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2. What disease mechanisms lead to impaired blood flow in glaucoma?

2.A Ocular versus systemic causes

Leopold Schmetterer

Generally it is not known to which extent ocular perfusion abnormalities in glaucoma are caused by systemic factors and to which extent by ocular factors. Theoretical considerations indicate that both is the case. Blood flow in the eye (Q) is given by OPP/R, where OPP is the ocular perfusion pressure and R is the vascular resistance. OPP is given as the difference between arterial and venous pressure. Whereas arterial pressure is obviously dependent on systemic blood pressure, venous pressure in the ocular vessels almost equals the intraocular pressure (IOP).[1,2] Hence, OPP, the driving force of ocular blood flow is dependent on both systemic and local factors. This also holds true for R. According to Hagen-Poiseuille's law R is inversely proportional to the fourth power of the vessel radius, and directly proportional to its length and to the viscosity of the fluid. The vessel radius is, however, regulated by a complex interaction between myogenic, metabolic, hormonal, and in some cases neurogenic mechanisms.[3]

This concept is well compatible with the notion that glaucoma is associated with a variety of ocular and systemic risk factors,[4] which may well contribute to impaired blood flow regulation. Among the ocular factors, IOP and IOP fluctuations may contribute the most, as outlined in detail below. Among the systemic factors, a huge number of conditions including arteriosclerosis, systemic hypertension, systemic hypotension, vasospasm, migraine, rheological factors, sleep disturbances and alterations in the autonomic nervous, the immune and the endocrine system[5] may be involved in the ocular vascular dysregulation.

2.A.1 The role of intraocular pressure

Increased IOP is the most important risk factor for primary open-angle glaucoma.[4] This is of hemodynamic relevance, because it will affect ocular perfusion pressure. It needs to be considered, however, that interindividual variability as well as fluctuations in systemic blood pressure by far exceed those of IOP. As such, the influence of IOP is small. Another factor by which IOP plays a role in ocular blood flow regulation is often overseen.

As mentioned above, it is assumed that at least some ocular vascular beds are under myogenic control. The myogenic theory, however, predicts that changes in perfusion are dependent on the site of perfusion pressure manipulation. Accordingly, a change in IOP is associated with a change in OPP, but also with a change in the transmural pressure gradient. This will elicit a smooth muscle relaxation in response to the OPP change, in an effort to keep vessel wall tension

constant. The situation is different when the OPP changes via the arterial system during isometric exercise and the full myogenic response is initiated. A full myogenic reaction in the arterial system is initiated resulting in an effective counter-regulatory response. According to this theory, the vascular beds of the eye should regulate more efficiently in response to a change in systemic blood pressure than to a change in IOP.

Experimental evidence for this has been gained for the choroid in rabbits[6,7] and humans,[8] but is lacking for the other vascular beds. In the rabbit the capacity of the choroid to regulate in response to changes in perfusion pressure is higher at lower IOPs than at higher IOPs.[6,7] This has been shown in a model where both, arterial and venous pressure can be manipulated mechanically. In the human, choroidal blood flow is regulated better during isometric exercise-induced changes in systemic blood pressure than during experimental increased IOP with the suction cup technique[8]. Hence, IOP may not only affect OPP, but may also strongly determine the regulatory capacity of the ocular vascular beds.

2.A.2 The role of systemic factors

At least in a subset of patients, dysregulation of the ocular circulation appears to be closely related to systemic vascular dysregulation. It is particularly the primary vasospastic syndrome that has been blamed to induce vascular dysregulation in the eye.[9] This is supported by the observation that patients with vasospastic disorders often have visual field defects.[10] A number of studies reported systemic vascular dysregulation in glaucoma patients, particularly in those with normal pressure levels. Normal tension glaucoma patients have reduced blood velocities in the nailfold capillaries and an abnormal response to cold stimulation.[11] This abnormal response in the nailfold capillaries also appears to be related to vascular dysregulation of retinal and optic nerve head blood flow as shown in studies using color Doppler imaging and laser Doppler flowmetry.[12,13]

Evidence has accumulated that endothelial dysfunction may be a link between systemic and ocular dysregulation in glaucoma, as reviewed recently.[14] Endothelial dysfunction is a multifactorial term referring to the inability of endothelial cells to perform their normal physiological function. Chronic endothelial dysfunction is induced by oxidative stress leading to a decrease in the biosynthesis and/or bioavailability of NO and an excess of endothelin production. A number of studies indicate that the bioavailability of NO is reduced in glaucoma. Decreased NO levels were reported in the aqueous humor of patients with primary open-angle glaucoma.[15] Reduced NADPH-diaphorase levels were observed in the trabecular meshwork of primary open-angle glaucoma patients.[16]

Abnormal vascular response can be seen in glaucoma patients, at a systemic level. In glaucoma patients the forearm of the vasodilator response to acetylcholine is blunted[17] as is the flow-mediated vasodilator response.[18] Primary open-angle glaucoma patients do, however, also have an abnormal ocular blood flow response to systemic NO synthase inhibition.[19] Evidence has also accumulated

that glaucoma is associated with abnormalities in the endothelin system, which will be summarized in the following paragraph.

2.A.3 Disorders associated with endothelin abnormalities

As in other vascular beds, endothelin-1 (ET-1) is a key regulator of ocular vascular tone. Intravenous administration of ET-1 dose-dependently reduces retinal, choroidal and optic nerve head blood flow in healthy subjets.[20-22] Blockade of the ET_A receptor subtype antagonizes these effects of ET-1.[21,22] ET-1 also appears to play a major role in ocular blood flow regulation during changes in perfusion pressure, because the choroidal blood flow response to isometric exercise is modified under ET_A receptor blockade.[23]

Evidence that the ET system is involved in the pathogenesis of glaucoma is not limited to the vascular system.[24,25] Patients with primary open-angle glaucoma have increased levels of ET-1 in the aqueous humor.[26,27] Some,[28,29] but not all studies,[30,31] have reported that normal-tension glaucoma patients have increased ET-1 plasma levels. One study has reported that progressive, but not stable, glaucoma patients have elevated ET-1 concentrations in plasma.[32]

A number of studies indicate that glaucoma is associated with abnormal vascular responses when the ET system is challenged. An *in-vitro* study revealed an abnormal response to ET-1 in arteries dissected from gluteal fat biopsies of normal tension patients.[33] Another study reporting abnormal systemic reactivity to ET_A receptor blockade used forearm blood flow measurements in patients with normal tension glaucoma.[34] Finally, an abnormal inverse correlation between ET-1 induced peripheral vasoconstriction and blood pressure was observed in glaucoma.[35]

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2.B Systemic factors

Robert Ritch

2.B.1 Blood pressure

Epidemiologic studies have implicated both high and low blood pressure (BP) in association with glaucoma. The subject has been recently reviewed.[1,2] Leighton *et al.*[3] found BP similar in normals and NTG patients, but higher in HTG patients. In a Japanese study, NTG patients had a higher BP than controls and, while the nocturnal BP dip was similar between NTG patients and controls, those NTG patients who progressed had a lower BP dip than patients with stable visual fields.[4] Most other studies have found NTG to be associated with low BP.

Nocturnal overdipping of BP may lead to optic nerve ischemia and be an important IOP-independent risk factor. A number of studies have suggested a relationship between progression of damage in NTG and systemic hypotension.[5-13] In 1963, Sachsenweger[14] demonstrated that low BP was associated with more rapid visual field loss and optic disc damage. Demailly[9] suggested that postural hypotension might play a role in the pathogenesis of NTG. Kaiser and Flammer[5] observed low systemic BP and a sustained BP drop during sleep in rapidly progressing glaucoma patients with normal or well-controlled IOP. The same authors monitored 24-hour BP and found that both POAG patients with progression despite well-controlled IOP and patients with NTG have a markedly reduced systolic BP during day and night.[6] Béchetoille and Bresson-Dumont[7] found lower systolic and diastolic BP in patients with focal ischemic glaucoma compared to those with POAG and also in patients with normal or moderately elevated IOP compared to those with high IOP, emphasizing the importance of measuring diurnal blood pressures in these patients[15]. Hayreh *et al.*[16,17] monitored 24-hour BP and IOP in 166 patients with NTG or AION and found a significantly lower nighttime mean diastolic BP and a significantly greater mean percentage decrease in diastolic BP in NTG than in AION. Moreover, hypertensive patients taking oral hypotensive agents showed a significant association between visual field progression and nocturnal hypotension. Greater fluctuations of BP may

lead to ocular perfusion pressure fluctuation and may cause ischemic episodes at the optic nerve head.[18]

This relationship is not restricted to NTG. Graham *et al.*[19] found no difference in BP parameters of NTG and HTG patients, but that all nocturnal BP parameters were lower in patients with progressive field defects. Reevaluation of the visual fields of these patients after 5 years showed that those patients who had shown greater nocturnal BP dips were more likely to have visual field progression at some stage, despite good IOP control.[20] Conversely, those who progressed had significantly larger dips of the systolic, diastolic, and mean arterial BP. Others found a strong correlation between overdipping of nocturnal systolic BP and disease progression in both NTG and HTG.[21,22]

Ghergel *et al*.[23] found that glaucoma patients with a marked drop in nocturnal systemic BP had altered retrobulbar blood flow. Patients with unstable visual fields had lower BP and lower end-diastolic velocity in the central retinal artery compared with normals and patients with stable visual fields.[24] Analyzing the relation between peripheral vasospasm assessed by nailfold capillaroscopy and circadian BP rhythm, Pache *et al.*[25] found no significant differences between non-dippers, dippers, and over-dippers with respect to peripheral vasospasm. This group concluded that vasospasm and low BP may be two distinct risk factors for glaucomatous damage.[25,26] In a recent study, the use of calcium channel blockers as systemic antihypertensive agents was associated with a greater risk of developing open-angle glaucoma, and their use was advised against for the treatment of NTG.[27] Hayreh *et al.*[28] reported that patients using topical beta-blockers had a lower minimum nocturnal heart rate, lower minimum nocturnal diastolic BP, and a greater percentage nocturnal drop in diastolic BP.

2.B.2 Sleep apnea

Obstructive sleep apnea syndrome (SAS) results from repetitive upper airway obstruction during sleep, most often due to collapse of the soft tissue in the rear of the throat, leading to hypoxia and sleep disruption. In central sleep apnea, the brain fails to signal the muscles to breathe. Mixed apnea is a combination of the two. With each apneic event, the brain causes brief arousal in order to reinitiate breathing, and sleep becomes fragmented and of poor quality. It affects about twelve million people in the United States, most commonly overweight, middle-aged men. Most people with sleep apnea remain undiagnosed. It is associated with hypertension, cardiovascular disease, weight gain, restless leg syndrome, impotence, intracranial hypertension, memory difficulties, daytime somnolence, and decreased daily functioning. Both forms of sleep apnea are found in patients with congestive heart failure and are associated with greater mortality.[29]

Several eye disorders have been linked to sleep apnea. These comprise reduced tear film break-up time, nocturnal lagophthalmos, floppy eyelid syndrome, central serous chorioretinopathy, and lacrimal gland prolapse.[30-35] Patients with nonarteritic ischemic optic neuropathy (NAION) have a very high prevalence of SAS, and visual loss from NAION is noted soon after awakening.[36,37]

An association between sleep apnea and high-tension glaucoma with an early morning maximum IOP was first reported in 1982 in five members of a Canadian family.[38] Numerous subsequent studies have found an association with both high- and normal-tension glaucoma.[39-41] Mojon *et al.*[42] reported a high prevalence of glaucoma in patients with SAS and recommended screening such patients for glaucoma. Bendel *et al.* recently reported an astounding 27% prevalence of glaucoma in patients with SAS.[43] An even higher proportion of persons with SAS than with glaucoma are unaware that they have it, and this population represents a potentially important pool of undiscovered glaucoma. Marcus *et al.*[44] found 57% of NTG patients, 43% of NTG suspects, and 3% of conrols with a positive sleep history. Other studies have also found a positive correlation of SAS with visual fields, cupping, and retinal nerve fiber layer thinning.[45,46] A minority of reports have not found a correlation between sleep apnea and the general population.[47,48]

Ocular blood flow in SAS both with and without glaucoma requires further study. In one report, there was no difference by orbital Doppler ultrasonography in the resistivity indices in the ophthalmic artery and central retinal artery of patients with SAS and controls.[49] Mojon *et al.*[50] found SAS and a greater oximetry disturbance index grade more prevalent among POAG patients compared to normal historic controls.

Treatment with continuous positive airway pressure (CPAP) has been reported to stabilize visual field loss.[51, 52] However, one study has reported that CPAP itself is associated with increased IOP and decreased ocular perfusion pressure.[53] Treatment may also help floppy eyelid syndrome and reduce intracranial pressure in patients with associated papilledema.[54] Weight loss improves symptoms of SAS.[55] The effect of weight loss on ocular blood flow, nocturnal perfusion, and progression of glaucoma remains to be elucidated.

There have been some interesting biomarker associations in SAS which have also been reported to be of importance in normal-tension glaucoma. Soluble cell adhesion molecules are associated with the development of atherosclerosis. Serum soluble cell adhesion molecule-1 levels are elevated in SAS and reduced by nasal CPAP treatment.[56] Circulating ICAM-1, VCAM-1, and L-selectin levels were increased in SAS patients compared with the normal subjects.[57] Leptin and ghrelin, two key hormones in appetite, are elevated in SAS. Endothelin-1 levels were elevated in both hypertensive and normotensive SAS patients, but not reduced by CPAP.[58]

2.B.3 Atrial fibrillation

In 1992, Peräsalo *et al.* reported on the relationship of atrial fibrillation (AF), systemic blood pressure and nerve fiber loss in a screening of 213 institutionalized geriatric glaucoma patients (mean age 83.9 years) and 100 age-matched control patients.[59,60] Atrial fibrillation was present in 17% of the glaucoma patients and 8% of the controls. Patients with AF had lower systolic blood pressure, worse visual acuity, and more frequent severe visual field defects than the other pa-

tients. The mean IOP of patients with AF was significantly lower than that of the other patients. Patients with severe visual field defects had lower systolic blood pressures. The glaucoma patients had a greater frequency of ischemic heart disease on EKG than the control patients. There have been no further studies of AF and glaucoma.

2.B.4 Positional factors

Intraocular pressure varies with body position, increasing between the upright, sitting, and supine positions.[61-67] Krieglstein *et al.*[68] evaluated postural effects on IOP and speculated that they correlated with changes of episcleral venous pressure. In normal eyes, IOP may double going from a sitting to an inverted position.[69,70] Episcleral venous pressure increases concomitantly and on gonioscopy, blood can be seen in Schlemm's canal, suggesting that the mechanism of a sustained intraocular pressure rise during gravity inversion appears to be closely related to increased venous pressure in the orbit.[69] Pressures in the central retinal artery underwent similar increase, while the caliberg of the retinal arterioles decreased, impairing ocular perfusion.[61] Similar findings were recorded by Mader *et al*.[71] External ocular findings associated with gravity inversion included orbital congestion, conjunctival hyperemia, petechiae of the eyelids, excessive tearing (epiphora), and subconjunctival hemorrhage.[61] Reversible visual field defects developed in 11 of 19 eyes during gravity inversion. In another study, pattern reversal amplitudes were significantly reduced.[72] Simultaneous retinal and cortical biopotentials were significantly reduced in another study.[73] Aqueous production measured fluorophotometrically does not appear to be affected by these conditions.[74]

Moving from the sitting to the recumbent position can also induce a rise in IOP.[75-78] Using pneumatogonography and McKay Marg tonometry, Jain and Marmion[65] recorded an average rise of 1-4 mmHg in normal volunteers in the supine position and 1-13 mmHg in patients with glaucoma. Mardin *et al.*[79] found a significant elevation of IOP in patients with NTG going from the sitting to the supine position, and this was accompanied by a signifcant lowering of diastolic BP. Twelve of 28 patients had an IOP < 22 mmHg in the supine position and these patients had a higher incidence of disc hemorrhages, higher values for flow and volume parameters of the optic nerve head, and a higher incidence of migraine and vasospastic disorders.

Kiuchi *et al.*[80] found the progression of visual field damage in NTG to be associated with IOP in the supine position and the magnitude of IOP elevation accompanying postural changes, suggesting that progression of glaucoma may occur when patients are lying flat during sleep. The same group found that the magnitude of IOP elevation associated with the postural change did not alter significantly by the application of any eyedrops.[81] Leonard *et al.*[82] also found greater rises in IOP in ocular hypertensives than in normals and suggested that an IOP measurement in the lying position should be included in the routine evaluation of the patient with ocular hypertension. Similarly, Hirooka and Shiraga[83]

found that the greatest difference in IOP between the sitting and supine positions was observed in the worse eye of patients with POAG, again suggesting that damage to the optic nerve in POAG might occur when patients are asleep in the supine position. Anecdotally, Ted Krupin and I had a patient with 'normal-tension glaucoma' who had been performing yoga headstands for 20 years. In the inverted position, her IOP rose from 15 mmHg to 60 mmHg and it was 25 mmHg in the supine position. Her visual field progression, already a 5-degree island, ceased when she was instructed to use a wedge pillow plus two pillows to achieve a 30-degree angle, at which her IOP was 15 mmHg.

Yoga in the inverted position can have serious adverse effects. Baskaran *et al.*[84] studied 75 subjects from a yoga training institute. The mean increase in IOP at baseline and immediately after assuming the headstand position was 15.1 ± 4.1 mmHg and after 5 minutes was 15.8 ± 4.6 mmHg, representing a twofold increase in IOP from baseline. Others have published case reports.[85-87]

These findings lead to the question as to what would happen to IOP during space flight. Specific alterations in systemic circulation due to fluid shift in microgravity could theoretically lead to a rise in IOP. During the first German Spacelab mission D1, changes of IOP were investigated. The first readings were obtained 44 min after entering microgravity and showed a rise of 20 to 25% compared to baseline.[88] Mader *et al.*[89] found that IOP in 11 subjects increased 58% during 20 seconds of microgravity produced by parabolic flight on board a KC-135 aircraft.

Patients with autonomic failure often have posture-related lability of BP with both orthostatic hypotension and recumbent hypertension. Dumskyi *et al.*[90] measured mean arterial pressure and IOP in response to variations in posture between +45 degrees and -20 degrees in normals and patients with autonomic failure. Patients with autonomic failure showed significantly larger changes in both parameters.

Other alterations in ocular vascular physiology accompany supine and inverted body positions. Feke and Pasquale[91] measured arterial diameter and blood velocity simultaneously in the sitting and recumbent positions and found that glaucoma patients showed a much broader range of blood flow changes in response to postural change compared to baseline. Galambos *et al.*[92] used color Doppler imaging to find that flow velocities in the short posterior ciliary arteries of controls were unaltered between the sitting and supine positions suggesting tight autoregulatory control, while NTG and POAG patients demonstrated an insufficient compensatory response to postural change, leading to accelerated flow in these arteries. Kaeser *et al.*[93] found that choroidal blood flow decreased by 6.6% and ocular perfusion pressure by 6.7% in healthy volunteers. Longo *et al.*[94] found that tilting normal volunteers from the standing to supine position decreased heart rate by 16%, increased IOP by 29%, and increased choroidal blood flow by 11% by color Doppler flowmetry. Trew and Smith[95] found decreased pulsatile ocular blood flow in normal and ocular hypertensives. Flow was significantly decreased in patients with POAG and topical timolol did not

improve the postural response.[96] Plasma atrial natriuretic factor also increased significantly after 30 minutes of head-down tilt in normal volunteers.[97]

2.B.5 Spinal surgery

Marked increases in IOP can occur after prolonged positioning in the prone position in anesthetized patients.[98] In a retrospective review of 3450 spinal surgeries, Stevens *et al.*[99] found 7 patients whose postoperative course was complicated by loss of visual acuity on the basis of posterior optic nerve ischemia, occipital lobe infarcts, and central retinal vein occlusion. Myers *et al.*[100] reviewed 37 patients who experienced visual loss after spinal surgery. Most cases had significant intraoperative hypotension, with a mean drop in systolic blood pressure from 130 to 77 mmHg. Visual loss occurred because of ischemic optic neuropathy, retinal artery occlusion, or cerebral ischemia. Eleven cases were bilateral, and 15 patients had complete blindness in at least one eye. Most deficits were permanent. Other causes have included cortical blindness,[101] ischemic orbital compartment syndrome,[102] globe compression,[103] and cavernous sinus thrombosis.[104] The effect of prolonged spinal surgery on patients with glaucoma, particularly with regard to visual field changes before and after has not been studied and needs to be assessed prospectively.

2.B.6 Atherosclerosis

Arteriosclerosis is the thickening and hardening of the arteries due to the build-up of calcium deposits on the inside of the artery walls. Atherosclerosis is a similar condition due to the build-up of fatty substances. Atherosclerosis is now known to have a significant inflammatory component. The vascular theory of glaucoma considers glaucomatous optic neuropathy (GON) as a consequence of insufficient blood supply due to either increased IOP or other risk factors reducing ocular blood flow (OBF).[105] The major cause of this reduction in blood flow is not atherosclerosis, but rather a vascular dysregulation, leading to both low perfusion pressure and insufficient autoregulation.[105]

Despite the extensive literature implicating ocular ischemia, ischemia-reperfusion injury, and reduced ocular blood flow in the pathogenesis of glaucoma, particularly non-pressure-dependent mechanisms, there is scant evidence for a relationship between atherosclerosis and open-angle glaucoma. In the Rotterdam Study, a prospective, population-based cohort study, carotid artery plaques, carotid intima-media thickness, aortic calcifications, ankle-arm index, and CRP levels were not significant risk factors for open-angle glaucoma.[106] It was concluded that neither atherosclerosis nor serum CRP level was an important risk factor.

Risk factors for arteriosclerosis are also risk factors for elevated IOP. Oxidative stress plays a role in both disorders, but when corrected for IOP, these factors only play a minor role.[107] On the other hand, insufficient autoregulation increases the chance for an unstable ocular perfusion and thereby an unstable oxygen supply.[107]

In patients with POAG, both systemic arteriosclerosis and sclerotic changes in the ocular vessels and in the internal carotid artery have been observed but also questioned. However, in large and well-planned studies concerning this issue, few authors found dysliproteinemia[108,109] and elevated cholesterol levels[110] in glaucoma patients. Both studies included only a small sample size and were not designed to identify arteriosclerosis as an independent risk factor. In a larger cross-sectional study in glaucoma suspects, Chisholm *et al.*[111] found neither presence nor absence of dyslipoproteinemia to be associated with glaucoma. In addition, Stewart *et al.*[112] found no correlation between elevated IOP and high-density lipoprotein, total cholesterol levels, and cholesterol/high-density lipoprotein in 25 patients with POAG or OHT.

Smoking, an established and independent risk factor for arteriosclerosis, was not identified as an independent risk factor for glaucoma in the Beaver Dam Eye Study.[113] Others found smoking to be a dependent risk factor in arteriosclerotic glaucoma suspects and glaucoma patients in retrospective case-control studies.[114,115] (These two paragraphs are taken from[1])

2.B.7 Hemorheologic abnormalities

Platelet hyperaggregability

Drance *et al.*[116] first reported increased platelet adhesiveness in patients with NTG. Hoyng *et al.*[117] found a higher incidence of spontaneous platelet aggregation in older patients with POAG compared to ocular hypertensives. The proportion of POAG patients with spontaneous platelet aggregation was greater for those with visual field progression than for those without progression, while disc hemorrhage occurred more frequently in those with progression and in those with normal-tension glaucoma.[118]

In another study, circulating platelet aggregates were more common in patients with advanced POAG than in healthy volunteers,[119] but the same group found no relationship between increased platelet aggregation and visual field progression.[120] Platelet aggregation was more frequent in Japanese patients with NTG than with HTG.[121] One study found no difference in platelet function, blood coagulability, and fibrinolytic activity between NTG patients and controls.[122]

The pathogenic role of altered platelet aggregation remains unclear.[1] Theoretically, increased platelet aggregation should adversely affect blood flow in the small branches of the short ciliary arteries supplying the optic disk.[118] A medical intervention study, such as with acetylsalicylic acid, would help to confirm such a cause-effect relationship.[1]

Blood viscosity

Klaver *et al.*[123] found blood and plasma viscosity to be significantly higher in NTG patients than in controls. Within the NTG group, viscosity was highest in those with focal ischemic glaucoma, whereas those with senile sclerotic glau-

coma did not show significant differences compared with controls. The authors suggested that these findings may indicate a factor in the pathogenesis of visual field defects and disc cupping in some patients with NTG. Other studies also found greater blood viscosity in patients with POAG than in controls.[124,125]

Increased erythrocyte aggregability in POAG has been reported.[126] Erythrocyte rigidity was found to be significantly increased in POAG compared to controls in another study, but there was no difference in erythrocyte aggregability between the two groups.[127] Vetrugno *et al.*[128] found reduced erythrocyte deformability and increased aggregability in patients with NTG compared to both POAG and controls, suggesting a causative role in pathogenesis. On the other hand, Ates *et al.*[129] found no difference in erythrocyte aggregability in similar groups.

Zabala *et al.*[130] found increased erythrocyte acetylcholinesterase activity in patients with POAG, indicating altered erythrocyte membrane integrity. Another study found that patients with HTG had higher prothrombin fragments 1 and 2 and D-dimer levels than patients with NTG and controls.[131]

In summary, there appears to be some evidence for an abnormal hemorheology, especially in NTG. Blood or plasma viscosity, established parameters for chronic vascular disease, are elevated and erythrocyte function and deformability seem to be decreased.

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2.C Vascular dysregulation/perfusion instability

Michael Kook

As one of the disease mechanisms leading to impaired blood flow in glaucoma, there is increasing evidence that systemic vascular dysregulation may play a role.[1-3] Patients with systemic vascular dysregulation have the propensity to react inadequately to various stimuli, such as cold temperature, hunger and emotional stress. Vascular dysregulation can be primary or secondary in nature.[4-6] A secondary dysregulation is due to other systemic disease such as autoimmune disease. They may have a high baseline level of circulating endothelin-1.[7] Autoregulation is a normal physiological process in which the vascular resistance changes dynamically to keep flow at whatever constant level is required by the local metabolic activity despite changes in perfusion pressure. Primary vascular dysregulation interferes with autoregulation. This, in turn, leads to unstable blood supply to various organs, including the eye.

In terms of the evidence of primary vascular dysregulation in the impairment of blood flow in general, it has been shown that cold provocation elicited a different blood pressure, and ocular blood flow response, in patients with primary open-angle glaucoma compared with control subjects, suggesting a systemic autonomic failure manifesting with ocular as well as systemic vascular dysregulation in glaucoma patients.[3] Furthermore, in a study by Gherghel *et al.*[9] blood flow alterations occurred in the retinal circulation of subjects with systemic vasospasm due to alterations in autoregulation. In the subjects with systemic vasospasm, the peak systolic and end diastolic velocities and the resistivity index of the central retinal artery correlated significantly with the mean ocular perfusion pressure while such correlations were not found in the control group.

The pathogenesis of the primary systemic dysregulation is not clear. Vasospasm, characterized by exaggerated vascular responses to various stimuli such as temperature and stress, might result from impaired endothelium(ET)-dependent regulation of vascular tone. Endothelial cell dysfunction produces an imbalance between vasodilator and vasoconstrictor pathways: most notably the nitric oxide (NO) and endothelin systems. Endothelin-1 (ET-1) is a potent vasoconstrictor produced predominantly by endothelial cells, thought to be involved in a variety of disease associated with deficient or dysregulated blood flow, such as ischemic heart disease, cerebral vasospasm, diabetes, Raynaud's disease, and others. Clinical studies have documented that patients with open-angle glaucoma have increased levels of ET-1 in response to vasospastic stimuli (cold provocation test) or impaired endothelium derived nitric oxide activity with resultant reduced vasodilation during ET-receptor antagonism activity compared with normal control subjects.[10,11] These findings suggest that alterations in ocular and systemic NO and ET-1 activity may play an important role in a generalized vascular dysregulation and pathogenesis of normal-tension glaucoma. Study by Su *et al.*[12] showed that there is an endothelium-dependent vascular dysregulation in patients with normal-tension glaucoma demonstrated by both venous occlusion plethysmography and ultrasonic imaging of the brachial artery. This finding

also suggested that there may be a generalized peripheral vascular endothelial dysfunction in patients with normal-tension glaucoma.

Ocular perfusion pressure (OPP) is calculated as a function of intraocular pressure (IOP) and mean arterial blood pressure (MABP).[13] Under usual circumstances with normal autoregulation, it is of no particular consequence that the intraocular pressure is 10 mmHg higher than the venous pressures. A 10 to 20 mmHg reduction in perfusion pressure might also occur just as easily with a 20 mmHg fall in arterial pressure, as a result of physiological blood pressure fluctuations throughout the 24-hours. Such variations occur regularly without any harm. However, in the eyes with disturbed autoregulation due to vascular dysregulation, ocular blood flow is reduced when patients are stressed psychologically or by coldness and ocular blood flow regulation can less efficiently compensate for changes in perfusion pressure. Blood flow fluctuations due to vascular dysregulation have been suggested to lead to ischemia-reperfusion injury in the eye.[14-18]

IOP fluctuation is known to be increased in open-angle glaucoma.[19] In addition, ocular perfusion pressure is influenced by circadian IOP fluctuations.[20] Higher IOP fluctuation during the night time is a well know phenomenon in glaucoma and increased IOP variability at night time will also lead to a further variability in ocular perfusion pressure. Increased blood pressure fluctuations effect higher perfusion pressure variability, and may induce ischemia of ocular tissues in glaucoma, if the autoregulatory capacity of ocular and optic nerve head blood flow is exceeded. Furthermore, not the absolute blood pressure level alone, but fluctuations of blood pressure, specifically in the form of 'excessive' blood pressure dip at night time, may account for deficits of ocular perfusion pressure.[16-20]

There have also been several studies that indicate the relationship between blood flow instability and end-organ damage. According to Shimda *et al.*,[21] the mean 24-hour and awake blood pressures in the extreme dippers were no different than those in the dippers. Hence, the advanced cerebrovascular damage observed in members of extreme dippers was not directly related to the mean blood pressure or perfusion level over time or the peaking of blood pressure during the awake period, but rather to an 'abnormal' variation in blood pressure or perfusion pressure itself. One reason that a marked nocturnal fall in blood pressure was associated with cerebrovascular disease could be that the lower limit of blood pressure in the autoregulation of cerebral blood flow was shifted upward. Especially in elderly hypertensive patients with brain damage, a marked fall of blood pressure at night due to antihypertensive treatment might lead to a repeated excessive reduction of cerebral perfusion. An enhanced fall of blood pressure due to antihypertensive medication might accelerate the brain ischemia.

Choi *et al.* followed up 101 patients with chronic normal-tension glaucoma for glaucomatous progression by automated Humphrey field analyzer and scanning laser polarimetry over 10 years. They found that glaucomatous progression was more frequent among the patients treated with antihypertensive agents and

with unstable perfusion pressure among the excessive night time dippers than those with relatively stable perfusion pressure among the nondippers and physiological dippers ($P < 0.05$).[22,23] This finding was consistent with other studies that lower limits to autoregulation of end-organ blood flow are reset upward in patients with hypertension and may not completely readapt downwards with treatment. Perfusion pressure instability as caused by antihypertensive agents may reduce end-organ perfusion pressure, such as that to the optic nerve, below these levels in some patients.[24,25]

There is now a substantial body of experimental evidence that free radicals are produced during reperfusion after an episode of ischemia from perfusion instability.[26-32] For example, free radicals are produced in excess when myocardium is reperfused following an episode of ischemia and that free radicals can injure myocytes and endothelial cells. Free radicals may contribute to either reversible or irreversible manifestations of cell injury from ischemia and reperfusion. In addition, several investigators have observed that post-ischemic contractile dysfunction in myocytes can be attenuated by a variety of anti-free radical therapies, and there seems to be general agreement that free radical injury contributes to post-ischemic/reperfusion contractile dysfunction. Furthermore, oxidative stress following ischemia/reperfusion injury may also contribute to the generalized vascular disturbances leading to systemic conditions such as atherosclerosis, Alzheimer's disease, diabetes, and aging as well as glaucoma.

In conclusion, there is an increasing evidence that systemic vascular dysregulation leading to ocular vascular dysregualtion, has been found to induce decreased blood flow or perfusion instability at the optic nerve head as a result of a diminished capacity to autoregulate. An endothelium-dependent vascular dysregulation may underlie systemic vascular dysfunction in patients with normal-tension glaucoma as one of the mechanisms. However, it is still not clear whether ocular perfusion pressure instability in association with vascular dysregulation increases the risk and/or progression of glaucomatous optic nerve damage. Large prospective multi-racial clinical studies of this distinct subgroup of patients with unstable ocular perfusion pressure would be needed to establish the validity of this concept.

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3. What is the impact of medication and other modifiable factors on ocular blood flow?

Makoto Araie

3.A IOP-lowering topical medication

3.A.1 Muscarinic receptor agonist (pilocarpine)

In studies using radioactive microsphere technique in experimental animals, topical instillation of pilocarpine showed no significant effect on ocular blood flow in the retina, choroid,[1] iris or ciliary processes.[2] Dose-dependent muscle relaxation in isolated ciliary artery[3] by pilocarpine may explain increased retinal and choroidal blood flow after its instillation in experimental animals reported in another report.[4] In a placebo-controlled study in healthy humans, no significant effect of single drop of 2% pilocarpine was found on fundus pulsations amplitude or blood velocities in the central retinal artery (CRA) or ophthalmic artery (OA) measured by color Doppler imaging (CDI).[5] One placebo-controlled study in ocular hypertension (OHT) subjects found significant increase of pulsatile ocular blood flow (POBF) after 3 time-instillation of 2% pilocarpine,[6] while another study reported it remained unchanged after single instillation of 4% pilocarpine.[7]

3.A.2 Alpha-1 receptor agonist (phenylephrine)

In experimental animals, a single or chronic topical administration of phenylephrine produced significant vasoconstriction in retrobulbar arterioles around the optic nerve head (ONH)[8,9] and significant decrease of the ONH or choroid circulation measured by the laser speckle method (laser speckle flowgraphy, LSFG),[10,11] and decrease in anterior chamber PO2.[12] In placebo-controlled double masked normal human studies, topical or systemic phenylephrine showed no significant effects on the perimacular leucocyte velocity or retinal vessel diameter.[13-15] A recent placebo-controlled double masked study showed that topical phenylephrine transiently, but significantly reduced the ONH circulation (LSFG), but showed no effects on the hemodyamics in CRA in normal humans.[10]

3.A.3 Alpha-2 receptor agonists (clonidine, apraclonidine, brimonidine)

In primary open-angle glaucoma (POAG) patients, topical clonidine significantly reduced ocular perfusion pressure (OPP)[16] and its intravenous administration significantly reduced retinal blood flow measured by laser Doppler velocimetry (LDV), but increased the ONH and choroid circulation measured by laser Doppler flowmetry (LDF) in normal subjects.[17]

Topical apraclonidine induced blanching in conjunctiva[18] and decreased conjunctival oxygen tension[19] in humans. In a study using the LDF in 17 normal subjects, single instillation of apraclonidine showed no significant effect on the ONH and peripapillary retinal blood flow.[20] On the other hand, decreased blood flow velocities and increased resistive indices in OA, but not in CRA, were observed after single instillation of apraclonidine in normal subjects.[21,22] In another in POAG subjects, thrice daily 1% apraclonidine use for 15-30 days resulted in a decrease of peak-systolic velocity (PSV) in OA compared to the pretreatment measurements.[23]

In a study in OHT subjects, twice-daily 8 week-instillation of brimonidine showed no significant change in retinal capillary blood flow measured by the Heidelberg retina flowmeter (HRF).[24] In POAG subjects, significant reduction in IOP and increase in POBF were observed during 6 months use of twice-daily brimonidine,[25] and increase in it was also reported in NTG subjects.[26] In another trial in 17 POAG subjects, twice-daily 4 week-topical brimonidine showed no significant change in hemodynamics in the retrobulbar vessels or ocular pulse amplitude (OPA) despite significant IOP reduction.[27]

3.A.4 Alpha-1-antagonist (bunazosin)

Treatment with an oral alpha-1 antagonist, nicergoline, was found to improve retrobulbar hemodynamics in POAG subjects.[28] Bunazosin exerts a vasodilating effect on isolated ophthalmic and ciliary arteries by antagonizing the effect of alpha-adrenoceptor agonists.[29] In experimental animals, topical bunazosin showed no significant effect on the ONH circulation (LSFG),[30] although its topical instillation could attenuate the intravitreal phenylephrine- or endothelin-1 (ET-1)-induced constriction of retinal arteries.[31] Ameliorative effects of topical bunazosin on the impaired ONH circulation (LSFG) were also found after twice a week 4 week-repeated intravitreous injection of 20 pmol ET-1 or after intravenous injection of 50 mg/kg L-NAME, a nonselective nitric oxide synthase inhibitor, in experimental animals.[32,33] One placebo-controlled and double-masked study in 15 normal humans showed that single drop of topical 0.3% bunazosin had no significant effect on the POBF of the treated eyes in spite of significant decrease of IOP and evidences of α-adrenoceptor blockade, such as miosis, ptosis or conjunctival hyperemia.[34]

3.A.5 Beta-antagonists (timolol, metipranolol, carteorol, betaxalol, levobunolol, nipradilol)

Timolol is a non-selective β-blocker. Blockage of β-2 receptors may lead to a vasoconstriction in vessels, and the β-receptors are found in ocular tissues including the retina.[35] Effects of topical timolol on blood flow in various ocular tissues including the iris, choroids, retina and ONH in experimental animals using invasive or the non-invasive laser speckle method or CDI are controversial, but most of the studies reported no significant or rather unfavorable effects.[2,4,8,36-43] The effects of timolol on the ocular blood flow are also controversial in humans. Studies in normal or POAG subjects using HRF showed that blood flow in the ONH or peripapillary retina was significantly decreased[44] or not changed[45-47] after a single instillation of timolol or chronic treatment with timolol. A double-masked and randomized study in 140 subjects with POAG or OH reported that 6 months of treatment with twice-daily timolol showed no significant effect on the blood flow in the ONH (HRF) or on the pulsatile choroidal blood flow (POBF) as measured with a laser interferometric measurement of fundus pulsation amplitude,[48] which was compatible with the result obtained by LSFG in normal subjects.[49] On the other hand, perimacular leucocyte velocity was reportedly increased by chronic treatment with timolol in normal subjects.[50] In a study in OHT subjects using the laser Doppler velocimetry (LDV), blood flow through a major retinal vein was reported to be increased after a single instillation of timolol,[51] but a decrease of blood flow through a major retinal vein after twice-daily 2-week treatment of timolol was also reported using the same method.[52] Studies using CDI in subjects with POAG, OH or normal tension glaucoma (NTG) found no significant effects of a single instillation of timolol on the retrobulbar hemodynamics.[53,57-59] But one study reported a significant increase of restive index (RI) in the short posterior ciliary artery (SPCA) (54) and two other studies found a significant decrease of RI or increase of mean end diastolic velocity (EDV) in the central retinal artery (CRA) in POAG-subjects.[55,56] Two studies in normal subjects or POAG patients found a decrease in the POBF after a single instillation of timolol or chronic treatment of timolol,[60,61] but three other studies could not find significant effects on POBF in POAG subjects.[62-64] Timolol was reported to show no significant effects on the arteriovenous passage times (AVP times) measured by fluorescein angiography in POAG subjects.[123]

Topical metipranolol, another non-selective beta-antagonist, was found to significantly increase the retinal blood flow velocity measured by digital video fluorescein angiography in normal subjects.[65]

Carteolol is another non-selective β-blocker characterized by its intrinsic sympathomimetic activity (ISA),[66] and may potentially be vasodilative. But ISA *in vivo* is not always evident.[67]

Animal studies using invasive methods or non-invasive laser speckle method showed beneficial effects of a single instillation of carteolol or chronic treatment with carteolol on the iris or the ONH circulation,[68-70] but a study on the bovine arterially perfused eyes found maximal IOP-reducing dose of carteolol

significantly reduced blood flow in the iris, ciliary body and choroid measured by radiolabelled microsphere technique.[36] Studies using the LSFG or HRF reported beneficial effects of chronic treatment with carteolol on the ONH or peripapillary retinal circulation in normal or NTG subjects.[30,49,71,72] Studies using CDI also suggested beneficial effects of chronic treatment with carteolol on the retrobulbar hemodynamics,[71,73] but a study using LDV could not find any significant effects on the blood flow through a major retinal vein after a single instillation.[4]

Betaxolol is a β1-selective adrenoceptor antagonist with a weak calcium channel blocking action.[75-77] Short-term or chronic treatment with betaxolol was reported to show beneficial effects on the iris, ciliary body, choroids or ONH circulation without significant effects on the microvessel calibers supplying the anterior ONH.[78-81] One study using invasive microsphere technique found the ocular blood flow through the retina and choroid was decreased after single instillation of 0.5% betaxolol in ocular hypertensive rabbits.[4]

A study using the laser speckle method found no significant effects of chronic betaxolol treatment on the ONH circulation in normal subjects,[82] while studies using LDV found significantly beneficial effects of short-term or chronic treatment with betaxolol on the blood flow through a major retinal vein in normal or OHT subjects.[52,83] Although not always confirmed, most of the studies using CDI found a significantly beneficial effect of chronic treatment with betaxolol on the retrobulbar hemodynamics in POAG or NTG patients,[54,57,59,84-86] while no such effects were seen under chronic timolol treatment parallelly studied.[57,59] Chronic treatment with betaxolol is also reported to be more beneficial to the POBF than timolol.[61] A study using digital image analysis of scanning laser fluorescein angiograms in normal subjects that assessed the macular capillary blood velocity (MCBV), epipapillary blood velocities (EBV), AVP times and arterial and venous diameters after a single instillation of timolol, betaxolol or levobunolol found that each drug produced significant decrease in AVP time and a significant increase in MCBV and EBV without a significant effect on the venous diameters.[87]

Levobunolol is a non-selective β-blocker that is converted into an equipotent and polarized metabolite, dihydrobunolol (DHB), after instillation *in vivo*.[88] Lovobunolol also has a weak α1-antagonistic action and blocking action of Ca_2+ entry and change of Ca_2+ sensitivity in vascular smooth muscle.[89] The effects of a single instillation or twice-daily 1-week instillation of levobunolol were investigated in normal subjects and blood flow rate through a major retinal vein, but not perimacular leucocyte velocity, was found to be slightly, but significantly increased.[90,91] Studies using CDI could not find significant effects of a single instillation or chronic treatment of levobunolol on retrobulbar hemodynamics in normal or POAG subjects.[4,54] An increase in POBF was reported in normal and POAG subjects after a single instillation of levobunolol and in POAG and OHT subjects after twice-daily 1-week instillation of levobunolol.[65,92]

Nipradilol is a non-selective β-blocker with weak α1-blocking and NO-donating activity that was registered as a topical anti-glaucoma drug in Japan.[93,94] *In vivo*

and *in vitro* experiments, nipradilol showed a vasodilating being comparable to that of nifedipine or nitroglycerin.[95,96] Studies using LSFG reported beneficial effects of a single or chronic instillation of nipradilol on the ONH circulation in both experimental animals and humans,[30,97] and single instillation of nipradilol was also reported to beneficially affect the blood flow rate through a major retinal artery measured by LDV and retrobulbar hemodynamics measured by CDI in normal subjects.[98,99] In monkeys, nipradilol distribution was studied using [14C] nipradilol after an unilateral single instillation. The drug concentration in the periocular tissue around the optic nerve insertion was significantly higher on the ipsilateral side than on the contralateral side (140 ± 25 ng/g and 42 ± 10 ng/g, respectively; $p = 0.022$), which suggested that topically instilled nipradilol diffused to retrobulbar tissues by diffusion through periocular tissues and could exert vasodilative effects on the retrobulbar vessels.[100]

3.A.6 Prostaglandin analogues (latanoprost, unoprostone, bimatoprost, travoprost, tafluprost)

Latanoprost is a prostaglandin F2α analogue most widely used as an antiglaucoma drug. Effect of latanoprost studied on isolated ciliary arteries showed a dose-dependent relaxation being independent of intrinsic prostaglandins, CGRP or nitric oxide.[101] Topical latanoprost increased the ONH circulation (LSFG) in experimental animals and the increase was independent of the decrease of IOP and abolished by systemic pretreatment with indomethacin.[102] It also increased retinal blood flow (LDV) in experimental animals.[103] In normal humans, latanoprost significantly increased the ONH circulation measured by the laser speckle method,[102,104] while its effect on the ONH or peripapillary retina (HRF) was insignificant.[105,106] Reported effects of latanoprost measured by HRF in POAG subjects are also conflicting with one study showing its significantly beneficial effects and the other study showing no significant effects.[107,109] Most of the studies using CDI in POAG, NTG or OHT subjects failed to find significant effects of latanoprost on the retrobulbar hemodynamics,[53,104,108-113] while some studies found its significantly beneficial effects on some of the parameters of the retrobulbar hemodynamics.[84,114] In contrast to the results obtained by HRF or CDI, there seems to be agreement in that latanoprost had favorable effects on POBF.[66,115-121] Latanoprost showed little effects on the AVP times measured by fluorescein angiography in POAG or NTG subjects.[122,123]

Unoprostone is a prostaglandin-related compound that resembles naturally occurring oxygenated metabolites of docosahexaenoic acids, and was first introduced into clinical use as an antiglaucoma drug.(124) *In-vitro* studies using isolated arteries showed vasodilative activities of unoprostone[125,126] and *in- vivo* animal studies showed that topical unoprostone caused increase in the ONH circulation (LSFG) presumably through its effects on the endogenous prostaglandins.[127,128] In a double-masked and placebo-controlled trial in 24 normal subjects, it was found that a continuous intravenous administration of ET-1 (2.5 ng/kg per minute) produced significant reduction in the choroidal blood flow

and fundus pulsation amplitude, while this effects were significantly blunted when 0.12% topical unoprostone was coadministered.[129] In normal or NTG subjects, unoprostone was reported to increase the ONH circulation (LSFG or HRF),[130-132] but one study using LDF failed to find such effects in vasospastic NTG subjects.[133]

Bimatoprost reportedly showed vasoconstricting effect at rather higher concentrations (> 0.1 micro-M) while travoprost did not showed significant effect in the similar condition in isolated ciliary arteries.[134,135] In experimental animals, travoprost significantly increased the ONH tissue blood velocity (LSFG) which persisted for 24 hrs after the instillation and was abolished by indomethacin pretreatment.[128]

In normal subjects, bimatoprost was reported to show significantly beneficial effects on the retrobulbar hemodynamics.[136] In studies in POAG, NTG or OHT subjects, however, bimatoprost was reported to show little effects on it.[112,114,137-139] In chronic angle closure glaucoma subjects already treated with timolol and pilocarpine, bimatoprost significantly increased POBF.[140] In normal subjects, travoprost was also reported to show beneficial effects on the retrobulbar hemodynamics,[136] which was found to be also the case in POAG or OHT subjects.[114] However, one study in POAG subjects failed to confirm this effect of travoprost.[139]

Tafluprost, a recently developed selective prostanoid FP receptor agonist,[141] showed vasodilating effects on the isolated arteries.[142] Tafluprost was found to increase the blood flow through major retinal vessels (LDV) in experimental animals.[103]

3.A.7 Carbonic anhydrase inhibitors (dorzolamide, brinzolamide)

Dorzolamide hydrochloride is the first developed water-soluble topical carbonic anhydrase inhibitor (CAI) that distributed at a sufficient level in the ciliary process for inhibition of CA-II and it causes significant IOP reduction with extremely low drug concentration in the plasma that minimizes the potential severe systemic adverse effects of CAIs.[143] In experimental animals, the effects of long-term dorzolamide treatment on the ONH circulation and those of a single instillation of dorzolamide on the choroidal circulation were studied using LSFG and LDF, respectively, and no effects were found in both tissues, although ciliary blood flow was significantly increased after its single instillation.[141,145] In another animal study, the ONH blood flow (LDF) increased slightly, but significantly after twice-daily for 1 week instillation of dorzolamide.[146]

In normal subjects, a single instillation of dorzolamide showed no significant effects on the blood flow though a major retinal vessels (LDV).[147,149] Another study in normal subjects also showed no significant effects of thrice-daily 3-day instillation of dorzolamide on the ONH circulation (HRF and LDF).[148] On the other hand, a study in POAG or OHT subjects showed that long-term treatment with dorzolamide caused significant increase in the ONH circulation (HRF) and POBF,[48] and a study in juvenile POAG subjects also showed that adjunctive use

of dorzolamide on timolol resulted in a significant increase in the ONH circulation (HRF).[150] Reported effects of dorzolamide on the retrobulbar hemodynamics in POAG or NTG subjects were rather conflicting; some reported significantly beneficial effects,[23,58,112,151,152] while others reported insignificant effects.[86,108,153-157] Ocular pulse amplitude was reported to be increased by dorzolamide treatment in POAG subjects,[158] and one recent study suggested that dorzolamide increased retinal oxygen saturation in POAG subjects.[157]

Most of the studies measuring AVP times by fluorescein angiography found that dorzolamide significantly facilitated retinal circulation (decreased AVP times) in POAG or NTG subjects.[86,108,122,123] However, one controlled double-masked study with relatively large sample size (47 OAG subjects) could not detect any measurable effects of dorzolamide on AVP times.[156]

Dorzolamide is also used in fixed combination with timolol. Twice-daily timolol-dorzolamide combination therapy was reported to increase the ONH circulation (HRF),[159,160] to improve retrobulbar hemodynamics,[113,161,162] to increase POBF,[163] and to reduce AVP times.[164]

Brinzolamide is another topical carbonic anhydrase inhibitor currently available. In an animal experiment, the ONH circulation (LDF) increased significantly after twice-daily for 1 week treatment of 2% brinzolamide.[146] Two CDI studies failed to find significant effects of brinzolamide on the retrobulbar hemodynamics in both normal and POAG subjects, respectively.[157,165] In another study in glaucoma patients, the ONH circulation (HRF) was found to be significantly increased after brinzolamide treatment.[166] One recent study suggested that brinzolamide increased retinal oxygen saturation in POAG subjects.[157]

3.B Systemic drugs

Makoto Araie, Alon Harris, Rita Ehrlich

3.B.1 Carbonic anhydrase inhibitors

Acetazolamide and dorzolamide decreased pH in the extracellular space in enucleated rat eyes, which was followed by dilation retinal capillaries concomitant with the pH changes.[167] A variety of animal studies indicated that intravenous acetazolamide significantly increased oxygen tension in the retina and ONH, dilate retinal arterioles, and increased blood flow in the retina or choroids,[4,168-170] although one earlier study using the microsphere method could not find any effects of intravenous acetazolamide on the uveal or retinal blood flow.[171]

In normal subjects, intravenous acetazolamide was also reported to increase the retinal blood flow (LDV), POBF or blood flow velocity though OA,[172-174] without involvement of NO.[174] On the other hand, one study in normal subjects indicated decrease of blood flow velocity through OA and POBF despite decreased IOP after intravenous acetazolamide administration,[175] and the other study showed that oral acetazolamide had reportedly little effect on the paramacular leucocyte velocity.[176]

3.B.2 Calcium channel antagonists

Calcium channel antagonists have been widely used for treatment of various systemic disorders, such as systemic hypertension, and its primary effect is to inhibit intracellular calcium ion influx and lead to relaxation of vascular smooth muscle cells and increasing blood flow in several organs.[177,178]

Vasodilative effects of various calcium channel antagonists were documented on isolated retinal or ciliary arteries,[179-181] and in experimental animals in vivo, blood flow-increasing effects of various calcium channel antagonists in ocular tissues including the ONH after their systemic or topical administration were well documented using various techniques such as LDF, LSFG, microsphere technique or hydrogen gas clearance method.[182-191]

Nifedipine is the first calcium channel antagonist of which ocular effects were investigated in humans. The results of the studies, however, almost agreed in that 3 week- to 6 month-treatment with oral nifedipine resulted in no significant changes in the ocular pulse amplitude or retrobulbar hemodynamics in POAG or NTG subjects,[192-196] except for those with vasospastic hyperactivity.[194] Nimodipine is a calcium channel antagonist with high lipid solubility which should facilitate crossing the blood-retinal or -brain barrier.[197] In normal subjects, a short-term use of oral nimodipine reportedly had no significant effects on the blood flow in the juxtapapillary retina or ONH measured (HRF or LDF),[198,199] while one study reported that 5-day oral nimodipine significantly increased the juxtapapillary retinal blood flow (HRF) by about 10% compared with placebo.[200] In NTG subjects, a short-term use of nimodipine caused no significant effects on the perimacular leucocyte velocity or density,[201] but significantly increased the blood flow in the juxtapapillary retina and ONH (HRF) in those with vasospastic hyperactivity[198] or ocular fundus pulsation and the ONH circulation (LDF).[202]

Nilvadipine is another calcium channel antagonist with high lipid solubility and antioxidant action[203] and there were several reports in NTG subjects using LDF, LSFG or CDI that found significant improvement in the ONH, choroid or retrobulbar circulation after 4-12 week oral treatment with nilvalipine.[188,204-207] In a randomized, placebo-controlled, and double-masked study in NTG patients with low IOP of 16 mmHg or less, 3-year administration of 4 mg oral nilvadipine significantly increased the ONH and choroidal circulation by about 30% measured by the laser speckle method over 3 years.[207]

Regarding other calcium channel antagonists, 3 month-use of oral flunarizine was reported to improve retrobulbar hemodynamics in NTG subjects,[208] 7-day use of oral lomerizine to significantly increase the ONH circulation measured by the laser speckle method in normal subjects,[189] while a single dose of felodipine showed no significant effects on the blood flow in the retina, ONH and choroid measured by LDV or LDF in normal subjects.[209]

Topically administered verapamil was reported to significantly increase the ONH circulation (LDF) or improve retrobulbar hemodynamics in normal subjects.[210,211]

3.B.3 Drugs affecting the renin-angiotensin system

Trandolapril, an oral angiotensin-converting enzyme inhibitor, was reported to increase the blood flow velocity of the central retinal artery and posterior ciliary artery in subjects with essential hypertension.[212] Reported effects of oral intake of losartan, an angiotensin II subtype AT1 receptor, in normal subjects are somewhat conflicting; little effects on the choroidal flood flow (LDF) or retrobulbar hemodynamics were reported,[213,214] while one study found significantly increased fundus pulse amplitude.[214]

3.B.4 Drugs affecting the NO system

Chronic nitrate treatment may dilate retinal veins in glaucoma patients.[215] Intravenous administration of NG-monomethyl-L-arginine, a NO synthase inhibitor, significantly reduced the ONH blood flow (LDF) and fundus pulse amplitude both in normal and POAG subjects, but the reduction in these parameters was less prominent than that in age-matched normal subjects.[216] Being compatible with the above result, intravenous administration of l-arginine, a NO precursor, significantly increased retinal blood flow (LDV) and POBF in normal subjects.[217]

3.B.5 Sildenafil (Viagra, a selective phosphodiesterase type-5 inhibitor)

A study using isolated retinal arterioles indicated that pathways via NOS activation and phosphodiesterase inhibition both contribute to vasodilation of this drug with the former being the major pathway.[218] Studies using CDI in humans showed that hemodynamics in OA and SPCAs rather than CRA were affected by sildenafil.[219,220] Studies in normal subjects or those with age-related macular degeneration indicated that sildenafil had little effects on the subfoveolar choroidal or ONH blood flow (LDF),[221,222] while it significantly dilated retinal vessels, especially veins, and increased retinal blood flow (LDV).[223-225] Pentoxifylline, a phosphodiesterase type-4 inhibitor, has been used for treatment of intermittent claudication. Intravenous administration of pentoxifylline was reported to increase the retinal circulation (HRF).[226]

3.B.6 Other systemic drugs

In normal subjects, intravenous administration of dopamine was found to increase the blood flow velocity through major retinal vessels measured by LDV and fundus pulse amplitude, but showed no significant effects on the ONH circulation measured by LDF,[227] while intravenous droperidol, a dopamine antagonist, showed beneficial effects on retrobulbar hemodynamics probably due to reduced IOP.[228] Intravenous administration of histamine increased choroidal blood flow measured by LDF and POBF, while it little affected blood flow through major retinal veins measured by LDV in normal subjects,[229] and these effects were

thought to be mediated mainly through H1 receptors, but not H2 receptors.[230,231] Intravenous administration of endothelin-1 (ET-1) significantly reduced the blood flow through major retinal vessels (LDV) in normal subjects, and this effect was blunted by co-administration of BQ123, an ET-A receptor antagonist, of which administration alone showed no effects on retinal hemodynamics.[232] Intravenous administration of bosentan, an ET-A and ET-B receptors antagonist, significantly increased the blood flow through major retinal vessels (LDV) and ONH and choroidal blood flow (LDF) in both POAG and normal subjects to a similar extent.[233] Intravenous administration of adenosine significantly increased the ONH and choroidal blood flow (LDF) and fundus pulse amplitude in normal subjects, showing adenosine-induced vasodilation.[234] Intravenous administration of moxaverine, a papaverine derivative, increased choroidal blood flow (LDF) in normal subjects without significantly affecting the blood flow in the ONH and retina (LDF and LDV, respectively).[235] Oral intake of ginkgo-biloba extract may a little improve the retrobulbar hemodynamics, but the blood flow in the retina and choroid measured by LDV and LDF, respectively, and fundus pulse amplitude were reported to be little affected in normal subjects.[236,237]

3.C Ocular surgery, exercise

Makoto Araie

3.C.1 Ocular hypotensive therapy and trabeculectomy

Since systemic blood pressure or ocular perfusion pressure (OPP) was known to positively correlate with the perimacular leucocyte velocity and blood velocity in the central retinal artery,[238] it is reasonable to assume ocular hypotensive therapy also affects ocular circulation. Although it is not clear whether observed effects are attributable to the IOP reduction itself or to drug effects, IOP reduction by means of medical, laser and/or surgical therapy was reported to be associated with increase of the POBF in NTG subjects,[239] and the ONH circulation measured by HRF in POAG subjects, while the effect of IOP reduction was not evident in the juxtapapillary retinal circulation (HRF) in the OHT subjects.[240,241] Reported effects of trabeculectomy were conflicting. Two studies found that trabeculectomy was associated with improvement in the retrobulbar hemodynamics[242] and the ONH circulation (LDF),[243] while other studies could not find significant effects on the POBF and the ONH and juxtapapillar retinal circulation (LSFG or HRF).[244-246]

3.C.2 Scleral buckling procedures

One study reported that successful retinal detachment surgery using scleral buckling significantly improved the macular area retinal circulation (HRF).[247] The most of the studies, however, reported adverse effects of scleral buckling

procedures on the POBF, ONH circulation (HRF or LSFG), retinal blood flow (LDV), and choroidal circulation (LSFG).[248-253]

3.C.3 Exercise

Studies on the exercise effects on ocular circulation involve either isometric or dynamic exercise, but results do not seem to differ between them. Exercise significantly increased the choroidal blood flow (LDF, HRF or LSFG), but its increase was much less than directly expected from the co-existing increase in the OPP, indicating the autoregulatory mechanism was keeping the choroidal circulation relatively unchanged.[254,255,256-259] The results obtained for POBF showing little change by exercise are also compatible with the above findings,[260,261] and vasoconstriction is thought to be involved in the relatively small change in choroidal circulation associated with exercise.[261-263] Several studies suggested involvement of NO and/or ET-1 rather than beta-receptors, muscarinic receptors or blood PCO_2 level in the exercise-induced change of the choroidal circulation.[256,258-260,264] Exercise was associated with little change in the ONH blood flow (LDF), retinal blood flow (HRFor LDV) or that estimated by paramacular leucocytes in retinal capillaries,[259,265-269] indicating more efficient autoregulatory mechanism including vasoconstriction in these tissues than in choroid.[265,266] In chronic smokers or patients with central serous chorioretinopathy, this autoregulatory mechanism may be compromised.[257,270]

3.C.4 Others

Ocular warming was associated with transient increase in the retinal blood flow (LDV) and decrease in the choroidal blood flow (LDF).[271] The blood velocity in the carotids is closely correlated with the POBF and blood velocity in the ophthalmic artery,[272] and carotid endarterectomy was found to improve the ONH and paramacular retinal blood flow (HRF).[273]

3.D Does modulation of blood flow alter glaucoma progression?

Alon Harris, Rita Ehrlich, Makoto Araie

Since several retrospective and cohort studies suggested that eyes with compromised retrobulbar circulation are more likely to be associated with further progression of glaucoma,[274-279] it may be tempting to assume that glaucoma progression may be altered by modulating ocular blood flow. As reviewed in the former chapters, some of the antiglaucoma eye drops such as betaxolol, nipradilol, dorzolamide or prostaglandin analogues may have potential to improve circulation in the ocular tissues relating to glaucoma in patients, if it is not substantial. However, it would be difficult to discriminate between the effects of the lowered IOP and those of the improved circulation.[280] Systemic administration of some of the calcium channel antagonists or other drugs is

thought to improve ocular circulation and some of them were reportedly associated with slowing down of visual field progression in POAG, especially in NTG subjects. Although many of these studies are randomized and placebo-controlled, they utilized a small sample size and it is unknown whether the obtained results may be attributed to pharmacological effects of these drugs other than blood flow-increasing effects or those on the blood flow.[281-287] Some studies suggested beneficial effects of nifedipine or nimodipine on the visual field in NTG subjects,[199,202,283-285] but as reviewed in the former chapter, effects of nifedipine on the ocular blood flow seems doubtful. However, previous studies did not always agree in the beneficial effects of nimodipine on the ocular circulation. Oral brovincamine, a weak calcium channel antagonist, was reported to slow down the visual field progression in a subset of NTG patients,[286,287] but animal studies revealed that systemic brovincamine had little effects on the ocular blood flow.[288,289] One randomized and placebo-controlled study showed that long-term use of oral nilvadipine was associated with significant increase in the ONH and choroidal blood flow and significantly slower progression of visual field damage over 3-year period,[207] but it is again unknown if the observed effect was attributable to calcium antagonistic or others action of nilvadipine on neural cells or increased blood flow.[207]

There are several limitations in the studies investigating effects of topical or systemic drugs on the human ocular blood flow cited above. Many of them utilized a small to moderate sample size with subjects' number of less than 50. Most of the studies focused on short-term effects on the ocular blood flow and did not examine the year-long effects of the medications. Additional limitations include the usage of a large variety of technologies.

Important questions remain to be asked:

- Which blood vessels should be targeted for treatment?
- Which technology is the most useful to detect changes in blood flow?
- What is the best medication to modify blood flow?
- Do different ocular vessels respond differently to a given medication? And if so, what is the physiological mechanism?

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4. Glaucoma and systemic vascular disease

Doina Gherghel

The occurrence of cardio- and cerebrovascular disease is the result of many pathological mechanisms, including endothelial dysfunction (ED) and autonomic nervous system (ANS) disturbances; the very same risk factors have also been included in the long list of risk factors for glaucomatous optic neuropathy (GON). Therefore, glaucoma patients are often expected to also suffer from various systemic vascular pathologies. Indeed, although primary open-angle glaucoma (POAG) is associated more closely with elevated intraocular pressure (IOP), other risk factors already implicated in the aetiology of this disease and especially in the etiology of normal-tension glaucoma (NTG) are: abnormal ocular circulation,[1-11] ocular and systemic vascular dysregulation,[12-15] as well as systemic blood pressure (BP) alterations.[16-24] Oxidative stress, which occurs as a result of an imbalance between generation of reactive oxygen species (ROS) and antioxidant defence mechanisms and is implicated in the pathogenesis of disorders ranging from atherosclerosis to neurodegenerative disorders, diabetes and aging[25-26] may also contribute to the general vascular disturbances observed in glaucoma. Moreover, increasing evidence shows that oxidative stress plays a role in promoting ED, which is a key factor in progression of vascular diseases.[26] We have demonstrated that independent of age and gender systemic antioxidative capacity, defined by circulatory glutathione (GSH) levels, is reduced in newly diagnosed POAG patients when compared to age-matched controls;[27] a possible explanation for this phenomenon could reside in an abnormal nitric oxide (NO) homeostasis in these patients.[28] Indeed, pathogenesis of glaucomatous optic nerve damage has been related to endothelial damage/dysfunction, as indicated by abnormal plasma vascular endothelial growth factor (VEGF) and von Willebrand factor (vWf) levels.[29]

Clinical studies have suggested that there is an endothelium-dependent vascular dysregulation in patients suffering from (NTG) demonstrated by both venous occlusion plethysmography and ultrasonic imaging of the brachial artery (flow-mediated dilation, FMD, and nitroglycerine-mediated dilation, NMD).[14] Both studies have concluded that NTG patients have shown signs of systemic endothelial dysfunction that might contribute to the etiology of this disease. In addition, ocular and systemic vascular risk factors have also been implicated in the disease progression in patients suffering from 'high-tension' POAG.[22,24,30-36]

Interactions between endothelial function and ANS are complex and imbalance between the sympathetic and parasympathetic divisions of the ANS could contribute to the occurrence of (ED) by either platelet activation or by mechanical injury to the vascular wall as a result of high systemic BP and increased blood velocity.[37,38]). A high sympathetic tone during both day and night has previously been reported in NTG[21] and in POAG patients.[24] A constant high sympathetic tone can lead to an abnormal HRV;[39] it can also be an indicator of increased oxygen demand in various tissues[37] and results in a low ischemic threshold in all organs, including the eye. We can hypothesize that in glaucoma patients suffering from

either abnormal circadian fluctuations of HRV or high diurnal sympathetic tone, the eye is more susceptible to minor changes in perfusion pressure, and ocular diseases with vascular risk factors (such as glaucoma) could occur with higher frequency. As glaucoma patients with and without silent cardiac ischemic events demonstrated HRV behaviour consistent with constant high sympathetic tone, we suggest that such autonomic dysfunction appears to be present in glaucoma patients more than normal subjects even when cardiovascular abnormality is either not evident, or exists only at a subclinical level.[24] Either way, systemic indicators of autonomic dysfunction are a feature of patients exhibiting GON and may be linked to the onset and/or further progression of the disease.

ED also contributes to the pathogenesis of Alzheimer's disease (AD). POAG and AD share some common features: (1) Aging and female gender seem to be aggravating factors;[40] (2) Neurodegeneration plays an important factors in the aetiology of both diseases; patients with AD demonstrate axonal degeneration at the optic nerve level and loss of ganglion cells;[41] (3) Some genetic risk factors are common for both diseases;[42] (4) Dynamic cerebral autoregulation is impaired in both diseases;[43] (5) The neuronal damage and vasculopathies act synergistically to accelerate neuronal loss.[44] Indeed, it seems that GON progresses more severely in patients suffering from AD than in patients free of dementia.[45] Moreover, glaucoma is associated with ischaemic events in other organs such as the heart and brain.[46,24] In addition, in a recent study, Sugiyama *et al.*[47] found that almost 24% of patients suffering from normal-tension glaucoma (NTG) exhibited an AD-like cerebral perfusion pattern. This percentage seemed noticeably higher than the 1.08% incidence rate of AD reported in a normal population cohort aged 75 and over.[48] As the eye and the brain vessels share a large number of embryological and anatomical similarities, this observation does not come as a surprise. Therefore, the high association between the two diseases in the same patients could have common vascular starting points. We have shown for the first time (Benavente-Perez, Gherghel and Bentham-unpublished data) that patients suffering from AD show an abnormal retinal vascular function; this was similar to patients suffering from glaucoma and significantly different from normal age-matched population. Moreover, the anti-oxidative stress power was also reduced in patients suffering from AD in similar way that it was in patients suffering from glaucoma. All these results show for the first time that a systemic vascular dysfunction can indeed be an element that links AD to glaucoma.

Consequences

More extensive investigations are necessary to determine the risk factors for each individual case of POAG. Clinicians should consider potential autonomic effects of various systemic and ocular therapies in patients suffering from glaucoma. It is well known that any therapy that activates the sympathetic division of ANS will increase the risk of systemic circulatory events and any drugs that increase the vagal tone or decrease the sympathetic hyperactivity may improve cardiovascular outcome.[49,50] As both chronic cardiovascular diseases and their

treatment may represent important contributory factors in glaucoma pathogenesis, clinicians should consider carefully any possible danger arising from this strategy. Moreover, IOP-lowering treatment often consists of drugs that either mimic or inhibit the sympathetic and parasympathetic divisions of ANS.[51] For these reasons, an autonomic assessment, together with 24-h BP measurement could be useful in monitoring the efficacy and possible circulatory side effects of selected therapies in patients suffering from both glaucoma and systemic diseases. In addition, new avenues against antioxidant deficit and/or endothelial dysfunction that could help selected glaucoma patients by improving both ocular and general vascular health could be developed.

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5. Systemic disease and glaucoma patients

Stuart Graham

5.A Diabetes

Diabetes has been reported to be either a risk factor for POAG, as not associated with POAG, or possibly even protective in ocular hypertension (OHT). The Ocular Hypertension Treatment Study (OHTS) suggested in its initial report that diabetes may confer a protective role in the development of glaucoma in OHT

subjects.[1] However, a subsequent re-analysis removed the potential beneficial effect.[2]

There are several biases in recruitment of subjects that may have influenced the many studies in the literature – including the finding that diabetics tend to have thicker corneas and higher IOPs, and that in most studies on the association between the two conditions, elevated IOP was used as a diagnostic inclusion criteria. The quandary of whether diabetes could be deleterious or protective is dealt with in an excellent recent editorial by Quigley,[3] where several theories as to how it could be protective in early disease are forwarded.

Pasquale *et al.*[4] observed 76,3128 women who were enrolled in the Nurses' Health Study from 1980 to 2000. Eligible participants were at least 40 years old, did not have POAG at the beginning of the study, and reported receiving eye exams during follow-up. After controlling for age, race, hypertension, body mass index, physical activity, alcohol intake, smoking and family history of glaucoma, they found that type 2 diabetes was positively associated with POAG. However, the relationship between type 2 diabetes and POAG did not increase with longer durations of type 2 diabetes.

The Blue Mountains Eye Study[5] found glaucoma prevalence was increased in people with diabetes, diagnosed from history or elevated fasting plasma glucose level (5.5%), compared with those without diabetes (2.8%; age-gender adjusted odds ratio [OR] 2.12, 95% confidence intervals [CI] 1.18-3.79). Ocular hypertension was also more common in people with diabetes (6.7%), compared with those without diabetes (3.5%; OR 1.86, CI 1.09-3.20).

In the historical cohort study in Tayside, Scotland,[6] which used the DARTS regional diabetic register, no significant association was found between diabetes and glaucoma or OHT. However, the study reported the problem of selection bias may have influenced the results.

The Los Angeles Latino Eye Study[7] found that of 5894 participants with complete data, 1157 (19.6%) had type 2 diabetes and 288 (4.9%) had OAG. The prevalence of OAG was 40% higher in participants with diabetes than in those without (age/gender/intraocular pressure – adjusted odds ratio, 1.4; 95% confidence interval, 1.03-1.8; $P = 0.03$). Trend analysis revealed that a longer duration of type 2 diabetes was associated with a higher prevalence of OAG ($P < 0.0001$).

Several other studies have reported a link between diabetes and glaucoma including a meta-analysis,[8] but equally there are several large studies with no association found.[9-12]

Overall, there appears to be divided evidence to support or refute a positive link, with the weight of evidence perhaps on the side of no added risk. The overlap of the diseases and their mechanisms of interaction is yet to be defined.

5.B Cardiovascular diseases

5.B.1 *Cardiovascular events, mortality and glaucoma*

The EMGTS recently reported new baseline predictors for the progression of glaucoma.[13] These included lower ocular systolic perfusion pressure in all patients (≤ 160 mmHg; HR, 1.42; 95% CI, 1.04-1.94), cardiovascular disease history (HR, 2.75; 95% CI, 1.44-5.26) in patients with higher baseline IOP, and lower systolic blood pressure (BP) (≤ 125 mmHg; HR, 0.46; 95% CI, 0.21-1.02) in patients with lower baseline IOP. This study supports the findings of several recent studies suggesting low perfusion pressure may be important, but adds the concept of cardiovascular disease history.

In a case control study examining focal arterial narrowing near the disc in glaucoma, 58 pairs of cases and controls were matched.[14] The prevalence of hypertension and diabetes was exactly equal in both groups, 65.5% and 27.6%, respectively. Similarly, the prevalences of myocardial infarction, cardiac surgery, angioplasty, family history of heart disease and smoking were nearly identical in both groups. There was no significant difference in the prevalence of strokes or transient ischaemic attacks. The prevalence of hypercholesterolemia and mortality was greater in the case group (mean differences of 8.6, $p = 0.42$ and 5.2, $p = 0.25$, respectively), however, these differences were not statistically significant. However, this study chose to use focal arterial narrowing as its selection criteria, so may not be generalized to all glaucoma.

In a study using 24-hour ECG monitoring, an increased rate of silent myocardial ischemia was reported in glaucoma, especially normal-tension glaucoma. Cataract patients, however, had only a slightly, statistically not significantly increased frequency compared with normals.[15]

There are several small studies suggesting increased cerebral white matter lesions (WMLs) and therefore implied silent cerebral ischemia, in glaucoma.[16,17] A logical argument can be raised as to why there might be an associated sign of a vascular link with glaucoma. WMLs are associated with age, hypertension, cognitive decline, and are reported as increased in women with migraines, so there is a strong overlap with glaucoma (*see* Yücel and Gupta for review[18]).

The Blue Mountains Eye Study[19] found age-standardized, all-cause mortality was 24.3% in persons with and 23.8% in those without glaucoma, whereas cardiovascular mortality was 14.6% in persons with and 8.4% in those without glaucoma. After multivariate adjustment, those with glaucoma had a nonsignificant increased risk of cardiovascular mortality (RR 1.46; 95% confidence interval [CI], 0.95-2.23). Increased cardiovascular mortality was observed mainly in glaucoma patients aged < 75 years (RR, 2.78; 95% CI, 1.20-6.47). Further stratified analyses showed that cardiovascular mortality was higher among those with previously diagnosed glaucoma (RR, 1.85; 95% CI, 1.12-3.04), particularly in those also treated with topical timolol (RR, 2.14; 95% CI, 1.18-3.89). Similarly, the Barbados Eye Study[20] found that cardiovascular mortality tended to increase in persons with previously diagnosed/treated OAG (n = 141; relative risk [RR],

1.38, P = .07) and was significantly higher with treatment involving timolol maleate (RR, 1.91, P = .04). Cardiovascular deaths also tended to increase in persons with ocular hypertension at baseline (n = 498; RR, 1.28, P = .06).

However, a recently published meta-analysis[21] found 9 cohort studies with relative risk (RR) estimates for all-cause mortality and glaucoma. A significant risk was not detected in the final pooled analysis (RR, 1.13; 95% confidence interval [CI], 0.97-1.31) for all-cause mortality. Also, a meta-regression across diabetes status in 3 of the 9 studies did not demonstrate significant results (P = .94). Subgroup analysis on cardiovascular mortality from 4 of the 9 studies was marginally significant (RR, 1.20; 95% CI, 1.00-1.43; P = .05), but insignificant after removal of a study in which POAG was ascertained by self and proxy report (RR, 1.12; 95% CI, 0.87-1.46). In conclusion, the meta-analysis does not demonstrate an association between POAG and all-cause or cardiovascular mortality.

Therefore, while there are many small studies covering all aspects of cardiovascular disease that imply an association with the glaucomatous process, and many new studies linking ocular perfusion pressure and hypotension (covered in other sections of the consensus), there are few large clinical trials demonstrating a link between glaucoma and systemic cardiovascular disorders such as heart attack and stroke, and the risk for increased mortality is not confirmed by all studies. It is possible, and even likely, that conditions that cause small vessel disease and impairment of vascular regulation may contribute to the generation of glaucomatous damage, but we do not yet have the evidence needed to define these relationships.

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SHOULD MEASUREMENTS OF OCULAR BLOOD FLOW BE IMPLEMENTED INTO CLINICAL PRACTICE?

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SHOULD MEASUREMENTS OF OCULAR BLOOD FLOW BE IMPLEMENTED INTO CLINICAL PRACTICE?

Neeru Gupta, Robert N. Weinreb

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Consensus points

- Measurements of ocular blood flow are currently research tools for the study of glaucoma.
  Comment: Assessing ocular blood flow has been of interest to clinicians and scientists over several decades, and sophisticated diagnostics directed at measuring ocular perfusion have emerged.
  Comment: Before deciding whether to implement measurements of blood flow into clinical practice for glaucoma management, however, these measurements need to be critically assessed in clinical studies.
- Although there is an association between measurements of ocular blood flow and glaucoma progression, a causal relationship has not been established.
- There are insufficient data to support the measurement of ocular blood flow for clinical decision making in glaucoma practice.
  Comment: Prior studies of ocular blood flow in glaucoma have varied considerably in their methodologies, numbers of patients, and study design pertaining to design, conduct and analysis.
- Evidence that measurement of blood flow leads to better clinical outcomes for the glaucoma patient is lacking.
- There is no evidence that altering blood pressure changes the course of glaucoma.

Interpreting clinical studies

Considering the strength of the evidence

When critically appraising the literature regarding ocular hemodynamics in glaucoma, strength of evidence is an important consideration. Weakest to strongest

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levels of evidence include consensus or opinion, case reports and case series (with or without controls), observational studies, randomized clinical trials, and systematic reviews of randomized trials, respectively.[1] Systematic reviews provide strong evidence to underpin evidence-based medicine. The majority of publications related to ocular blood flow in glaucoma are designed as case series and observational studies. There have been few high-quality studies that could be considered part of such a systematic review.

The randomized clinical trial

The randomized clinical trial (RCT) provides a high strength of evidence regarding the outcomes of an intervention. The important advantage of randomization is the prevention of selection and confounding biases. With flawed methodology however, even a RCT has the potential to mislead healthcare decisions. When evaluating the results of a RCT, there are a number of important considerations in the study design and analysis to consider. In an RCT, the sample size and/or power determinations to detect a specific size effect should be clear, and calculated prior to enrollment. A reported negative result by investigators should prompt attention as to whether the study was adequately powered to even detect a difference between groups. Multiple sites can increase the enrollment and generalizability of results, however, because equipment, examiners and subjects have the potential to significantly vary between sites, the investigators need to rigorously control for these factors. Recognizing the importance of promoting high quality RCTs, the Consolidating Standards of Reporting Trials (CONSORT) Group-created guidelines for those designing, evaluating or reporting on clinical trials, including a checklist of key questions to be asked,[2,3] as shown in Table 1.

Critical appraisal of studies

The critical assessment of the credibility of clinical reports is an important issue for all clinicians, and is the cornerstone of evidence-based medicine. Key elements of high quality studies in glaucoma ocular blood flow will include a design to directly address the question, details of the methods to select patients and collect and analyze data sufficiently to allow their evaluation and replication, data that is reliable and accurate, and an adequate control group or basis for comparison. The similarity of the control group to the glaucoma group, other than the intervention, should be clearly evident. If one or more of these elements is not present, the validity of the report should be questioned. Whether the author is objective or an advocate of a particular point of view, and whether he/she would have published the data had the opposite findings been observed, might also be considered by the reader.

Generalizability

Consideration to the generalizability of study results related to ocular blood flow in glaucoma should be given. If the study conditions are very different from those encountered in clinical practice, the results would be less applicable. Specific characteristics of the study patient with glaucoma such as age, gender, race, type of glaucoma and severity must be assessed. For example, results obtained by a study of patients with vascular risk factors and low tension glaucoma may not be applicable to all patients with open angle glaucoma. Confirming the results of a single study in a broader population will help to establish the extent of applicability to those with glaucoma.

Table 1. Guide to evaluating a randomized clinical trial

CHECKLIST	SHORT EXPLANATION
1. Title and abstract	How participants were allocated to interventions (*e.g.*, 'random allocation,' 'randomized,' or 'randomly assigned')
2. Introduction & Background	Scientific background and explanation of rationale
3. Methods & Participants	Eligibility criteria for participants and the setting and locations where the data were collected
4. Interventions	Precise details of the interventions intended for each group and how and when they were actually administered
5. Objectives	Specific objectives and hypotheses
6. Outcomes	Clearly defined primary and secondary outcome measurements and, when applicable, any methods used to enhance the quality of measurements (*e.g.*, multiple observations, training of assessors)
7. Sample size	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules
8. Randomization sequence generation	Method used to generate the random allocation sequence, including details of any restriction (*e.g.*, blocking, stratification)
9. Allocation concealment	Method used to implement the random allocation sequence (*e.g.*, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned
10. Implementation	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups
11. Blinding (masking)	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated
12. Statistical methods	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses
13. Results Participants flow	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the number of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, and reasons

CHECKLIST	SHORT EXPLANATION
14. Recruitment	Dates defining the periods of recruitment and follow-up
15. Baseline data	Baseline demographic and clinical characteristics of each group
16. Numbers analyzed	Number of participants (denominator) in each group included in each analysis and whether the analysis was by 'intention-to-treat.' State the results in absolute numbers when feasible (*e.g.*, 10/20, not 50%)
17. Outcomes and estimation	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (*e.g.*, 95% confidence interval)
18. Ancillary analyses	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory
19. Adverse events	All important adverse events or side effects in each intervention group
20. Comment interpretation	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes
21. Generalizability	Generalizability (external validity) of the trial findings
22. Overall evidence	General interpretation of the results in the context of current evidence
Adapted from: Moher D, Schultz, KF, Altman D. The CONSORT Statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001; 285: 1987-1991.	

Special considerations in ocular blood flow studies

In specialized disciplines, such as ocular blood flow, evaluation of the methods, observations and interpretations often requires additional knowledge and experience. Clinical data on the ocular circulation in glaucoma is derived from a relatively small number of ocular blood flow imaging techniques that include color Doppler imaging, confocal scanning laser ophthalmoscopic angiography, scanning laser Doppler flowmetry and retinal photographic oximetry. When interpreting the literature that evaluates glaucoma patients with these technologies, it is important to be aware of the capacity of the instrument to define vascular function and pathology[4] (Table 2).

While the design of the study has an inherent value, addressing different kinds of questions may require the use of different study designs. As an example, a question about the accuracy of any of these blood flow imaging tests to detect glaucoma would require a study design that prospectively evaluates, recruits eligible patients, employs the test, and the reference standard investigation to confirm or refute the presence of glaucoma, and that determines the accuracy with which the test correctly identifies disease.[5]

There is a growing body of evidence that ocular vascular changes are related to glaucoma. Despite this, there is uncertainty in the clinical community regarding the value of current blood flow measures. Thus, the fate of ocular blood flow

Table 2. Blood flow technologies

TECHNOLOGY	VASCULAR BED	MEASUREMENTS	MAIN LIMITATIONS
Color Doppler imaging	Retrobulbar blood vessels	Velocity	Measures velocity not flow
Scanning laser ophthalmoscopic angiography	Retina and choroid (dye dependent)	Velocity	Measures velocity and filling time not flow
Laser Doppler flowmetry	Optic nerve head and choroidal capillaries	Flow in arbitrary units	No absolute flow measurements. Comparison between subjects difficult.
Confocal scanning laser Doppler flowmetry	Optic nerve and retinal capillaries	Flow in arbitrary units	Flow measured in arbitrary units. Comparison between subjects difficult
Retinal oximetry	Retina vessels	Oxygen saturation in arteries and veins	Not fully validated
Pulsatile ocular blood flow	Mainly choroid	Pulse amplitude, pulsatile ocular blood flow (POBF)	No direct measurement is made. Relation to flow unclear
Retina vessel analyzer	Large retinal vessels	Retinal vessel diameter	No flow or velocity information. Retinal vessel diameter in arbitrary units
Bi-directional laser Doppler velocimetry (CLBF)	Large retinal vessels	Velocity, diameter and calculated flow	Good fixation and clear media required
Interferometry	Choroid	Fundus pulsation amplitude	Doubtful relationship between fundus pulsation amplitude and ocular blood flow
Laser Speckle Flowgraphy	Optic nerve head and subfoveal choroid	Tissue blood velocity	Measurement is not clearly understood
Doppler FD-Optical Coherence Tomography	Branch retinal vessels	Volumetric flow rate, velocity, and cross-sectional area	Not fully validated. Cannot measure microcirculation

testing in clinical practice will depend upon studies with rigorous design and methods with multiple centers and masked reading centers.[6] Prospective clinical trials of ocular blood flow in glaucoma will need to compare various blood flow measurements to a gold standard of diagnosis. Adequate intra- and inter-operator reproducibility will be necessary. Glaucoma patients with a spectrum of disease from mild to severe, in addition to treated and untreated disease, will need to be studied. Establishing a normative database also will be necessary.

Large epidemiological studies of glaucoma have reported that ocular perfusion pressure (OPP) (calculated as the difference between blood pressure and

intraocular pressure) is a risk factor for the prevalence, incidence and progression of glaucoma.[7-13] Blood pressure measurement in glaucoma patients is not routine, however, it is possible that using blood pressure to calculate an abnormality in a glaucoma patient may be a surrogate marker for possible blood flow abnormalities within the eye. There is no evidence that the finding of an abnormal blood pressure or OPP in a patient with progressive glaucoma, despite well controlled intraocular pressure, is related to glaucoma progression. Additionally, there is no evidence that normalization of blood pressure or OPP alters the course of glaucoma. However, a diagnosis of high or low blood pressure could at the least trigger medical interventions beneficial to the overall health of the patient. Clinical studies to investigate ocular blood flow in glaucoma should incorporate blood pressure monitoring in their design, and control for medications that may affect blood pressure.

Future clinical studies may establish abnormal blood flow as a contributor to glaucomatous damage in a sub-group of glaucoma patients with a distinct clinical picture, perhaps needing a targeted treatment approach. Identifying these patients reliably would attract innovative vasoprotective therapies to prevent vision loss. Ultimately, the introduction of blood flow measurements into clinical practice will depend on evidence that the results will help us to care for patients with glaucoma.

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WHAT DO WE STILL NEED TO KNOW?

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WHAT DO WE STILL NEED TO KNOW?

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Consensus points

- Clinical studies are essential to establish the clinical application of ocular blood flow measurements in glaucoma.
  Comment: Appropriately designed studies utilizing standardized measurement techniques are needed to ascertain the relationships among ocular blood flow, metabolism and glaucoma progression.
  Comment: Future studies should ascertain the relationship between blood pressure and glaucoma.
- The physiology of ocular blood flow regulation needs to be elucidated. Laboratory studies designed to detect molecular and cellular mechanisms in vitro and in vivo that support the presence of ischemia are needed.
  Comment: Experimental research is needed to elicit the existence and role of hypoxia/ischemia in relevant glaucoma models.
- Longitudinal studies are necessary to confirm whether blood flow abnormalities precede visual field defects and correlate with their severity.
- The hypothesis should be tested that treatment of OPP, rather than IOP alone, is beneficial in glaucoma.
- There is a need to determine at what levels IOP and OPP increase the risk for the onset and/or progression of glaucoma for an individual eye.
- The clinical outcome of ocular blood flow fluctuation, perfusion pressure and their impact on glaucoma needs to be investigated.
  Comment: The contribution of the blood flow within the entire central visual pathway is unknown and still needs to be determined.
- A normative database for ocular blood flow measurements that can be used in research and clinical practice should be established.

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Ocular blood flow and visual function in glaucoma patients

A number of publications have examined the relationship between blood flow abnormalities and visual field defects, either directly or indirectly. Plange *et al*.[1] reported that asymmetric visual field defects correlate with asymmetry in the flow velocities of the central retinal artery and ophthalmic artery (OA). Zeitz *et al*.[2] reported that glaucoma progression is associated with decreased blood flow velocity in the short posterior ciliary artery. Galassi *et al*.[3] reported that patients with resistive index (RI) > 0.78 in the OA had 6 times the risk of visual field deterioration than patients with lower RI; and Martínez[4] reported that patients with RI > 0.72 in the OA correlated with glaucoma progression over 3 years of follow-up. Blood flow in the neuroretinal rim was found to correspond to regional visual field defects in eyes with NTG.[5] The rate of visual field defects progression correlates with retrobulbar blood velocity independent of the extent of glaucomatous damage and IOP.[6] Martínez[7] reported the outcome of patients with OAG treated with timolol/dorzolamide compared to timolol over 4 years of follow-up. Forty patients were included in the study. The combined treatments produced a greater increase in blood flow velocity in the OA and posterior ciliary artery (PCA) and a greater decrease in RI than with timolol alone. The combination treatment also reduced the risk of glaucoma progression. The study is limited because each therapy resulted in a different IOP outcome; the difference in progression rate and blood flow may be due to the difference in the IOP effect. Sato[8] observed 3 cases of progressive visual field defect caused by a decrease in the neuroretinal rim (measured by LDF) as a result of buckle surgery. When the buckle was removed, the blood flow increased and the visual field defect remained stable. Kozobolis *et al*.[9] studied the effect of endarterectomy in carotid stenosis on ocular blood velocity and visual field. His group observed improvements in both blood velocity and mean deviation of the visual field after surgery.

The limitations of the studies are their small sample sizes, length of follow-up, use of different technology, and differences in IOP control. There are many questions that remain unanswered regarding the correlation between visual field and ocular blood flow. Before we can answer whether we can utilize ocular blood flow clinically, we need to decide what method should be used and we must establish a normative database for blood flow/velocity values corrected for age, gender, race, IOP level and blood pressure status. At this stage neither the circadian or diurnal fluctuation in ocular blood flow has been established.

Ocular perfusion pressure and prevalence and progression of glaucoma

Several studies have implicated vascular risk factors in the pathogenesis of primary open-angle glaucoma (POAG). Among them, ocular perfusion pressure (OPP) has become increasingly important. Perfusion pressure is defined as the difference between arterial and venous pressure. In the eye, venous pressure is equal to or slightly higher than IOP. OPP can therefore be defined as the

difference between arterial BP and IOP. OPP can be further broken down into diastolic perfusion pressure (diastolic BP minus IOP) and systolic perfusion pressure (systolic BP minus IOP).

The Baltimore Eye Survey indicated that individuals with diastolic perfusion pressures lower than 30 mmHg had a six-fold higher risk of developing glaucoma than individuals with diastolic perfusion pressures greater than 50 mmHg.[10] In the Barbados Eye Study, subjects with the lowest 20% of diastolic perfusion pressures were 3.3 times more likely to develop glaucoma.[11] In a subsequent study among participants of the Barbados Eye Study, risk factors for the incidence of glaucoma over 9 years of follow-up were evaluated. Again, lower OPPs were identified as a risk factor.[12] Similarly, the Egna-Neumarkt study reported a 4.5% increase in the prevalence of glaucoma in patients with diastolic perfusion pressures less than 50 mmHg compared with those whose diastolic perfusion pressures were 65 mmHg or greater.[13] In the Proyecto VER Study,[14] patients who presented with a diastolic perfusion pressure of 45 mmHg had a three times greater risk of developing glaucoma than those with measurements of 65 mmHg.

Recently published data from the Early Manifest Glaucoma Trial (EMGT) established lower systolic perfusion pressure as a new predictor for disease progression. Individuals with systolic perfusion pressure lower than 125 mmHg had a 42% higher risk of progressing over time compared to patients with systolic perfusion pressure above 125 mmHg.[15] This effect was present even after adjustment for other risk factors such as age, intraocular pressure, treatment, presence of exfoliation, worse baseline mean defect on perimetry, bilateral disease, and disc hemorrhages. In accordance with the EMGT, Choi *et al*.[16] performed a retrospective chart review of 113 eyes with NTG to investigate systemic and ocular hemodynamic risk factors for glaucomatous damage. Systolic and diastolic BP fluctuations were defined as the difference between the highest and lowest SBP and DBP recorded during the 24-hour period. Of the functional and anatomic outcome variables, circadian mean OPP fluctuation was the most consistent clinical risk factor for glaucoma severity in eyes with NTG.

The limitations in interpretation of the results are the confounding factors that may exist in these studies. Large studies that will investigate whether there is a direct correlation between the OPP and the ocular blood flow are essential. Different calculations for OPP have been used for sitting and supine positions, and the results from these calculations are not always comparable.[17] Sitting ocular perfusion pressure = 2/3 X mean blood pressure - IOP. Supine ocular perfusion pressure = 0.88 X mean blood pressure - IOP. Calculations should be consistent with the position of the studied iindividual.

Some general comments and questions that need to be considered include:

Systemic hypertension and its treament always need to be considered and consultation with the primary physician should be encouraged.

Do we need to measure OPP in daily clinical practice? If so, should OPP be measured for every patient or just those that seem to progress despite IOP control?

How often should OPP be measured, and is 24-hour monitoring of OPP appropriate?

Will the patient experience other systemic consequences when changes to blood pressure treatment are undertaken?

Ocular blood flow and optic nerve head structure

The relationship between structure of the optic nerve head (ONH) and ocular blood flow is both interesting and intriguing. In a study by Harris *et al*.[18] on 20 healthy subjects, the inferior sector of the retinal nerve fiber layer (RNFL) and of the optic nerve head had lower blood flow per unit tissue volume compared to the superior sector. A significant finding regarding ONH structure and blood pressure came from the Thessaloniki Eye Study.[19] In patients without glaucoma, diastolic blood pressure (DBP) less than 90 mmHg resulting from antihypertensive treatment was associated with increased cupping and decreased rim area of the optic disc. This suggests that blood pressure status is an important independent factor initiating optic disc changes and/or is a contributing factor to glaucomatous damage. Logan *et al*.[20] studied 76 NTG patients, 58 POAG patients and 38 control subjects with the use of the Heidelberg Retinal Flowmeter and Tomograph (HRF and HRT). In this study, glaucoma patients had significantly lower retinal blood flow than controls, and there was a relationship between retinal blood flow and structural damage of the ONH. Hafez *et al*.[21] performed a prospective non-randomized study on 20 OHT patients, 20 OAG patients, and 20 controls using Laser Doppler Flowmetry (LDF) and HRT. In their study, OAG patients had significantly lower blood flow in the ONH compared to OHT patients and normals. The blood flow in the neuroretinal rim was significantly inversely correlated to the C/D ratio. In a prospective randomized study utilizing CDI and GDxVCC on 30 OAG patients and 30 healthy controls, glaucoma patients showed statistically significant thinning of the RNFL, reduced blood flow velocities, and increased resistance to flow compared to age-matched healthy subjects.[22] In early stage glaucoma, Berisha *et al*.[23] reported a significant reduction in retinal blood speed and flow in OAG patients compared to controls. The RNFL was significantly thinner in OAG patients compared to controls. There were significant inverse correlations between retinal blood flow and average RNFL thickness. The highest retinal blood flow rates were observed in patients with the thinnest RNFL. This finding is consistent with previous results reported by Feke and associates,[24] who found an inverse correlation between ONH capillary blood speed and RNFL thickness at the disc margin in untreated OHT patients. Plange *et al*.[25] found a significant positive correlation between CRA blood speed and neuroretinal rim area and volume in patients with more advanced glaucomatous optic neuropathy. Berisha and colleagues[23] speculated that the relationship between blood flow and progressive glaucomatous damage may be bimodal. Retinal blood flow may increase with

increasing RNFL loss until a critical level is reached in which the blood flow decreases with further RNFL loss. They further hypothesize that during the early development of OAG, circulatory abnormalities can lead to ischemia and an increase in nitric oxide (NO) production which in turn can lead to vasodilation and an increase in blood flow.

Fluctuations in mean ocular perfusion pressure were reported to be associated with functional and anatomical outcomes in NTG patients. An increase of 1 mmHg in mean perfusion pressure was associated with a 0.23 increase in AGIS score and a 0.53 decrease in TSNIT average score. Blood flow in the neuroretinal rim was also found to correspond to the regional visual field defect in eyes with NTG.[26]

These studies are limited by their use of different techniques for measuring blood flow and the structure of the optic nerve head. The questions that need to be answered include:

- What is the best technique to measure blood flow?
- What vessels are most important to measure?
- What vascular beds correlate best with the structural changes?
- Should we measure blood flow in the neuroretinal rim, lamina cribrosa, or another location?
- Which of the structural changes correlate the best? Is there a direct relationship between the two?

We need large standardized studies that use a uniform measurement of blood flow and structure of the optic nerve head. We need longitudinal long term studies that will potentially reveal the time course of events and reveal which of the changes precedes the other.

The relationship between intraocular pressure and ocular blood flow

Over the last thirty years, several studies have sought to investigate the relationship between IOP and ocular blood flow. Unfortunately, these studies lack uniformity in methodology, imaging technology, subdivision of patients, and other aspects. Despite these discrepancies, nearly all of the studies suggest that IOP is inversely related to ocular blood flow.[27-34] In one study, acute elevations of IOP led to decreases in juxtapapillary retinal and ONH blood flow of 7.4% and 8.4% per 10-mmHg IOP increase, respectively.[34] The relationship appears to be somewhat linear in nature for some tissue beds.[35-37] Several studies suggest that blood flow in the ONH, retina, and choroid diminishes only after a certain threshold of IOP increase is reached.[33,38-42] One study investigated ten healthy subjects using LDF and increasing IOP to 25, 35, 45 and 55 mmHg with a scleral suction cup. Seven patients with intact autoregulatory response were reported to maintain the baseline level of blood flow over the lower part of the range of elevated intraocular pressure, but showed a decline in flow by

the time IOP reached 45 or 55 mmHg. Patients that were lacking autoregulation showed a linear decline in blood flow beginning with the smallest increment of IOP elevation.[33] The results of the study show that in healthy subjects, the ONH blood flow is typically kept nearly constant despite substantial elevation of the IOP. The maintenance of flow rate with initial increments of IOP elevation represents autoregulation of blood flow, which keeps the blood flow nearly constant despite reduced vascular perfusion pressure. The point at which ONH blood flow decreases most prominently is after the IOP is above 45 mmHg.[33]

The change in ONH blood flow during IOP alteration was suggested to be influenced by systemic blood pressure in primates. Altering IOP in primates with increased blood pressure did not change ONH blood flow, but the same alteration in those with low blood pressure significantly changed ONH blood flow.[43]

Changes in OPP had similar effects to changes in IOP, as might be expected.[44-46] Several studies found oxygen saturation to be reduced in the retina and ONH during IOP increases.[47-49] Two studies found no relationship between IOP and ocular blood flow parameters.[50,51]

These studies are limited by the different techniques that are used to measure the blood flow response in different vascular beds and at different measurement locations.

Some questions that remain:

- What is the mechanism of IOP's impact on blood flow?
- How does that impact the nutrient delivery within the ONH and lamina cribrosa?
- What is the nutrient delivery for any given blood flow?
- Does regional autoregulation within the optic disc vary between subjects, and would this have clinical significance?

The relationship between cerebrospinal fluid pressure and glaucoma

The susceptibility of the axons to IOP-related stress within the lamina cribrosa is determined by the interplay between (1) the level of IOP related tensile strain; (2) the laminar capillary perfusion pressure (*i.e.*, volume flow); (3) the ease of diffusion from the capillary to the axon bundles; and (4) the material properties and diffusion characteristics of the laminar extracellular matrix.[52] In the past few years, there has been a growth in interest about the role of the gradient between the CSF pressure and the IOP in glaucoma pathogenesis. Jonas suggested that the translamina-cribrosa pressure difference may be more important than the transcorneal pressure difference in relation to the optic nerve head. The translamina-cribrosa pressure difference is obtained by subtracting the pressure of the CSF surrounding the optic nerve from the IOP.

The CSF pressure may be correlated with arterial blood pressure, which has been reported to be a risk factor for glaucoma by itself or as a determinant of

OPP. The CSF pressure should change in the same direction as the arterial blood pressure to allow adequate perfusion of the brain in a state of low arterial blood pressure and to prevent a cerebral hemorrhage in the case of high blood pressure. If blood pressure is medically reduced, the CSF pressure may also, therefore, be indirectly decreased without a marked change in IOP, and this can lead to an elevated translamina-cribrosa pressure difference.[53] Berdahl *et al.* present data from a population that consisted of 31,786 subjects who had a lumbar puncture between 1996 and 2007 at the Mayo Clinic. Of this population, 28 met criteria for inclusion into the primary open-angle glaucoma (POAG) group and 49 subjects met criteria for the control group. The study data indicated that patients with POAG have low CSF opening pressure on lumbar puncture compared with a group of normal controls without glaucoma.[54] In addition, multivariable analysis showed that lower CSF opening pressure was correlated with a larger cup-to-disc ratio. There was no correlation between CSF opening pressure and visual field severity.[54] One limitation of the study is that the population studied does not include all the populations at risk for POAG. Additionally, the study group included patients with neurologic signs and symptoms that warranted LP which can bias the results.

In another study, Berdahl *et al.* compared the intracranial pressure of 57 patients with POAG, 11 patients with NTG, 27 patients with OHT, and 105 normal subjects. This study was a retrospective review of medical records of 62,468 subjects who had lumbar puncture between 1985 and 2007 at the Mayo Clinic. The authors found that although the intracranial pressure in subjects with POAG and NTG was lower than that in controls, the intracranial pressure was higher in OHT patients. In this study, the cup-to-disc ratio and the visual filed severity did not correlate with the ICP or the translaminar pressure difference.[55] The translaminar pressure difference may lead to abnormal function and potential nerve damage due to changes in axonal transport, deformation of the lamina cribrosa, or altered blood flow.[55]

The central retinal artery travels through cerebrospinal fluid in the orbital portion of the optic nerve sheath before entering the optic nerve proper. The ophthalmic artery is exposed to subarachnoid space before it enters the optic canal.[56] In addition, the pial system supplying the retrolaminar portion and the capillary network that supplies the laminar region can be influenced by the CSF pressure and the translaminar pressure gradient. Querfurth *et al*.[56] studied the relationship between ICP and ocular blood flow in patients with increased intracranial pressure. In their primary analysis, a population of referral patients with papilledema caused by chronically elevated intracranial pressure, ranging from 210 to 550 mm H_2O, had significantly reduced systolic and mean blood flow velocities of the CRA and OA compared with a normal, age or gender-matched control group. Yet, in a group with more severe chronic intracranial pressure, the trend was reversed with increased blood velocity. The authors hypothesize that in severe chronic intracranial pressure, local autoregulatory vascular changes and/or diversion of cerebral blood flow into the ophthalmic circulation may normalize these parameters.[56]

No study to date has examined whether there is a relationship between CSF pressure, translaminar pressure gradient, and ocular blood flow. There is currently no definitive explanation for the relationship between the CSF pressure and structural and functional abnormalities in glaucoma. No study has examined the role of the translaminar gradient on nutrient delivery within the lamina. There is no method to directly examine the blood flow within the laminar area and thus to examine the correlation with the CSF-IOP gradient.

Harris *et al.* reported reduced blood flow in the middle cerebral artery in glaucoma patients [57]. Furthermore middle cerebral artery flow velocity was found to be correlated with the mean deviation defect of the central visual field.[58] Whether there is a relationship between the CSF pressure and the decrease in the cerebral blood flow reported in glaucoma patients is an interesting query. Is there any correlation between these findings and the MRI abnormalities found in some patients with glaucoma?[59]

One major limitation in pursuing this topic in more depth is the fact the lumbar puncture is invasive, and it is probably not feasible or ethical to subject neurologically asymptomatic patients to LP. Perhaps in the future there will be a non-invasive clinical method for measuring the pressure gradient across the laminar cribrosa.

Future research

- A method for acquiring direct measurements from the circle of Zinn Haller and laminar capillaries needs to be developed.
- What affects the nutrient diffusion within the optic nerve head? Is it the IOP directly or the pressure gradient within the laminar beams?
- What is the role of the gradient between IOP and the CSF in the nutrient delivery within the laminar beams? What factors can influence that? Does the trans-laminar pressure gradient directly affect the axoplasmic flow and transport by mechanisms that are not related to blood flow and nutrient delivery?
- What is the role of genetic loci that produce vascular dysfunction in POAG?
- Need to establish what we are measuring and what the relationship is between biomechanics, tissue remodeling and blood flow
- What is the role of systemic vascular abnormalities in the pathogenesis of glaucoma, if any?
- Longitudinal, long term studies with a large number of patients utilizing standardized measurements methods are needed to confirm the relationship between ocular blood flow and structural and functional changes in glaucoma patients as well as the causative relationship between them.

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SUMMARY CONSENSUS POINTS

ANATOMY AND PHYSIOLOGY

- Blood supply to the retinal nerve fiber layer invariably comes from the central retinal artery and, when present, from the cilioretinal artery(ies).
  Comment: There are no anastomotic connections between the arteries, which function as end-vessels even though the capillaries are a continuous bed.
- Blood supply to the prelaminar and laminar portion of the optic nerve head comes from branches of the short posterior ciliary arteries.
  Comment: These often form an incomplete vascular ring around the optic nerve head ('Vascular ring of Zinn and Haller'), before giving off branches into the tissue of the optic nerve head located inside of the peripapillary scleral ring of Elschnig. These vessels feature an anastomotic blood supply.
- Retinal vessels are not fenestrated and are not innervated. Since they lack a continuous tunica musculosa, the retinal 'arteries', except for the main central retinal vessel trunk, are anatomically arterioles.
  Comment: These anatomical features may have implications for understanding how blood flow is regulated in this vascular bed.
- It is unclear whether the branches of the posterior ciliary artery that feed the intrascleral portion of the optic nerve are innervated and/or fenestrated.
  Comment: Such knowledge is essential to understand how the intrascleral papillary tissue responds to various insults, including abnormally high IOP.
- Branches of the short posterior ciliary arteries supply the choroidal vasculature. The majority of total ocular blood volume and flow (~80-90%) is derived from the choroidal vascular. The capillaries are among the largest in the body and are fenestrated. The arteries that feed them are innervated.
  Comment: These features have important implications for how the choroidal vasculature is regulated. It has remained unclear whether there is a clinically relevant anastomotic blood exchange between the choroidal vasculature bed and the vascular system of the ciliary body, which is fed by the two long posterior ciliary arteries and the 7 anterior ciliary arteries.
- The central retinal vein drains all blood from the entire retina and the optic nerve head.
  Comment: Upon contact-free ophthalmoscopy, a spontaneous pulsation of the central retinal vein can be detected in ~80 to 90% of normal eyes. Since the central retinal vein passes through the optic nerve and then through the cerebrospinal fluid space before piercing through the optic nerve meninges in the orbit, the blood pressure in the central retinal vein should be at least as high as the cerebrospinal fluid pressure within the optic nerve meninges in the orbit plus a (hypothetical) trans-lamina cribrosa outflow resistance.
- Blood flow to the optic nerve and retina is dominated primarily by myogenic and metabolic regulation. The blood flow to the choroid is believed to be primarily regulated mainly by hormonal and neuronal mechanisms. The extent of autoregulation in the choroid is not known.

Comment: Ocular vascular autoregulation maintains adequate blood flow that provides nutrients and oxygen, as well as adequate tissue turgor, to ocular structures in the face of changing metabolic needs and altered ocular perfusion pressure. Such functions are all designed to allow sharp vision at all times.

CLINICAL MEASUREMENT OF OCULAR BLOOD FLOW

- Color Doppler imaging of the ophthalmic artery, central retinal artery and posterior ciliary arteries measures blood flow velocity noninvasively and calculates resistive index.
  Comment: Color Doppler imaging does not measure flow.
  Comment: With careful interpretation, color Doppler imaging measures blood flow velocity and vascular resistivity in the retrobulbar blood vessels. The exact relationship between vascular resistivity index and resistance is not fully understood.
  Comment: The measurements with one color Doppler instrument are not necessarily compatible with those of another.
- Scanning laser Doppler flowmetry measures velocity, volume and flow limited to the retinal microcirculation and the optic nerve head.
  Comment: There is a lack of standardization for analysis, and flow is limited to arbitrary units of measure.
  Comment: The depth of the measurements is not known and may not be comparable among subjects.
- The retinal vessel analyzer provides a dynamic assessment of retinal vessel diameters of branch retinal arterioles and venules.
  Comment: The retinal vessel analyzer does not evaluate either velocity or blood flow.
  Comment: At the current time, vessels with a diameter of 90 micrometers or larger are measured.
- The relationship between ocular pulse amplitude and total blood flow to the eye and, specifically, to the optic nerve is uncertain.
- Laser speckle flowgraphy provides 2-dimensional *in vivo* measurements of blood velocity in the optic nerve head and subfoveal choroid.
  Comment: Measurements in human eyes of the retina and iris have been problematic.
  Comment: Measurement with laser speckle flowgraphy is not clearly understood.
- Digital scanning laser ophthalmoscope angiography allows direct visualization of retinal and choroidal microvasculature.
  Comment: Various aspects of observed blood flow parameters and filling characteristics can be quantified, including retinal velocity and circulation times with fluorescein dye, and relative regional choroidal filling delays with indocyanine green dye.
  Comment: At the current time, scanning laser ophthalmoscope angiography requires an intravenous dye injection.

- By combining bidirectional laser Doppler velocimetry with simultaneous measures of retinal vessel diameter and centerline blood velocity, it is possible to calculate retinal blood flow in absolute units.
  Comment: These measurements require clear optical media and pupil dilation.
  Comment: The method is limited to vessels greater than 60 micrometers.
- Doppler Fourier Domain Optical Coherence Tomography provides rapid measurements of volumetric flow rate, velocity, and cross-sectional area in branch retinal vessels.
  Comment: At the current time, the method is limited to vessels greater than 60 micrometers and there are limited data.
- Retinal oximetry is a non-invasive measurement of oxygen saturation.
  Comment: At the current time, there are limited data. The method is limited to retinal vessels greater than 60 micrometers. It may be applicable also to the optic nerve head..
- At the present time, there is no single method for measuring all aspects of ocular blood flow and its regulation in glaucoma.
  Comment: A comprehensive approach, ideally implemented in a single device, may be required to assess the relevant pathophysiology of glaucoma.

CLINICAL RELEVANCE OF OCULAR BLOOD FLOW (OBF) MEASUREMENTS INCLUDING EFFECTS OF GENERAL MEDICATIONS OR SPECIFIC GLAUCOMA TREATMENT

- Blood pressure (BP) is positively correlated with IOP.
- It is unclear whether the level of BP is a risk factor for having or progressing open-angle glaucoma (OAG) in an individual patient.
  Comment: It has been hypothesized that low blood pressure is a risk factor for patients with abnormal autoregulation.
- Lower ocular perfusion pressure (OPP = BP – IOP) is a risk factor for primary OAG.
- OBF parameters measured with various methods are impaired in OAG, especially in NTG, compared with healthy subjects.
  Comment: Reduction of OBF with aging has been confirmed by various methods.
  Comment: The optic nerve head blood flow may be reduced during the nocturnal period.
- Vascular dysregulation may contribute to the pathogenesis of glaucoma, more likely in people with lower intraocular pressure.
- Certain drugs, even when formulated in an eye drop, may have an impact on ocular blood flow and its regulation.
  Comment: The impact of eye drop related changes in ocular blood flow on the development and progression of glaucoma is unknown.
  Comment: Some data support increased blood flow and the enhancement of ocular blood flow regulation with carbonic anhydrase inhibitors. These ap-

pear to exceed what one would expect from their ocular hypotensive effect alone.

- Some systemic medications may have an impact on ocular blood flow and its regulation.
  Comment: The impact of systemic medications altering ocular blood flow on the development of glaucoma and the progression of glaucoma is unknown.
  Comment: Classes of systemic medications with agents that have been reported to increase ocular blood flow include calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor inhibitors, carbonic-anhydrase inhibitors, phospodiesterase-5 inhibitors.
- The association between diabetes and cardiovascular diseases with OAG still remains unclear.

SHOULD MEASUREMENTS OF OCULAR BLOOD FLOW BE IMPLEMENTED INTO CLINICAL PRACTICE?

- Measurements of ocular blood flow are currently research tools for the study of glaucoma.
  Comment: Assessing ocular blood flow has been of interest to clinicians and scientists over several decades, and sophisticated diagnostics directed at measuring ocular perfusion have emerged.
  Comment: Before deciding whether to implement measurements of blood flow into clinical practice for glaucoma management, however, these measurements need to be critically assessed in clinical studies.
- Although there is an association between measurements of ocular blood flow and glaucoma progression, a causal relationship has not been established.
- There are insufficient data to support the measurement of ocular blood flow for clinical decision making in glaucoma practice.
  Comment: Prior studies of ocular blood flow in glaucoma have varied considerably in their methodologies, numbers of patients, and study design pertaining to design, conduct and analysis.
- Evidence that measurement of blood flow leads to better clinical outcomes for the glaucoma patient is lacking.
- There is no evidence that altering blood pressure changes the course of glaucoma.

WHAT DO WE STILL NEED TO KNOW?

- Clinical studies are essential to establish the clinical application of ocular blood flow measurements in glaucoma.
  Comment: Appropriately designed studies utilizing standardized measurement techniques are needed to ascertain the relationships among ocular blood flow, metabolism and glaucoma progression.
  Comment: Future studies should ascertain the relationship between blood pressure and glaucoma.

- The physiology of ocular blood flow regulation needs to be elucidated. Laboratory studies designed to detect molecular and cellular mechanisms in vitro and in vivo that support the presence of ischemia are needed.
  Comment: Experimental research is needed to elicit the existence and role of hypoxia/ischemia in relevant glaucoma models.
- Longitudinal studies are necessary to confirm whether blood flow abnormalities precede visual field defects and correlate with their severity.
- The hypothesis should be tested that treatment of OPP, rather than IOP alone, is beneficial in glaucoma.
- There is a need to determine at what levels IOP and OPP increase the risk for the onset and/or progression of glaucoma for an individual eye.
- The clinical outcome of ocular blood flow fluctuation, perfusion pressure and their impact on glaucoma needs to be investigated.
  Comment: The contribution of the blood flow within the entire central visual pathway is unknown and still needs to be determined.
- A normative database for ocular blood flow measurements that can be used in research and clinical practice should be established.

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