Major review

Autoregulation and neurovascular coupling in the optic nerve head

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ABSTRACT

Impairments of autoregulation and neurovascular coupling in the optic nerve head play a critical role in ocular pathologies, especially glaucomatous optic neuropathy. We critically review the literature in the field, integrating results obtained in clinical, experimental, and theoretical studies. We address the mechanisms of autoregulation and neurovascular coupling in the optic nerve head, the current methods used to assess autoregulation—including measurements of optic nerve head blood flow (or volume and velocity)—blood flow data collected in the optic nerve head as pressure or metabolic demand is varied in healthy and pathologic conditions, and the current status and potential of mathematical modeling work to further the understanding of the relationship between ocular blood flow mechanisms and diseases such as glaucoma.

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1. Introduction

Glaucoma is an optic neuropathy characterized by progressive death of retinal ganglion cells (RGCs) and irreversible visual loss. Glaucoma is the second leading cause of blindness worldwide, and yet its etiology and treatment remain unclear. The main modifiable risk factor in glaucoma patients is elevated intraocular pressure (IOP); however, a high percentage of individuals with elevated IOP (a condition called ocular hypertension) never develop glaucoma, and many glaucoma patients continue to experience disease progression despite lowering IOP to target levels or have no history of elevated IOP—a condition called normal tension glaucoma (NTG).

Several studies suggest correlations between impaired ocular blood flow and glaucoma. In healthy conditions, vascular beds exhibit an intrinsic ability to maintain relatively constant blood flow over a large range of arterial pressures. This autoregulatory behavior is recognized in most vascular beds—including the eye, brain, heart, kidney, skeletal muscle, and gut—but the effectiveness of autoregulation differs among these vascular beds according to importance of function. For example, the brain and kidney receive stable flow over a range of arterial pressure, whereas autoregulation in other beds such as the gut is less effective. In the eye, the retinal and optic nerve head (ONH) vascular beds are known to exhibit autoregulation, though to differing extents. Details and experimental measures of autoregulation are better established in the retina than in the ONH. In experiments assessing hemodynamic responses to light stimulation, blood flow in the retina and ONH seems to be highly correlated to increased neural activity. This phenomenon is called neurovascular coupling.

In glaucoma the location of damage to nerve cells is hypothesized to be predominantly in the ONH, and thus a clearer understanding of the factors affecting the blood supply to the ONH is necessary to determine how this may be compromised and potentially contribute to the pathophysiology of glaucoma.

The aim of this review is to 1) summarize the mechanisms of autoregulation and neurovascular coupling that function in the ONH; 2) describe the current ability to assess autoregulation in the ONH using methodologies capable of determining ONH blood flow (or volume and velocity); 3) compare data on blood flow for varying pressure or metabolic needs in the ONH to assess autoregulation in healthy and pathologic conditions; and 4) describe the current status of ophthalmic research and support the potential of mathematical modeling to further the understanding of the relationship between ocular blood flow mechanisms and ocular diseases such as glaucoma. In order to help the reader, a list of the acronyms used in this paper is provided in Table 1.

2. Anatomy and vascular supply of the ONH

2.1. Anatomy

The ONH is where RGC axons leave the eye through the scleral portion of the neural canal, forming bundles by astrocytes, a particular type of glial cell. For the purpose of description, the anatomy and vascular supply of the ONH is best divided into 4 regions, from anterior to posterior segments (see Fig. 1).

The most anterior part of the ONH is the superficial nerve fiber layer (SNFL). Some vascular details of this layer can be resolved on ophthalmoscopy examination or angiography. A part of the appearance of the SNFL comes from light backscattered from deeper tissue. Immediately behind the SNFL is the “prelaminar region,” which lies adjacent to the peripapillary choroid. Posterior to the prelaminar region, the “laminar region” is composed of the lamina cribrosa, a structure consisting of fenestrated connective tissue beams through which the RGC axons pass on their path from the retina to the optic nerve. Finally, the “retrolaminar region” lies posterior to the lamina cribrosa. It is marked by the beginning of axonal myelination and is surrounded by meninges.

The lamina cribrosa bears the translaminar pressure difference: the difference between the IOP, which is the...
pressure in the intraocular space, and the retrolaminar tissue pressure, which is the pressure in the retrolaminar region. The retrolaminar tissue pressure is usually lower than the IOP and is strongly correlated to the cerebrospinal fluid pressure and the pressure in the subarachnoid space of the optic nerve when cerebrospinal fluid pressure > 2 mm Hg (1 mm Hg = 133.3224 Pa). A hoop stress is also transferred to the lamina by the sclera. There is evidence that an annulus of collagen fibrils exists around the scleral canal in the peripapillary sclera. These fibrils appear to be oriented mostly radially in the periphery of the lamina. The peripapillary annulus significantly reduces the IOP-related expansion of the scleral canal and shields the lamina from high-tensile stress. The radially oriented fibrils in the lamina periphery reinforce the lamina against transversal shear stresses and reduce laminar bending deformations. The lamina cribrosa remodels into a thicker, more posterior structure, which incorporates more connective tissue after chronic IOP elevation.

In the prelaminar, laminar, and retrolaminar regions, RGC axons are surrounded by astrocytes, which are believed to maintain the homeostasis of the extracellular environment. In particular, astrocytes remove potassium and glutamate from the extracellular space, provide cellular support to the axons, and synthesize extracellular matrix macromolecules. In the prelaminar and retrolaminar region, it is presumed that nutrient delivery to the axons occurs both via diffusion and advection. In the laminar region, the extracellular matrix of laminar beams lies in between capillaries and astrocytes. Consequently, nutrients likely diffuse from laminar capillaries, across the endothelial and pericyte basement membranes, through the extracellular matrix of the laminar beams, across the basement membranes of astrocytes. From there, they may go into the astrocytes or percolate in the extracellular space between them, ultimately reaching the adjacent axons.

2.2. Vascular supply

The vascular system nourishing the ONH is quite complex and shows high interindividual and intra-individual variability. An important anatomic distinction between the different portions of the ONH is that blood flow to the ONH is primarily supplied by the posterior ciliary arteries (PCAs), whereas the SNFL receives oxygenated blood primarily from retinal arterioles. These small vessels, called “epipapillary vessels,” originate in the peripapillary SNFL and run toward the center of the ONH (see Fig. 2).

In approximately 30% of all people, a cilioretinal artery may be present and supply the temporal SNFL. This artery, if present, may be a direct branch of the ciliary or choroidal arteries, emerging from the temporal SNFL of the ONH and extending laterally along the papillomacular bundle. The retinal arteries and the cilioretinal arteries lack anastomotic blood exchange in the case of an artery occlusion, leading to an ischemic infarct in the area supplied by the artery or its branches.

The prelaminar region is mainly supplied by direct branches of the short PCAs and by branches from the circle of Zinn-Haller (see Fig. 3). The circle of Zinn-Haller, if present, is a complete or incomplete ring of arterioles within the perineural sclera formed by the confluence of branches of the short PCAs. The arterial circle branches into the prelaminar region, lamina cribrosa, and retrolaminar pial system and supplies the peripapillary choroid. This vascular ring can be recognized in vivo using indocyanine green videoangiography in highly myopic...
eyes. These vessels exhibit an anastomotic blood exchange, but it is unclear whether this exchange can counterbalance an insufficiency of a single PCA. There is also evidence of direct arterial supply to the prelaminar layer arising from the choroidal vasculature, even though the extent to which it contributes to the perfusion of the region is still a matter of debate. Blood flow to the laminar region is provided by centripetal branches of the short PCAs (see Fig. 4).

Such a 3-D architecture differs from, without effectively denying, what is proposed in some histology studies, where the lamina is viewed as a set of stacked perforated sheets containing vessels, with pores in each sheet aligned to create tunnel for bundles of nerve fibers to exit from the eye. Unlike in vivo imaging, histology imaging suffers from distortions because of the loss of pressure (IOP, intracranial pressure, and blood pressure), distortions during tissue preparation, and tissue degradation after death. Nevertheless, care is needed when comparing optical coherence tomography (OCT) results to histology because of differences in optical resolution and sampling density. OCT has significantly worse

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**Fig. 2** — Superficial nerve fiber layer (SNFL). The SNFL receives oxygenated blood primarily from retinal arterioles. These small vessels, called epipapillary vessels, originate in the peripapillary SNFL and run toward the center of the optic nerve head.

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**Fig. 3** — Prelaminar region. The prelaminar region is mainly supplied by direct branches of the short posterior ciliary arteries (PCAs) and by branches of the circle of Zinn-Haller. The circle of Zinn-Haller, if present, is a complete or incomplete ring of arterioles within the perineural sclera formed by the confluence of branches of the short PCAs.
lateral resolution when compared with electron microscopy or other forms of microscopy used to study the lamina cribrosa, and it likely overemphasizes beams, compared to histology. Hence, many questions still need to be answered to characterize the 3-D geometry of the lamina cribrosa accurately.

The centripetal branches arise either directly from the short PCAs or from the circle of Zinn-Haller. These precapillary branches perforate the outer boundary of the lamina and then branch into an intraseptal capillary network, which runs inside the laminar beams. It is still unclear whether there are anastomoses between the capillary or precapillary bed of the laminar region, the prelaminar region, and the SNFL region. If these anastomoses exist, it is unclear whether they play a role when a sudden (or slowly progressive) vascular occlusion on the precapillary or intracapillary level happens. The retro-laminar region is supplied by the central retinal artery (CRA) and the pial system (see Fig. 5). The pial system is an anastomosing network of capillaries located immediately within the pia mater. The pial system originates from the circle of Zinn-Haller and may also be fed directly by the short PCAs. The branches of the pial system extend centripetally to nourish the axons of the optic nerve. The CRA may supply several small intraneural branches in the retrolaminar region. Some of these branches may also anastomose with the pial system.

In the ONH the capillaries form a continuous network throughout its entire length, being continuous posteriorly with those in the rest of the optic nerve and anteriorly with the adjacent retinal capillaries. It is unclear whether this implies that blood flow regulation is similar or not in both vascular regions, independent of the arterial source. Critical questions remain unanswered. The CRA within the intraorbital optic nerve is innervated, but innervation stops (at least) anterior to the lamina cribrosa, and it does not follow the branches of the CRA inside the eye. Neurotransmitter receptors, however, are present on the surface of retinal vessels. In addition, normal retinal vessels lack fenestrations. Hence, vasoactive hormones cannot leak from capillaries and reach the muscular coat of nearby arterioles where they can influence blood flow. The branches of the PCA that feed the intrascleral portion of the optic nerve may or may not be innervated and/or fenestrated. Such knowledge is crucial to understand how blood flow is regulated in the ONH.

Venous drainage of the ONH occurs primarily through the central retinal vein (CRV). In the SNFL, blood is drained directly into the retinal veins, which then join to form the CRV. In the prelaminar, laminar, and retrolaminar regions, venous drainage occurs via the CRV or axial tributaries to the CRV.

3. Techniques for in vivo studies of ONH hemodynamics

As described in section 2, the complex vasculature of the ONH is comprised of small diameter vessels arranged in an intricate 3-dimensional geometry. At present, no technology allows a noninvasive measurement of volumetric blood flow in absolute units; however, some hemodynamic measurement techniques provide surrogates for ONH blood flow in arbitrary units. Four of these measurement techniques for in vivo studies of ONH hemodynamics are discussed and compared in the following sections. Table 2 summarizes their main features, advantages, and limitations.
3.1. Laser Doppler flowmetry

Laser Doppler flowmetry (LDF) is a noninvasive method of assessing blood flow and perfusion in the ONH. LDF is based on the Doppler effect. It measures the shift in frequency that occurs when light is scattered by the red blood cells moving through capillaries. LDF uses a fundus camera and a computer system to detect these changes in frequency. This information is used to calculate 3 hemodynamic parameters: velocity, blood volume, and blood flow within the ONH. Velocity is defined as the average speed of red blood cells traveling through capillaries and is proportional to the mean change in Doppler shift frequency. Blood volume is defined as the number of red blood cells in the given sample. Blood flow or flux is defined as the flux of red blood cells through a specific part of a capillary at a given time. The main advantage of LDF is its ability to measure 3 different hemodynamic parameters; however, LDF only provides measurements of blood perfusion in arbitrary (and not absolute) units, which limits its usefulness in a clinical setting. Moreover, LDF measurements depend significantly on the depth of the sampled tissue. This depth determines the relative contribution to the Doppler signal of the superficial layers, the layers supplied by the CRA, and the deeper layers supplied by the short PCAs. Blood flow autoregulation may or may not differ within these vascular beds. In a study on monkey eyes, LDF appeared to be more heavily influenced by blood flow changes in the more superficial layers of the ONH than in deeper ones, but to what extent remains uncertain.

![Fig. 5 – Retrolaminar region. The retrolaminar region is supplied by the central retinal artery (CRA) and the pial system. The pial system is an anastomosing network of capillaries located immediately within the pia mater.](image)

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CRA, central retinal artery; OCT, optical coherence tomography; ONH, optic nerve head; PCA, posterior ciliary artery.
3.2. OCT angiography

OCT angiography, a combination of high speed OCT and a new 3D angiography system called split-spectrum amplitude-decorrelation angiography, is a noninvasive method used to estimate blood flow in the ONH, especially within the microcirculation.\textsuperscript{108} It computes the flow index, which is a surrogate for blood flow in arbitrary units.

OCT is a technique that takes cross-sectional images of a biologic tissue using a low-coherence interferometer. These cross-section images are captured using a low-coherence beam directed at the target tissue. The light signals reflect off of the tissue back to the interferometer, which stacks a series of longitudinal tomographic 2D-scans to derive a 3-dimensional image. Doppler OCT, a commonly used subtype of OCT, can detect the Doppler frequency shift of the reflected light, providing additional information on blood flow. The split-spectrum amplitude-decorrelation angiography algorithm allows 3-dimensional angiography to be done 4 times faster than previous algorithms and also improves blood flow detection, creates better visualization of the microvasculature, and removes motion errors automatically.\textsuperscript{105}

OCT angiography has many advantages over Doppler OCT. Doppler OCT can only quantify blood flow in large superficial vessels of the ONH and cannot visualize the microvasculature.\textsuperscript{105} OCT angiography minimizes the pulsatory bulk motion noise along the axial direction and optimizes flow detection along the transverse direction.\textsuperscript{108} As with all measuring techniques, OCT angiography has limitations. One of the main disadvantages is that blood flow from superficial layers can be projected to deeper layers, thereby incorrectly indicating that the imaged blood flow is a few layers deeper than its location in vivo.\textsuperscript{108} Also, split-spectrum amplitude-decorrelation angiography cannot distinguish between perfusion defects caused by damaged tissue or ischemia,\textsuperscript{105} and ONH blood flow estimates are provided in arbitrary units. Despite these limitations, OCT angiography is a very useful tool to measure blood flow in the ONH.

3.3. Color Doppler imaging

Color Doppler imaging (CDI), also known as color Doppler ultrasound, is a noninvasive procedure that allows the user to visualize a color-coded image of blood velocity against a grayscale image of the surrounding structures. This technique uses the principle of Doppler frequency shift to measure blood flow velocity in absolute units. Various transducers are used to measure the Doppler frequency shift, which produces color pixels.\textsuperscript{239} The color red represents blood flowing toward the ultrasound probe, whereas blue represents blood flowing away from the probe.\textsuperscript{214}

CDI is most commonly used to measure the peak systolic velocity (PSV) and end diastolic velocity (EDV), which are then used to measure the resistive index [RI = (PSV – EDV)/PSV] and pulsatility index [PI = (PSV – EDV)/Tmax, where Tmax is the time averaged peak velocity]. These values estimate resistance to blood flow caused by the microvasculature distal to the site of measurement. The RI is particularly suitable for investigating the low resistance retrobulbar vasculature.\textsuperscript{239} The major advantages of CDI are that it is noninvasive, vessel selective, reproducible, and does not require pupil dilation, clear media, or fixation. CDI is limited in its ability to measure only velocity (not flow) and calculate vascular resistance and requires for an experienced operator to obtain accurate results.\textsuperscript{87} CDI has particular difficulty imaging and interpreting small vessels, and the PCAs are close to the size limit that can be studied.

3.4. Laser speckle flowgraphy

Laser speckle flowgraphy (LSFG) is a noninvasive method of measuring blood flow and velocity in the ONH. LSFG measures blood flow by using the laser speckle phenomenon, which is an interference event that occurs when laser light scatters off of a diffusing tissue. This creates a speckle pattern that varies in proportion to the velocity of red blood cells and thus represents capillary blood flow. The faster the velocity of the red blood cells, the greater the rate of pattern variation. Although the velocity cannot be measured directly, the normalized blur and square blur ratio values can be calculated as quantitative indicators of blood velocity. Normalized blur values are well correlated with blood flow measurements simultaneously taken with the hydrogen gas clearance method, colored microspheres technique, and other methods in the ONH, iris, choroid, and retina.\textsuperscript{218,220–226} The distribution of blood flow can be displayed in a 2 dimensional color-coded map, which reflects the time variation of the speckles at each pixel point.\textsuperscript{217} This allows for visualization of blood flow in real time.

LSFG uses a diode laser, image sensor, infrared charge-coupled device camera, and digital charge-coupled device camera. The diode laser and image sensor are used for laser speckle measurements. The laser is focused on the image sensor and creates a speckle pattern, which is scanned at 512 scans/second.\textsuperscript{217} The digital charge-coupled device camera measures vessel diameter and takes pictures of the fundus.

The advantages of LSFG are that its results are adequately reproducible and that the change in velocity at the same site of the same eye can be followed over time. A major disadvantage of LSFG is that the meaning of its measurement is not clearly understood and does not allow for intereye or interindividual comparisons.\textsuperscript{87}

4. Evidence of blood flow autoregulation in the ONH

Autoregulation is the intrinsic ability of vascular beds to maintain relatively constant blood flow over a large range of pressure, while meeting the metabolic demand of the tissue. Autoregulation is evaluated most often on a flow versus pressure graph, where pressure may be expressed as mean arterial pressure (MAP), IOP, or ocular perfusion pressure (OPP) (see Fig. 6).

OPP refers to the arterovenous pressure difference driving blood flow through the intraocular vasculature. The intraocular venous pressure is very close to IOP,\textsuperscript{15,46,73,81} and thus, OPP is usually estimated as the difference between the arterial BP and IOP in the upright position. OPP may be defined as mean, systolic, or diastolic OPP. Mean OPP is typically calculated as
mean OPP = \frac{2}{3} MAP – IOP

where
MAP = diastolic BP + \frac{1}{3} (systolic BP – diastolic BP).

The factor 2/3 accounts for the drop in BP between the brachial and ophthalmic artery when the subject is seated\(^ {182}\) and the fact that the orbital arteries are further downstream. In clinical studies, the brachial arterial pressure has been often considered as representative of systemic BP and is used as the basis for calculating the ophthalmic arterial pressure in the calculation of OPP. The pressure in the brachial artery, however, is not a precise predictor of the pressure in the ophthalmic artery. It is not clear how accurately the above formula approximates the difference between the ocular arterial BP and the brachial arterial pressure because of the hydrostatic column effect when an individual is sitting.\(^ {30}\) We also cannot assume that the difference between the ocular and brachial arterial pressures is the same in normal and diseased vascular beds. Moreover, blood flow is determined not only by OPP but also by vascular tone. Regulation of blood flow may occur through changes in vascular resistance (vasoconstriction or vasodilation, see section 5) independently of changes in OPP. Physical exercise may or may not cause a change both in cardiac output and in the net resistance of the many microvascular pathways in parallel. Equating venous pressure to IOP is also sometimes erroneous. For example, if the cerebrospinal fluid pressure is higher than IOP, the venous pressure must exceed cerebrospinal fluid pressure in the subarachnoid space for the CRV to remain patent, and thus venous pressure could not be approximated by IOP. In this way, the estimate for OPP involves systematic errors; however, even if more reliable formulas for computing the OPP have been proposed, the previously mentioned relations are consistently used in clinical studies. A reliable, direct measure of OPP would of course be desirable, but without this, care is needed when interpreting blood flow regulation studies.

4.1. Evidence of ONH autoregulatory capacity during OPP changes in healthy subjects

In several animal\(^ {70,186,212}\) and human studies,\(^ {166,181}\) the ONH vascular bed was shown to maintain autoregulatory capacity over a wide range of perfusion pressures. Autoregulatory capacity is conventionally assessed by a “two-point” blood flow measurement: blood flow or other hemodynamic parameters are measured before and after the OPP is artificially modified by a step challenge in either the IOP or the systemic arterial BP. If blood flow changes significantly from normal after the pressure challenge, then autoregulation is said to be impaired; if blood flow remains nearly constant over the pressure change, autoregulation is said to be intact.

When the pressure step challenge is applied rapidly, it induces 2 phases of hemodynamic response: 1) an initial transient, or dynamic, phase lasting a few seconds during which the vasculature tries to return blood flow to its original level by adjusting vascular resistance and 2) a steady-state phase when transient blood flow changes have equilibrated to a steady-state level. High temporal resolution blood flow measures made during the initial phase following pressure changes are referred to as dynamic autoregulation (dAR), whereas those made during the steady-state phase are referred to as static autoregulation (sAR).\(^ {120}\) To date, most studies assessing autoregulatory capacity in the ONH have been limited to sAR.

In this section, some important clinical studies that address dAR and sAR in the ONH in healthy conditions are reviewed.

4.1.1. Dynamic autoregulation studies

The dAR refers to the transient vascular changes preceding the equilibrated steady state. Interestingly, dAR was pointed out as a more sensitive indicator of cerebral blood flow autoregulation than sAR since dAR is better correlated to neuronal activities than sAR.\(^ {160,191}\) Moreover, a dynamic blood flow response contains both time and frequency information that can effectively reveal potential autoregulation dysfunction. In fact, dAR measurements have become the standard method for assessing cerebral blood flow autoregulation in cerebral diseases.\(^ {230}\)

A blood flow time course similar to that described in the brain was observed in the ONH of rabbits\(^ {220}\) and nonhuman primates\(^ {115}\) after an acute increase in IOP. The time course of relative ONH blood flow changes from baseline (IOP = 10 mm Hg) to elevated IOP (IOP = 30 mm Hg), and then back to baseline, was tracked for 3 different ranges of BP in monkeys.\(^ {119}\) In the high-BP group, there was no significant change in ONH blood flow during the IOP alterations; however, the same IOP alterations caused a significant ONH blood flow change in the 2 lower BP groups, suggesting that autoregulation of the ONH is deficient in the lower BP groups.

To characterize dAR in the ONH, time-domain parameters were extracted from high temporal resolution blood flow measurement obtained using an LSFG device in a group of monkeys.\(^ {120}\) A rapid OPP decrease induced by a sudden IOP step increase evoked a transient and reproducible dAR in the ONH. The duration of blood flow decrease was much shorter.
than that of the pressure change. In other words, while the IOP was still increasing, the blood flow had already started recovering. This observation suggests that autoregulation is activated immediately after IOP elevation.

Responses of OPP, ONH blood flow, and vascular resistance to increases in BP were investigated by hand gripping. BP and ONH blood flow parameters were simultaneously and continuously measured by LDF. Healthy subjects could be subdivided into 2 groups because of marked differences in the efficiency and OPP range of autoregulation: in one group, autoregulation was found to be highly efficient once OPP was increased by approximately 15% above baseline; in another group, autoregulation was found to be less efficient. These findings are in accordance with other studies.

The sAR studies mentioned above are summarized in Table 3.

4.1.2. Static autoregulation studies

The sAR refers to steady-state responses of ONH blood flow to a wide range of OPP values. These responses constitute a classic autoregulation curve or pressure-flow relationship (see Fig. 6). This plateau of the autoregulation curve indicates the range of OPP where autoregulation is functioning. When the OPP values are outside the range defined by this plateau, autoregulation fails and blood flow will gradually decrease or increase passively as OPP changes.

Microspheres were used to measure blood flow in the various compartments of the monkey optic nerve following manometric IOP elevation. Small changes in IOP which reduced OPP as low as 29 mm Hg had small effects on prelaminar blood flow. At OPP less than 29 mm Hg, prelaminar flow was proportional to OPP. Laminar blood flow was nearly unchanged even at high IOP (low OPP).

OPP was decreased by increasing IOP with a scleral suction cup in normal human subjects. An LDF probing laser beam was directed at the ONH tissue at temporal and nasal disk areas, at least 200 μm from the disk margin and outside the physiologic cup. Autoregulation was active for OPP values as low as 15–20 mm Hg (IOP = 40–45 mm Hg) or until IOP reached 45 mm Hg. Apparently, the ONH vasculature was not fully dilated at this point, because diffuse luminance flicker increased ONH blood flow even more. Regional variability in the degree of autoregulation has been reported. Some optic disk locations of some individuals appeared unable to regulate blood flow under even a minimal IOP challenge.

Effects of elevated OPP on the ONH blood flow of healthy volunteers were investigated by increasing MAP through isometric exercise (squatting). An LDF probing laser beam was directed at temporal disk areas of the ONH, at least 200 μm from the disk margin and outside of the physiologic cup. In the range of OPP between 56 ± 4 and 80 ± 5 mm Hg (30% ± 8%), there was no significant variation of mean velocity, volume, and flux of red blood cells, but vascular resistance increased by about 50%. These results suggest that the maintenance of constant blood flow is achieved by an increase in vascular resistance. Similar results were obtained in another study.

Regulation of ONH blood flow was investigated during combined changes in IOP and systemic BP. ONH blood flow was measured in monkeys using LSFG during artificial changes in IOP and BP. When IOP was increased to 30 mm Hg and MAP was normal (102 mm Hg), no significant change was observed in ONH blood flow, indicating that autoregulation was functioning. However, when IOP was increased to 30 mm Hg and MAP was reduced to 56 mm Hg, significant reductions in ONH blood flow were observed, suggesting that autoregulation was unable to maintain blood flow at low OPP. These blood flow results, as well as those obtained in other studies, must be interpreted in the context of where and how they were measured.

ONH blood flow was investigated in 40 healthy subjects using continuous LDF during a separate increase in IOP and MAP as well as during their combined elevation. The laser beam was directed toward the neurovascular rim. MAP was increased by isometric exercise consisting of squatting, and IOP was raised via suction cup. During both experiments, the change in ONH blood flow was less pronounced than the change in OPP, indicating autoregulation.

The sAR studies mentioned in the previous paragraphs are summarized in Table 4.

In Figure 7, OPP-ONH blood flow relationships reported in a few studies have been gathered. Each data set has been normalized to its corresponding baseline OPP and ONH blood flow estimate. Care is needed to interpret this figure correctly. First, different species and different techniques for estimating ONH blood flow were involved in these 6 studies. Second, in one study, monkeys were supine,

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**Table 3 – Summary of dynamic autoregulation studies in healthy subjects**

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<tr>
<td>Liang et al</td>
<td>Sudden IOP step increase in monkeys</td>
<td>LSGF</td>
<td>While the IOP was still increasing, the blood flow had already started recovering</td>
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</table>

BP, blood pressure; IOP, intraocular pressure; LDF, Laser Doppler flowmetry; LSFG, laser speckle flowgraphy; MAP, mean arterial pressure; ONH, optic nerve head; OPP, ocular perfusion pressure.
whereas, in the others, human volunteers were standing. Third, some data were obtained by increasing IOP, whereas other data were obtained others by increasing MAP. Last, displaying all the data in a single graph presumes the use of a common baseline. Despite these limitations, Figure 7 shows that the static OPP-blood flow curve in the ONH is consistent with the curve schematized in Figure 6.

On reviewing a number of clinical studies addressing dynamic and static blood flow autoregulation in the ONH in healthy conditions, note the different sensitivity of autoregulation components. Dynamic and static aspects are 2 related, but different, components of the autoregulation process. Importantly, measuring dAR could succeed in revealing potential autoregulation dysfunction in situations where the conventional “two-point” method measured during the sAR phase would fail.

### 4.2. Clinical studies of static blood flow autoregulation in the ONH in pathologic conditions

Under pathologic conditions, ONH blood flow regulation may be disrupted. Impaired autoregulation in the ONH associated with altered blood flow has been observed in experimental diabetes and hypercholesterolemia. In glaucoma, and especially in NTG, impaired autoregulation in the ONH has been speculated to be an important risk factor for the progression of the disease. Glaucoma patients have been suggested to exhibit abnormal autoregulation especially in response to acute changes in OPP, as reviewed in the following paragraphs.

The autoregulatory control of retrobulbar blood flow in response to postural challenge was investigated in NTG patients in comparison with primary open-angle glaucoma patients and healthy volunteers. PSV, EDV, and RI in the short PCAs were recorded after a change from sitting upright to a supine body position using CDI. Ten minutes after postural change, blood flow velocities in the short PCAs remained unchanged in controls, whereas a significant increase of PSV and EDV occurred in both glaucoma groups. The RI in the short PCAs was significantly lower in the NTG group when compared to healthy and primary open-angle glaucoma individuals. The authors suggested that the unaltered flow velocities in the short PCAs of healthy controls might indicate tight autoregulatory control. In contrast, the accelerated flow in the short

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Table 4 – Summary of static autoregulation studies in healthy subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Technique</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geijer et al.70</td>
<td>IOP elevation in healthy monkeys</td>
<td>Microspheres</td>
<td>The laminar and retrolaminar portions of the ONH showed higher autoregulation capabilities than the prelaminar portion</td>
</tr>
<tr>
<td>Riva et al.181</td>
<td>IOP elevation in healthy humans</td>
<td>LDF</td>
<td>ONH blood flow was relatively constant to an OPP as low as 15–20 mm Hg</td>
</tr>
<tr>
<td>Pillunat et al.166</td>
<td>IOP elevation in healthy humans</td>
<td>LDF</td>
<td>ONH blood flow was regulated to an IOP up to 45 mm Hg</td>
</tr>
<tr>
<td>Movaffaghy et al.144</td>
<td>MAP was elevated in healthy humans</td>
<td>LDF</td>
<td>In the range of OPP between 56 ± 4 and 80 ± 5 mm Hg, there was no significant variation of mean velocity, volume, and flux of red blood cells, but vascular resistance increased by about 50% When IOP was increased to 30 mm Hg and MAP was normal (102 mm Hg), ONH blood flow did not change significantly. Instead, blood flow decreased when IOP was increased to 30 mm Hg and MAP was reduced to 56 mm Hg</td>
</tr>
<tr>
<td>Liang et al.119</td>
<td>Combined changes in IOP and MAP in monkeys</td>
<td>LSFG</td>
<td>When IOP was increased to 30 mm Hg and MAP was normal (102 mm Hg), ONH blood flow did not change significantly. Instead, blood flow decreased when IOP was increased to 30 mm Hg and MAP was reduced to 56 mm Hg</td>
</tr>
<tr>
<td>Boltz et al.24</td>
<td>Combined and separate IOP and MAP elevation in healthy humans</td>
<td>LSFG</td>
<td>ONH blood flow increased with OPP for OPP values of 66% above baseline. ONH blood flow decreased for OPP values of 40% below baseline</td>
</tr>
<tr>
<td>Wang et al.237</td>
<td>IOP elevation in monkeys</td>
<td>LSFG</td>
<td>ONH blood flow is effectively regulated for OPPs of approximately 41 mm Hg and above</td>
</tr>
</tbody>
</table>

IOP, intraocular pressure; LDF, Laser Doppler flowmetry; LSFG, laser speckle flowgraphy; MAP, mean arterial pressure; ONH, optic nerve head; OPP, ocular perfusion pressure.

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Fig. 7 – Pressure-flow relationships for ONH blood flow in 6 experimental studies in healthy monkeys (Geijer et al., circles and asterisks), and in healthy humans (Pillunat et al., squares), (Riva et al., downward-pointing triangles), (Movaffaghy et al., upward-pointing triangles), (Boltz et al., crosses). ONH, optic nerve head; OPP, ocular perfusion pressure.
PCAs exhibited by NTG and primary open-angle glaucoma patients might indicate an insufficient compensatory response to postural change. However, it is not clear to what extent these interpretations are consistent with the experimental data. It is unknown how the supine position affects intraocular venous pressure and, in turn, OPP.\textsuperscript{90} It is accepted that, in the supine position, there is a different interaction between orbital venous pressure and intraocular venous pressure than in the upright position. This interaction is affected by the tissue pressure, which experiences huge variations due to differences in body mass and the hydrostatic water column effect on venous pressure.\textsuperscript{26} Consequently, it is hard to establish how the supine position impacts OPP and, hence, blood flow.

Chronic unilateral elevation of IOP was induced in monkeys by laser treatment to the trabecular meshwork, leading to glaucomatous damage.\textsuperscript{234} The authors found compromised blood flow in the anterior ONH (including SNFL, prelaminar tissue, and lamina cribrosa) of glaucomatous eyes measured by both LSFG and the microsphere method. ONH blood flow was measured for IOP = 40 mm Hg in both control and glaucomatous eyes. In a parallel study, longitudinal changes in basal blood flow of the ONH were investigated in the same monkey model.\textsuperscript{47} There are a couple of possible explanations for the reduced flow observed in these 2 studies during the later stages of glaucoma. If there is a reduced amount of neural tissue requiring nutrition, the flow would be regulated to avoid supplying more blood than what is necessary for the remaining tissue. ONH blood flow could also be reduced if autoregulation is impaired.

There was no evidence of altered autoregulation in the ONH in glaucoma in some studies. Regulation of ONH blood flow in response to an increase of OPP was investigated through a challenge in systemic BP induced by isometric exercise in NTG patients and in age-matched healthy volunteers.\textsuperscript{171} ONH blood flow parameters, as determined by LDF, did not indicate abnormal blood flow regulation in either healthy subjects or NTG patients; however, NTG patients showed a greater percent increase in vascular resistance compared to the normal subjects for a similar percent increase in OPP in both groups during squatting.

To our knowledge, neither dynamic nor static mechanisms of ONH blood flow regulation have been quantified in patients with arterial hypertension. Arterial hypertension can potentially interfere with ONH blood flow in many ways.\textsuperscript{94} For example, atherosclerosis resulting from prolonged arterial hypertension can cause inadequate changes in vessel size in response to fluctuations in OPP.\textsuperscript{86} Chronic arterial hypertension can also cause the range of autoregulation to shift to higher levels to adapt to high BP.\textsuperscript{97} Such an adjustment makes subjects can cause anterior ischemic optic neuropathy.\textsuperscript{96,98} Systemic hypertension is associated with pathologic changes in retinal vasculature.\textsuperscript{123} Endothelial function of the retinal vasculature is impaired in early essential hypertension,\textsuperscript{90} and hypertensive retinopathy is associated with endothelial dysfunction\textsuperscript{111,112} (see section 5 for a discussion about the role of endothelial cells (ECs) in regulating blood flow). Hence, since systemic hypertension is linked to a wide range of major eye diseases, it is incredibly important to quantify its effects on ONH blood flow regulation.

In a study of the ONH of control and glaucomatous monkey eyes,\textsuperscript{237} static blood flow autoregulation was characterized, and impaired autoregulation was tested as a potential mechanism involved in the reduction of ONH blood flow observed in previous studies.\textsuperscript{57,234} Autoregulation curves were created based on a series of relative ONH blood flow changes, each measured with an LSFG device in response to an acute OPP decrease induced by instantaneous IOP elevation monitored across stages of glaucoma. Within the ONH of the control eyes, blood flow was effectively regulated within the OPP range from 41 mm Hg to 115 mm Hg. When OPP was below 41 mm Hg, blood flow declined linearly with OPP. Autoregulation curves of control and glaucomatous eyes were not significantly different from each other. Thus, the authors argued that aSR is not a predominant factor accounting for the reduced ONH blood flow observed in the monkey model.\textsuperscript{47,234}

All of these clinical studies addressing autoregulation in pathologic conditions are summarized in Table 5.

5. Mechanisms of blood flow regulation

Several important response mechanisms combine to cause changes in vascular tone that lead to blood flow regulation to a particular tissue. A complete overview of the biochemistry of all the mediators and modulators involved is beyond the scope of this review. We will focus on studies relevant for the control of blood flow in the ONH.

5.1. Mechanical influences

An important class of autoregulation is seemingly more dependent on mechanical influences. In the myogenic response, vascular smooth muscle cells constrict as intravascular pressure, and consequently the circumferential wall tension, is elevated. Indeed, circumferential wall tension depends on both the vessel radius R and transmural pressure $\Delta P$, defined as the difference between the intravascular and extravascular pressures. According to Laplace’s law, as $\Delta P$ rises, the vessel wall stretches, leading to increased wall tension $T$:

$$ T = \Delta P \times R. $$

In the myogenic response, arterioles respond to the increased wall tension by constricting to reduce the vessel radius R and restore the wall tension to a normal level. The myogenic response has been observed in the ONH. More effective blood flow autoregulation was observed in the ONH of healthy humans during an increase in MAP than IOP.\textsuperscript{24} Such behavior could be compatible with a myogenic mechanism of autoregulation.

The contractility of smooth muscle cells involved in the myogenic response is regulated by ECs. In addition to chemical agents, ECs respond to mechanical stimuli, such as fluid shear stress and stretch.\textsuperscript{38} Externally applied forces with a clear direction, such as shear stress from pulsatile flow or uniaxial stretch, induce the release of vasoactive substances which then
determine ECs remodeling. This remodeling phenomenon includes changes in the orientation of ECs cytoskeletal fibers, the morphology of cell surface and/or cell stiffness to minimize the alterations in intracellular stress. Whereas ECs remodeling results from molecular signaling due to mechanical influences, this adaptive behavior, in turn, modulates the molecular signaling. Thus, a close coupling exists between mechanics and vascular endothelium. In addition, experiments have shown that myogenic tone of the PCAs is regulated by NO, which has a short half-life, which is made even shorter in the presence of oxygen and superoxide and longer in the absence or lower concentrations of oxygen. Because NO cannot be stored in vivo, regulation of NO production is controlled at the level of the biosynthesis. Hence, NO synthesis largely depends on the amount of nitric oxide synthase (NOS). Inhibiting NOS in cats resulted in a decrease in ONH blood flow, both at baseline and with light flicker stimulation (NOS). Inhibiting NOS in cats resulted in a decrease in ONH blood flow, both at baseline and with light flicker stimulation.

### 5.1.1. Nitric oxide and endothelin-1

Two important vasoactive substances released by the ECs after local stimulation by, for example, shear stress from pulsatile flow or uniaxial stretch, are nitric oxide (NO) and endothelin-1 (ET-1). A constant balance between the opposing functions of NO and ET-1 is necessary for proper regulation of the vascular system. NO is a potent vasodilator secreted by smooth muscle cells that causes the dilation of arterioles via activation of smooth muscle cells and the dilation of capillaries via pericytes. Owing to the radical nature of NO, it has a short half-life, which is made even shorter in the presence of oxygen and superoxide and longer in the absence or lower concentrations of oxygen. Because NO cannot be stored in vivo, regulation of NO production is controlled at the level of the biosynthesis. Hence, NO synthesis largely depends on the amount of nitric oxide synthase (NOS). Inhibiting NOS in cats resulted in a decrease in ONH blood flow, both at baseline and with light flicker stimulation.

**Table 5 – Autoregulation studies in pathologic conditions**

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Technique</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pournaras et al</td>
<td>MAP elevation in NTG patients</td>
<td>LDF</td>
<td>NTG patients did not show abnormal ONH blood flow regulation but only a greater percent increase in vascular resistance compared to healthy subjects</td>
</tr>
<tr>
<td>Galambos et al</td>
<td>Investigation of autoregulatory control of retrobulbar blood flow in response to postural changes in NTG and POAG patients</td>
<td>CDI</td>
<td>NTG and POAG patients exhibited an insufficient compensatory response to postural change, leading to accelerated flow in the short PCAs</td>
</tr>
<tr>
<td>Shibata et al</td>
<td>IOP elevation in hypercholesterolemic rabbits</td>
<td>LSFG</td>
<td>Hypercholesterolemia induced impairment in the autoregulation of ONH blood flow and deterioration in visual function and histology</td>
</tr>
<tr>
<td>Shibata et al</td>
<td>IOP elevation in rabbits with induced diabetes and induced gap junction uncoupling</td>
<td>LSFG</td>
<td>Autoregulation was disrupted both in the animals who were induced diabetes and in those who received gap junction uncouplers</td>
</tr>
<tr>
<td>Wang et al</td>
<td>Chronic unilateral IOP elevation induced in monkeys by laser treatment to the trabecular meshwork</td>
<td>Microspheres and LSFG</td>
<td>Blood flow was compromised in the SNFL, prelaminar, and laminar tissues, possibly due to impaired autoregulation</td>
</tr>
<tr>
<td>Cull et al</td>
<td>Chronic unilateral IOP elevation induced in monkeys by laser treatment to the trabecular meshwork</td>
<td>LSFG</td>
<td>A 2-phase pattern of ONH blood flow alteration was observed in treated animals. ONH blood flow during the earliest stage (while retinal nerve fiber layer thickness was within 10% of baseline) followed by a linear decline strongly correlated with loss of RGCs</td>
</tr>
<tr>
<td>Wang et al</td>
<td>Chronic unilateral IOP elevation induced in monkeys by laser treatment to the trabecular meshwork</td>
<td>LSFG</td>
<td>Chronic IOP elevation caused no remarkable change to the static autoregulation of glaucomatous eyes</td>
</tr>
</tbody>
</table>

CDI, Color Doppler imaging; IOP, intraocular pressure; LDF, Laser Doppler flowmetry; LSFG, laser speckle flowgraphy; MAP, mean arterial pressure; NTG, normal tension glaucoma; ONH, optic nerve head; PCA, posterior ciliary artery; POAG, primary open-angle glaucoma; RGC, retinal ganglion cell; SNFL, superficial nerve fiber layer.
5.2. Metabolic response

Metabolic regulation results in the adjustment of blood flow during inadequate or excessive nutrient supply, because of either a change in the metabolic activity of the tissue or a change in flow by virtue of cardiovascular factors such as atherosclerosis or systemic vasospasm. No matter the cause, when tissues are not receiving the appropriate amount of blood flow, an adjustment is made by control mechanisms. Overall, the vascular response to tissue demand is influenced by the metabolic conditions in the tissue such as levels of oxygen, carbon dioxide levels (mediated by pH), NO, ET-1, and other chemical signals. For example, when the eye is exposed to a flickering light, the number of action potentials and the consequent need for (re)polarization of the RGC axon membranes in the ONH is increased with each “on” and “off” light switch. In response to this increased metabolic demand, blood flow in the ONH appears to increase. Importantly, metabolism in the various parts of RGC axons may be controlled independently. In the prelaminar and lamina cribrosa regions, RGC axons are unmyelinated and acquire a myelin sheath only after passing the posterior boundary of the lamina cribrosa. The unmyelinated portions of the axons are in need of energy to repolarize the axons along the entire surface, whereas, in the myelinated portion, only the axons at the nodes of Ranvier need to be repolarized. Thus, mitochondria are numerous and metabolic activity is much higher in the unmyelinated nerves, but less in the myelinated portion. According to the metabolic hypothesis of blood flow regulation, tissue perfusion and tissue metabolism are tightly coupled in such a way that any reduction in arterial inflow causes an increase of vasodilator metabolites in the tissue.

5.2.1. Oxygen

All living tissues require a steady supply of oxygen to meet, but not exceed, their nutritional needs. Oxygen tension in a tissue provides an important indication of its current metabolic status. In hypoxic conditions, ONH blood flow is regulated to establish a healthy partial pressure of oxygen in the tissue. Under moderate hypoxic conditions, the intravascular tissue’s partial pressure of oxygen at 200 μm depth within the ONH was observed to be constant, reflecting, probably, autoregulation of blood flow. Decreased partial pressure of oxygen was found in the ONH when IOP was increased (OPP was decreased) above 45 mm Hg. Both oxygen metabolism in the mitochondria of optic nerve cells and tissue oxygen tension were observed to decrease when hypoxia was induced. In contrast, under hypoxic conditions, capillary blood flow in the ONH decreases via vasoconstriction.

5.2.2. Carbon dioxide

CO₂ is a vasodilator in all vascular beds at the posterior pole of the eye. The mechanisms driving this vasodilation response are not clearly understood. In human and animal studies, hypercapnia-induced vasodilation was shown to depend on NO, whereas, in other animal studies, the vasodilation was shown to be independent of NO. Hypercapnia triggers an increase in flow to the short PCAs. Patients with untreated primary open-angle glaucoma have shown a normal increase in the blood velocity of the CRA with hypercapnia, but a decrease in blood velocity in the OA. Although the preponderance of data suggests that blood vessels dilate or constrict in response to CO₂ levels, it is possible that hypercapnia-induced vasodilation is mainly because NO is brought into play by lowered levels of oxygen, which would increase NO half-life. Future research further defining the mechanisms of this is needed.

5.2.3. Nitric oxide

NO was shown to mediate vasodilation in response to marked hypoxia in the forearm resistance vessels in healthy humans and in response to increased myocardial oxygen demand. As mentioned in the previous sections, the role of NO in hypercapnia-related vasodilation is not clearly understood.

5.3. Neurovascular coupling

Experiments measuring vascular responses to light stimulation have suggested that ONH blood flow and neuronal activity of RGCs are coupled. Traditionally, in the ONH and other regions like the retina and the brain, vascular responses to changes in neural activity were assumed to be controlled exclusively by a local metabolic feedback system in which neural activity leads to energy demand and thus vasodilation. This idea has been challenged, however, following the discovery that feedforward mechanisms mediate the vascular energy supply by neuronal activity. According to these mechanisms, active neurons either send a signal directly to blood vessels or activate astrocytes to release vasoactive agents onto the vessels to increase local blood flow, a process known as “functional hyperemia.” Both cases involve neurotransmitter signaling, particularly via glutamate. In the brain, blocking glutamate receptors reduces functional hyperemia but does not affect the energy use associated with neuronal activity, providing evidence that metabolic feedback and neurovascular feedforward mechanisms can be distinguished and both contribute to blood flow regulation in response to neuronal activity. The interplay between metabolic feedback and neuronal feedforward mechanisms should then be taken into account whenever considering clinical studies addressing ONH vascular responses to light stimulation.

Astrocytes exhibit extremely complex and dynamic behaviors. One of their functions is to control the extracellular environment for neurons; for example, by clearing the space of glutamate that leaks from synapses. Astrocytes also play a fundamental role in regulating blood flow to the brain. Astrocytes are the predominant glial cell type in the nonmyelinated ONH in most mammalian species. Structural similarities suggest that retinal and ONH astrocytes may behave similarly to cerebral astrocytes. Retinal and ONH astrocytes surround blood vessels, and this close relationship further supports a potential contribution of astrocytes to blood flow regulation in the retina and ONH.

There is evidence of neurovascular coupling in the retina and ONH occurring via glial signaling mediated by vasoactive
agents released onto the vessels (not through nerve fibers and synapsis with glutamate receptors on contractile cells). The retinal vascular branches are devoid of such innervation once they emerge onto the retinal surface, although the CRA within the intraorbital optic nerve is innervated.243 Yet, retinal vessels do retain receptors for various neurotransmitters on their surface.58,104 To our knowledge, the innervation of the arteriolar branches of the ONH has not been studied yet. Future research further elucidating the mechanisms of neurovascular coupling in the retina and the ONH is essential.

Axon-glia signaling pathways have been observed in the optic nerve.41,64,107 Following IOP elevation, autoregulation of ONH blood flow was not maintained in rabbit eyes where glial cells were selectively impaired by a gliotoxic compound, l-2-amino adipic acid, indicating a possible involvement of astrocytes in ONH blood flow autoregulation.206 The cell processes of astrocytes are connected to each other via gap junctions forming a functional syncytium that allows astrocytes to communicate and maintain control of the ionic and metabolic homeostasis in the ONH. Decreased gap junction communication between ONH astrocytes was reported under conditions of elevated IOP.131 Closure of gap junctions interrupts the continuity of astrocyte intercellular communication, causing loss of cell-cell contact and homeostatic regulation. Uncoupling gap junctions resulted in impaired ONH blood flow autoregulation in healthy rabbits.204 Such conditions may lead to RGC axonal loss and optic disk remodeling characteristic of glaucomatous optic neuropathy.100

In studies on brain slice and isolated retina, evidence is found that astrocytes contribute to blood flow regulation by producing and releasing metabolites of arachidonic acid. After glutamate is released at synapses following neuronal activity, some of the released neurotransmitter escapes the synaptic cleft and activates metabotropic glutamate receptors on astrocytes, increasing Ca\(^{2+}\) in astrocytes.170 The increased Ca\(^{2+}\) activates phospholipase A\(_2\) and results in arachidonic acid production. The build-up of arachidonic acid leads, in turn, to the production of its metabolites, including prostaglandin E\(_2\) and epoxyeicosatrienoic acids (EETs), which dilate vessels and relaxes vascular smooth muscle cells, leading to vasodilation and increased blood flow.34 NO has also been suggested to mediate neurovascular coupling in the ONH. Increased NO levels were found in the ONH of humans during changes in neuronal activity due to light flicker stimuli.26 In addition, in the retina of humans33 and the retina and the ONH of cats,114 systemic administration of nonselective NOS inhibitors reduces flicker-evoked increases in blood flow. These results would appear to support NO as an important mediator of neurovascular coupling in the retina and the ONH. However, evidence has been found that NO could be predominantly a modulator of neurovascular coupling, but not a mediator. In the whole-mount rat retina,138 at NO levels less than 100 nmol/L, flickering light-induced vasodilation, but not vasoconstriction. At increased NO levels, smaller vasodilation was observed, while vasoconstriction became more common. At 10 µmol/L NO, a flickering light evoked large vasoconstriction, mediated by 20-HETE. It is still not clear how NO inhibits flicker-induced vasodilation. The modulatory mechanism of NO has been suggested to be due to its inhibitions of P450 epoxygenase, which synthesizes the vasodilator EETs. With less EETs being produced, vasodilation will be smaller and vasoconstriction mediated by 20-HETE will prevail.148

5.3.3. Adenosine

Adenosine, which is produced when adenosine triphosphate is hydrolyzed, is a vasodilator that contributes to functional hyperemia in the human brain. Blocking adenosine receptors has been shown to reduce the increase in blood flow evoked by neuronal activity.113 Given its function in the brain, adenosine is also thought to be involved in the control of ocular blood flow. Intravenous administration of adenosine was shown to cause increased choroidal and ONH blood flow in humans168 and was established as an important participant in mediating retinal blood flow autoregulation during hypoxia and hypotension in piglets.71

5.3.4. Lactate

Lactate, which is produced by anaerobic glycolysis and released by both glial cells and neurons, is thought to contribute to neurovascular coupling as a metabolic negative-feedback mediator. Blood flow in the human retina is sensitive to changes in blood lactate levels.69 but lactate responses in the ONH have not been established yet.

5.3.5. Oxygen

Oxygen modulates neurovascular coupling in brain tissue by altering the synthesis of glial and neuronal messengers and by altering the levels of lactate and adenosine. O\(_2\) is needed for
the synthesis of NO and the vasoactive messengers derived from arachidonic acid. At in vivo levels of O₂, the synthesis of NO and 20-HETE is expected to be limited by the amount of O₂ available. More specifically, 20-HETE formation is suppressed in the presence of low O₂ concentrations, leading to a reduced vasoconstriction when arachidonic acid is generated in astrocytes. A lower O₂ also results in a reduced amount of NO being present to inhibit the formation of vasodilatory EETs in tissues. In addition, when O₂ concentrations decrease, the lack of energy for adenosine triphosphate synthesis causes an increase in the level of extracellular adenosine, which binds to adenosine A₂A receptors on vascular smooth muscle cells to depress vessel constriction. Moreover, low oxygen concentrations induce a decrease in the rate of oxidative phosphorylation relative to the rate of glycolysis, resulting in lactate production. Monocarboxylate transporters release the lactate into the extracellular space, where it reduces the reuptake of prostaglandin E₂ by the prostaglandin transporter, promoting vasodilation. Importantly, it is possible that oxygen modulates neurovascular coupling by affecting NO half-life. Future research to further elucidate the mechanisms involved is needed.

5.4. The anatomic agents of blood flow regulation in the ONH

Understanding which vessels in the ONH exhibit blood flow regulation is still an open problem. In general, the structures that control blood flow to a particular tissue are the resistance arterioles (arterial branches smaller than 40 μm), which change diameter actively to achieve autoregulation. Capillaries have smaller diameters than arterioles. Because resistance to flow is inversely proportional to the fourth power of the vessel radius (Poisuille’s law), capillaries exhibit high resistance individually; however, they are numerous and in parallel array outweigh the reduction in vessel size, having a large cross-sectional area that does not contribute much to the net resistance between arteries and veins. In addition to the arterial role in autoregulation, flow to a local capillary network is controlled by a precapillary sphincter (where it exists), a band of smooth muscle located where capillaries originate from small arterioles. Finally, blood flow could also be controlled by changes in the resistance of the capillaries themselves because of the contractile properties of pericytes. The retinal and optic nerve capillaries lack precapillary sphincters but have abundant pericytes.

It has been shown that pericytes respond to carbon dioxide concentrations (mediated by pH), oxygen levels (affected by changes in NO concentrations), and adenosine levels. Vascular smooth muscle cells respond in a very similar manner. Pericytes on isolated retinal capillaries were found to constrict or dilate in response to neurotransmitters, following Ca²⁺ alterations. In situ in brain slices, pericytes constricted in response to noradrenaline and dilated in response to glutamate, and in the isolated retina, blocking ionotropic receptors of the neurotransmitter γ-aminobutyric acid was shown to constrict capillaries, suggesting that endogenous transmitter release could regulate capillary diameter. Thus, capillaries are equipped to participate in the control of ONH blood flow through metabolic feedback and neuronal feedforward coupling mechanisms, but this still needs to be further investigated.

In contrast to retinal capillaries, choroidal capillaries are fenestrated and have sparse pericytes. The retinal tissue, part of the central nervous system, has a preserved blood-brain barrier due to the tight junctions between the retinal pigment epithelial cells. Circulating vasoconstrictive hormones, such as angiotensin, epinephrine, and so forth, raise intracellular Ca²⁺ when they occupy receptors. In vascular smooth muscle, as well as in pericytes, an increase of intracellular Ca²⁺ induces contraction of the cell. Consequently, ECs produce more NO, which relaxes vascular smooth muscle and pericytes. In this way, the circulating hormones leak through fenestrated vessels, 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 ECs and are prevented from reaching the contractile coat of the vessels to the blood-tissue barrier, exhibit vasodilation. It is unclear whether the branches of the PCAs that feed the intrascleral portion of the optic nerve are innervated and/or fenestrated. Such knowledge is fundamental to understand how the intrascleral papillary tissue reacts to various insults, including abnormally high IOP.

6. Pathologic effects of impaired blood flow regulation in the ONH

Impaired blood flow regulation has been suggested to render the ONH more susceptible to damage by compromising blood supply (leading to ischemia) and, consequently, oxygen delivery (leading to hypoxia) in potentially dangerous situations of reduced BP, increased IOP, and/or increased local metabolic demands. However, the mechanisms through which the damage occurs are still not completely understood. Evidence suggests that ischemia and related hypoxia might influence the astrocytes in the ONH and/or the mitochondria of RGC axons, and that the ultimate death of RGCs can occur via apoptosis and/or autophagy.

Astrocytes in the ONH are considered to be quiescent in normal conditions, but they appear to become reactive in response to pathologic conditions and contribute to changes in the ONH environment, which do not favor the survival or growth of the RGC axons. During ischemia, hydrogen peroxide was observed to be abundantly produced and to promote pathologic excitatory amino acid release and swelling of reactive astrocytes. In glaucoma, ONH astrocytes were observed to have lower basal levels of antioxidant glutathione, which plays an important role in protecting the mitochondrial electron transport chain from damage by oxidative stress in both astrocytes and neurons. Evidence suggests that reactive astrocytes also produce NO in supra-normal quantities, and this excessive production seems to have neurotoxic effects on the RGC axons. Ischemia, hypoxia, and perfusion instability can also damage the astrocyte-astrocyte gap junctions, and, as a consequence, compromise the homeostasis of the RGC axons and...
reduce the autoregulation capabilities of the ONH vasculature, thereby rendering the ONH even more susceptible to damage.

Impaired autoregulation might also cause perfusion instability in the ONH, which, in turn, might compromise the normal function of mitochondria in the RGCs and their axons. Mitochondria play a critical role in the maintenance of cellular homeostasis and they are abundantly present in the RGCs, both inside and outside the eye globe. Mitochondria are involved in numerous metabolic functions, including the metabolism of oxidative energy, the regulation of intracellular calcium levels and pH, and the production of reactive oxygen species, which promote and regulate apoptosis. Apoptosis ("self-killing") and autophagy ("self-eating") are 2 different mechanisms that regulate cell life. The relationship between apoptosis and autophagy is complex in the sense that, under certain circumstances, autophagy constitutes a stress adaptation that avoids cell death (and suppresses apoptosis), whereas in other cellular settings, it constitutes an alternative cell-death pathway. Ischemia and hypoxia increase the reactive oxygen species production rate from mitochondria and favor the mitochondria-mediated cellular apoptosis; however, reactive oxygen species accumulation stimulates cellular autophagy under conditions of nutrient deficiency. Hypoxia, ischemia, and perfusion instability and other pathologic conditions.

7. Mathematical modeling of ONH blood flow regulation

In the previous sections, we have reviewed experimental and clinical evidence of blood flow autoregulation in the ONH, the mechanisms contributing to autoregulation and the pathologic consequences of vascular dysregulation. Despite significant recent advances in the understanding of ONH blood flow autoregulation, important questions remain unanswered. What are the relative contributions of various mechanisms, including responses to mechanical, metabolic, and neurovascular stimuli, in achieving ONH blood flow autoregulation? Do these relative contributions change in health and disease? Is the vascular energy supply by neural activity in the ONH mediated by feedforward mechanisms, as it happens in the brain? Are capillaries involved in ONH blood flow autoregulation? To which extent do impairments in DAR and sAR mechanisms contribute to glaucomatous damage? Can dynamic and static mechanisms be independently impaired?

The quest for answers to these questions is hindered by limitations in both the technological and scientific tools currently available to the community. Major limitations in the current technologies for ONH measurements include the fact that LDF, LSFG, and OCT angiography only provide ONH blood flow estimates in arbitrary units and intereye comparison is problematic. LDF appears to be mainly influenced by blood flow changes in the more superficial layers of the ONH than deeper ones, but to what extent remains uncertain. OCT angiography provides measurements for the ONH deeper layers which may contain spurious projections from the superficial layers. In addition to the difficulties related to structural and functional imaging of the ONH, there are scientific challenges in designing experimental and clinical studies capable of disentangling the complex interplay between chemical, mechanical, and hemodynamic factors that contribute to the pathogenesis of optic neuropathies. Given these challenges, mathematical modeling provides a unique tool that can play a significant role in advancing the understanding of ONH physiology in health and disease. A mathematical model can serve as a virtual laboratory where the influence of each factor acting on the system can be singled out and investigated, from a theoretical viewpoint, in isolation or in relation with other factors. In the following, we review the main contributions to the modeling of the biomechanics, perfusion, and autoregulation in the ONH and indicate some interesting future directions of research.

7.1. Biomechanics of the ONH

Alterations in the ONH biomechanical response to changes in IOP have been identified as a major factor in the pathogenesis of glaucoma. Particular attention has been devoted to the mathematical description of the mechanical stresses and strains arising within the lamina cribrosa, which is thought to be a primary site of axonal injury in glaucoma. A linear model of elastic mechanics theory on the bending of thin circular plate was developed for the lamina cribrosa. Such an idealization allowed quantitative estimates to be obtained of the extent to which the degree of fixity offered by the connection with the sclera, the pretension caused by scleral expansion, and the ratio between flexural and in-plane stiffness influence the mechanical response of the lamina cribrosa to IOP. An idealized, analytical microstructural model of the ONH load bearing tissues based on an octagonal cellular solid description of the porosity within the lamina identified the material and geometrical properties of the sclera as major determinants in the strain distributions within the lamina. The analysis also showed that much larger strains are developed perpendicular to the major axis of an elliptical canal rather than in a circular canal. Eye-specific finite element models based on experimentally reconstructed geometries have been used recently. These models are used to study in depth influences of geometry and material properties of the ONH to changes in IOP and to investigate growth and remodeling mechanisms in glaucoma, including adaptation of tissue anisotropy, tissue thickening/thinning, tissue elongation/shortening, and tissue migration. Macro- and micro-scale strains are proposed as potential control mechanisms governing mechanical homeostasis. Further development of these sophisticated finite element models may benefit from the recent advances in OCT imaging aimed at providing a more accurate characterization of the architectural microstructure within the lamina cribrosa.

7.2. Perfusion of the ONH

Perfusion of the ONH results from the complex interplay between BP, which provides the driving force for the blood flow.
through the vasculature, “mechanical stress,” which acts as external forces on the vessels, and “vascular regulation,” which mediates vessel dilation/constriction to compensate for changes in the system. To the best of our knowledge, only one model combines biomechanics and hemodynamics in the lamina cribrosa. In this model, the lamina cribrosa is treated as a 2-dimensional poroelastic material, where blood vessels are viewed as pores in a solid matrix. The presence of blood vessels in the tissue defines a vascular porosity N which changes with the local state of stress and strain. The tissue permeability, which defines the ability of the porous material to allow fluid passing through it, is assumed proportional to the square of N; the solid matrix is assumed to behave as nonlinear elastic material. Blood flow is driven by the difference between the arterial pressure in the short PCAs and the venous pressure in the CRV. The lamina cribrosa deforms under the combined action of IOP, retrolaminar tissue pressure and scleral tension. This exploratory 2-dimensional analysis suggested that the degree of fixity at the conjunctiva with the sclera has a strong influence on the distributions of stresses and strains, as suggested in other studies, but also on the blood flow within the lamina. In particular, the inner surface of the lamina was found to be more susceptible to experiencing reduced blood supply following IOP elevation. Despite the many simplifying assumptions adopted in the model, most importantly the choice of a 2-dimensional geometry, the satisfactory qualitative agreement between experimental data and numerical simulations encourages further investigation of poroelastic models to describe the complex mechanisms governing ONH perfusion.

7.3. Autoregulation of ONH blood flow

Mathematical models have been used to describe autoregulation of blood flow in various organs, including brain, kidney, and skeletal muscle. To date, though, the theoretical modeling of autoregulation in the ONH has not yet been addressed. Our group has developed a vascular wall mechanics model to predict the relative importance of regulatory mechanisms in achieving blood flow regulation in the retina. Resistance vessels are assumed to respond to changes in pressure, shear stress, carbon dioxide (CO₂), and the downstream metabolic state communicated via conduct responses. The model quantifies the relative contributions of different mechanisms to retinal autoregulation and shows that the combined effects of the metabolic and CO₂ responses are critical for achieving retinal autoregulation. It would be extremely interesting to apply a similar modeling approach to the autoregulation in the ONH, combine it with the poroelastic model mentioned above, and explore the relative contributions of the various mechanisms described in section 5. Most of the models for blood flow autoregulation, including the one developed by our group for the retinal circulation, are not time dependent. Thus, they are suitable to study static, but not dynamic, autoregulation. The dAR has been addressed by models for brain and kidneys.

7.4. Conclusions and future directions

The mathematical modeling of the interplay between biomechanics, perfusion and autoregulation in the ONH is still at its early stages, but is quickly attracting attention. Elucidating the complex interactions of ONH perfusion and tissue structure in health and disease using current imaging methodologies is difficult, and mathematical modeling provides an approach to solving these limitations. One of the main difficulties lies in the fact that the biophysical phenomena governing the ONH physiology occur at different scales in time and space. For example, BP, IOP and retrolaminar tissue pressure oscillate within a cardiac cycle (1 second), but also during the course of a day (24 hours). The characteristic time for the onset of autoregulation is approximately 20 seconds and the biomechanically induced remodeling of the collagen network in the ONH takes several months or years. The accurate modeling and simulation of multiscale problems is still an open area of research, and therefore the modeling of the ONH offers stimulating opportunities for groundbreaking activities from both the clinical and theoretical viewpoints. The application of dynamic modeling to reveal the mechanistic interplay of previously unseen physiologic relationships holds the potential to advance medical care in ophthalmic disease and provide patients and clinicians new hope for future diagnosis and therapy.

8. Method of literature search

A literature search using the PubMed and Web of Science search engines and available library databases was used with reference cross-matching to obtain relevant peer reviewed articles published on blood flow autoregulation and ocular biomechanics and hemodynamics. The article search included available published studies from 1900 to April 2015. Separate searches were performed by the primary author (D.P.), and 3 independent researchers (G.G., A.M.H., and J.A.) until relevant articles were identified. A few selected articles published before 1990 are included for their clinical relevance, but the review is mainly based on articles published in the last 2 decades. The following were the major search terminologies used: “autoregulation in the optic nerve head,” “neurovascular coupling,” “ocular biomechanics and hemodynamics,” “mechanical influences on autoregulation,” “metabolic autoregulation,” “effects of impaired blood flow regulation,” “optic neuropathies,” “glaucoma,” “blood flow regulation modeling.” Articles published in languages other than English were also included during the literature search.

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