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Major review

Autoregulation and neurovascular coupling in the optic nerve head

Daniele Prada, PhD[a,*], *Alon Harris, MS, PhD, FARVO*[b], *Giovanna Guidoboni, PhD*[a,b,c], *Brent Siesky, PhD*[b], *Amelia M. Huang, BS*[b], *Julia Arciero, PhD*[a]

[a] *Department of Mathematical Sciences, Indiana University-Purdue University Indianapolis (IUPUI), Indianapolis, Indiana, USA*

[b] *Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, Indiana, USA*

[c] *LabEx IRMIA, University of Strasbourg, Strasbourg, Alsace, France*

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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.

* Corresponding author: Mr. Daniele Prada, PhD, Department of Mathematical Sciences, Indiana University-Purdue University Indianapolis (IUPUI), 402 North Blackford Street, LD 270, Indianapolis, IN 46202, USA. Tel.: +1 317 274 3460.
E-mail address: dprada@iupui.edu (D. Prada).

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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,[177] and yet its etiology and treatment remain unclear. The main modifiable risk factor in glaucoma patients is elevated intraocular pressure (IOP)[1,45,110,118,121]; however, a high percentage of individuals with elevated IOP (a condition called ocular hypertension) never develop glaucoma,[103] 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).[203]

Several studies suggest correlations between impaired ocular blood flow and glaucoma.[56,60,67,84,85,90,241] 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,[3,169] brain,[162] heart,[21] kidney,[178] skeletal muscle,[61] and gut[129]—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,[32,162] 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,[68,69,184,186] blood flow in the retina and ONH seems to be highly correlated to increased neural activity. This phenomenon is called neurovascular coupling.[130]

In glaucoma the location of damage to nerve cells is hypothesized to be predominantly in the ONH,[176] 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.

Table 1 – Table with abbreviations

Abbreviation	Full name
20-HETE	20-hydroxy-eicosatetraenoic acid
BP	Blood pressure
CCD	Charge coupled device
CDI	Color Doppler imaging
CO_2	Carbon dioxide
CRA	Central retinal artery
CRV	Central retinal vein
CSFp	Cerebrospinal fluid pressure
dAR	Dynamic autoregulation
EC	Endothelial cell
EDV	End diastolic velocity
EET	Epoxyeicosatrienoic acid
ET	Endothelin
IOP	Intraocular pressure
LDF	Laser Doppler flowmetry
LSFG	Laser speckle flowgraphy
MAP	Mean arterial pressure
NB	Normalized blur
NO	Nitric oxide
NOS	Nitric oxide synthase
NTG	Normal tension glaucoma
OCT	Optical coherence tomography
ONH	Optic nerve head
OPP	Ocular perfusion pressure
PCA	Posterior ciliary artery
PGE_2	Prostaglandin E_2
PI	Pulsatility index
PO_2	Oxygen partial pressure
POAG	Primary open-angle glaucoma
PSV	Peak systolic velocity
RGC	Retinal ganglion cell
RI	Resistive index
RLTp	Retro laminar tissue pressure
ROS	Reactive oxygen species
sAR	Static autoregulation
SBR	Square blur ratio
SNFL	Superficial nerve fiber layer
SSADA	Split spectrum amplitude decorrelation angiography

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 separated by astrocytes, a particular type of glial cell.[28] 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.[51] 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