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# Ocular hemodynamics and glaucoma: the role of mathematical modeling

*Alon Harris[1], Giovanna Guidoboni[1,2], Julia C. Arciero[2], Annahita Amireskandari[1], Leslie A. Tobe[1], Brent A. Siesky[1]*

[1]Department of Ophthalmology, Indiana University School of Medicine, Indianapolis - USA
[2]Department of Mathematical Sciences, Indiana University–Purdue University at Indianapolis, Indiana - USA

PURPOSE. *To discuss the role of mathematical modeling in studying ocular hemodynamics, with a focus on glaucoma.*

METHODS. *We reviewed recent literature on glaucoma, ocular blood flow, autoregulation, the optic nerve head, and the use of mathematical modeling in ocular circulation.*

RESULTS. *Many studies suggest that alterations in ocular hemodynamics play a significant role in the development, progression, and incidence of glaucoma. Although there is currently a limited number of studies involving mathematical modeling of ocular blood flow, regulation, and diseases (such as glaucoma), preliminary modeling work shows the potential of mathematical models to elucidate the mechanisms that contribute most significantly to glaucoma progression.*

CONCLUSION. *Mathematical modeling is a useful tool when used synergistically with clinical and laboratory data in the study of ocular blood flow and glaucoma. The development of models to investigate the relationship between ocular hemodynamic alterations and glaucoma progression will provide a unique and useful method for studying the pathophysiology of glaucoma.*

KEY WORDS. *Glaucoma, Mathematical modeling, Ocular hemodynamics*

## INTRODUCTION

Open-angle glaucoma (OAG) is an optic neuropathy characterized by progressive retinal ganglion cell death and structural changes to the retina and optic nerve head (ONH) ultimately leading to irreversible visual field loss. To date, elevated intraocular pressure (IOP) is the only treatable risk factor for OAG, although there is significant evidence that other factors might be involved in the disease. Many individuals with elevated IOP never develop OAG (1), and many patients develop OAG despite reduced IOP (2). In recent years, the definition of glaucoma has expanded to include vascular, genetic, anatomic, and other systemic factors (3). In particular, the scientific community continues to accrue evidence suggesting that alterations in ocular

hemodynamics may play a significant role in OAG pathophysiology (4-9). Several systemic and localized vascular abnormalities have been linked to OAG, including vascular dysregulation (9-11), arterial hypertension (12), nocturnal hypotension (13), optic disc hemorrhage (14), migraine (14), and aging of the vasculature (15). Significant correlations have been found between impaired vascular function and both glaucoma incidence and progression; however, the mechanisms by which vascular impairments may translate to glaucoma progression are still unclear (16).

A critical question that is still debated is whether ocular hemodynamic alterations are primary or secondary to optic nerve damage. It has been hypothesized that decreased ocular blood flow can cause the ischemic death of retinal ganglion cells (17). It has also been suggested that

decreased ocular blood flow could be a response to the decrease in metabolic demand for oxygen and nutrients secondary to retinal ganglion cell death (16). If decreased ocular blood flow is determined to cause retinal ganglion cell death via ischemia, vascular factors would be implicated in glaucoma progression.

Only a few studies have examined alterations of ocular hemodynamics in relation to clinical markers of glaucoma progression (18-23). In these studies, progressive glaucoma has been associated with decreased blood velocities in the retrobulbar vessels supplying the optic nerve head. The strongest evidence for vascular deficiencies in glaucoma comes from multiple population-based studies that have found low ocular perfusion pressure (OPP) (calculated as 2/3 mean arterial pressure [MAP] – IOP) to be associated with glaucoma incidence, prevalence, and progression (24-27). However, the underlying factors relating OPP and glaucoma have not been distinguished yet, such as whether low OPP is independent of the sum of the 2 separate risk factors of low MAP and high IOP (16). Several factors can affect OPP, including fluctuations in MAP and IOP (28, 29), alterations of cerebrospinal fluid (CSF) pressure (30), and impairment of blood flow regulation (9). The extent to which these different factors alter OPP has not been assessed, to our knowledge. Additionally, the vascular bed (retinal, choroidal, or ONH) that suffers most significantly from low OPP has not been determined (16).

While there is mounting evidence for a role of ocular blood flow in glaucoma, additional studies are needed before therapies targeting ocular hemodynamics can be considered. Clinical, population-based, and animal studies are the primary approaches implemented by the scientific and medical communities to investigate the hemodynamic contribution to OAG pathophysiology. In this review, the use of another emerging investigative tool, mathematical modeling, in predicting the relationship between vascular impairment and glaucoma progression is described.

## Mathematical modeling and glaucoma

Mathematical modeling consists of translating "real-world problems" into mathematical equations whose solutions simulate the behavior of a physical system. Statistical analysis of experimental and clinical data is one of the most common uses of mathematics in medicine.

While mathematics via statistical methods can be used to analyze trends observed in data obtained in laboratories and clinics, mathematics via differential equation modeling can also be used as a "virtual laboratory" to produce "virtual data" or to study the mechanistic relationships of a system's components that combine to yield the observed trends.

In the context of glaucoma, a virtual laboratory based on mathematical models can be used to simulate the relationship between ocular mechanics and hemodynamics, which is not easy to assess in vivo. In particular, mathematical models can assess the role of hemodynamic alterations in OAG pathophysiology by 1) describing the mechanical response of the ONH to variations in IOP, scleral tension, and CSF pressure; 2) elucidating the basic hemodynamic principles governing blood flow in retinal, choroidal, and ONH vascular beds; 3) unraveling the importance of the mechanisms underlying blood flow regulation in retinal, choroidal, and ONH vascular beds; and 4) providing quantitative estimates of OAG progression induced by hemodynamic alterations. By addressing these 4 points, mathematical models can provide a framework from which new therapeutic concepts for OAG, based on the coregulation of IOP and ocular blood flow, could be tested and tuned at low cost and in a relatively short period of time.

Most of the mathematical models developed in the last 2 decades describe the ONH mechanical response to IOP variations (step 1), while the mathematical modeling of ocular hemodynamics, i.e., step 2, has been developed only in the last few years. The first attempts of modeling the mechanisms underlying blood flow regulation (step 3) are even more recent (presented at the 2012 ARVO annual meeting), while modeling the relationship between hemodynamic alterations and OAG progression, i.e., step 4, has yet to be investigated. In the following, we summarize the new and innovative mathematical modeling approaches related to the aforementioned 4 steps, while identifying potential future directions of research.

## Mathematical modeling of the mechanical response of the ONH

The ONH is subject to the mechanical action of IOP, scleral tension, and CSF pressure. The lamina cribrosa within the ONH is particularly sensitive to these forces. The difference between IOP and CSF pressure gives rise to a trans-laminar pressure gradient. This gradient may cause bowing

of the lamina cribrosa towards the site of lower pressure; scleral tension exerted on the edge of the lamina cribrosa helps to limit this bowing by providing horizontal tension, as in a drum's membrane.

While the presence of these mechanical forces is physiologic, changes in these forces may be pathologic and induce abnormal deformation of the ONH tissues (31-33). For example, tissue deformation could alter the diameters of blood vessels supplying that tissue and thereby lead to hemodynamic alterations that could increase the tissue susceptibility to ischemic damage. Over the last 2 decades, multiple mathematical modeling techniques have been successfully utilized to understand and quantify the relationship between ONH deformations and mechanical forces due to IOP and scleral tension (34-37).

Analytical solutions of the equations for homogeneous elastic circular plates showed that the thickness, radius, and mechanical properties of the lamina cribrosa are the major factors influencing the IOP-induced laminar deformation (34, 35). The idealization of the lamina as a homogeneous elastic circular plate has allowed for quantitative estimates of the effect of the different degrees of fixity offered by the connection with the sclera, the pretension caused by scleral expansion, and the ratio between flexural and in-plane stiffness on the mechanical response of the lamina cribrosa to IOP (36).

More realistic geometries of the lamina cribrosa and the scleral canal have been considered using elasticity models based on finite elements. These models showed that peripapillary scleral thickness (37), scleral stiffness, ocular axial length, and stiffness of the lamina cribrosa (38-40) have the largest influence on the mechanical response of the ONH to variations in IOP.

The mechanical response of the ONH to variations in CSF pressure has not been studied to the same extent as IOP, even though it could be addressed using similar finite elements approaches. It is expected that IOP elevations and CSF pressure reductions would not have equivalent effects on the ONH, even if they yield the same trans-laminar pressure gradient, because, unlike CSF pressure, variations in IOP affect both the trans-laminar pressure gradient and the scleral tension acting on the edge of the lamina. This would imply that as the trans-laminar pressure gradient increases due to IOP elevation, the scleral tension also increases, aiding the lamina in its load-bearing function and making the ONH a relatively stable biomechanical system (41). It is unknown whether such compensatory mechanisms exist in the ONH structure to mitigate the effects of CSF pressure reduction, but mathematical modeling could be used to explore and predict potential CSF influences.

## Mathematical modeling of ocular hemodynamics

Mathematical modeling of ocular blood flow is still somewhat preliminary and has been mainly focused on the retinal vasculature. A mathematical model consisting of dichotomous symmetric branching was used to quantify the arterovenous distribution of hemodynamic parameters in the microvasculature of the human retina (42). A more realistic image-based network model of a murine retinal vasculature was used to show that the distribution of the blood hematocrit in the retinal network is extremely non-uniform, with lower values at the pre-equator region (near the optic disc) and higher values in the equator region of the retina (43).

These models did not account for mechanical forces acting on the retinal vasculature even though retinal arterioles, capillaries, and venules are directly exposed to changes in IOP. Moreover, blood flow through the central retinal artery (CRA) and central retinal vein (CRV), which are blood vessels that run through the center of the lamina cribrosa and supply and drain the retina, is influenced by laminar deformation due to the action of IOP, scleral tension, and CSF pressure.

A mathematical model has recently been developed to help to elucidate the mechanisms underlying the influence of the laminar deformation on the CRA hemodynamics (44, ARVO 2012, Program #2836, Abstract #A165). The lamina cribrosa is modeled as a homogeneous linearly elastic circular plate and the CRA is modeled as an elastic compliant tube filled with a viscous fluid (blood). The model showed that acute IOP elevations induce an increase in the compression that the lamina cribrosa exerts on the CRA walls and, consequently, a decrease in luminal diameter, blood flow, and velocity in the CRA.

A more comprehensive description of retinal blood flow has been achieved by a lumped network model including 5 compartments: CRA, arterioles, capillaries, venules, and CRV (ARVO 2012, Program #2838, Abstract #A167). The model accounts for the compression exerted on the CRA and CRV by the lamina cribrosa and for blood flow regulation in the retina. The model shows that the constriction of the CRV by the laminar compression (for given levels of

IOP, CSF pressure, and scleral tension) is more significant than the constriction of the CRA. Thus, IOP elevation causes a more severe constriction of the CRV than the CRA, leading to an overall increase of intraluminar pressure in the retinal arterioles, capillaries, and venules. The model also suggests that elevated IOP and reduced MAP might not contribute equally to low OPP, since retinal blood flow reductions due to IOP elevations benefit from a built-in compensatory mechanism that leverages the venous compressibility to increase the local blood pressure in the retinal vasculature. The lumped compartment model for the retinal vasculature has also shown that the geometric characteristics of the lamina cribrosa strongly influence retinal hemodynamics, suggesting that variations in individual susceptibilities to glaucomatous damage might result from a combination of mechanical, vascular, and anatomic factors (ARVO 2012, Program #2837, Abstract #A166).

Comprehensive models describing the hemodynamics in the choroidal and ONH vascular beds have not yet been developed, but could be investigated. Significant blood flow velocity reductions and resistivity index (RI) elevations have been reported in the CRA, short posterior ciliary arteries (PCAs), and ophthalmic artery of patients with OAG when compared to controls (45). It has also been reported in healthy individuals that acute IOP elevations induce RI elevations in the CRA and PCAs (46). This suggests that mechanical and vascular factors may be coupled and that changes in IOP may affect the perfusion of both the retina and ONH. However, the mechanisms underlying the relationship between the observed influence of mechanical changes on the blood flow to the PCAs and the ONH are not yet well understood. Mathematical models could be used to elucidate similarities and differences in the responses of the PCAs and CRA to changes in ocular mechanical forces, which in turn would help predict which vascular beds are more susceptible to ischemic damage, a current topic of interest in the vascular hypothesis in OAG pathophysiology.

## Mathematical modeling of blood flow regulation

Blood flow autoregulation is the ability of vascular beds to maintain relatively constant blood flow over a large range of perfusion pressure. Several mechanisms contribute to blood flow regulation, including responses to intraluminal pressure (myogenic response), shear stress on the endothelial lining of vessels (shear-dependent response), metabolite concentrations in vessels and/or tissue (metabolic

or conducted response), and neural stimuli.

Retinal, choroidal, and ONH vascular beds exhibit a combination of some or all of these regulatory mechanisms to varying degrees. Several studies describe correlations between impairment of blood flow regulation and OAG progression (11, 16, 47-49). These correlations suggest that vascular therapies aimed at restoring regulatory mechanisms hold the possibility of benefitting certain types of glaucoma. In combination with animal and human studies, mathematical modeling can help the design of such therapies by evaluating the relative importance of different regulatory mechanisms in achieving blood flow and by simulating the effects of certain drugs in the ocular vascular system.

Mathematical models describing the mechanisms contributing to blood flow regulation are available for several organs of the human body, including the brain (50), heart (51), kidneys (52), and skeletal muscle (53). Autoregulation in the retina has been studied extensively, and contributions of myogenic and metabolic mechanisms have been observed (54, 55). However, a mathematical model describing the mechanics of blood flow regulation in the eye was only recently presented (ARVO 2012, Program #6847, Abstract #D1177), where blood flow regulation in the retina was achieved by altering the tone of arteriolar smooth muscle cells and capillary pericytes according to myogenic and metabolic mechanisms. In the presence of only the myogenic response mechanism, the model predicts a very poor degree of autoregulation. Including the effects of both the conducted and lactate metabolic responses in arterioles yields strong autoregulation as the pressure exiting the CRA is varied between 28 and 42 mm Hg. In addition to confirming that regulation of blood flow in the retina is mainly governed by metabolic mechanisms, the model offers a virtual environment in which the contributions of single mechanisms can be altered and the consequent effects on the circulation can be evaluated, simulating the action of specific drugs on the system. Additional mechanisms can be examined using the model, such as the effect of carbon dioxide or shear stress on vascular tone.

The model has also been used to predict that autoregulation fails to operate over its expected pressure range if IOP is elevated. In particular, model predictions show a loss of autoregulation as OPP decreases. This is consistent with the observation that glaucoma is associated with low perfusion pressure (55). These predictions need to be related to glaucomatous damage by quantifying the effects of impaired autoregulation mechanisms and elevated IOP

on tissue oxygenation. Combining the model predictions in step 3 with the techniques proposed in step 4 could help to determine whether tissue ischemia occurs because the capacity for autoregulation is exceeded or because the mechanisms of autoregulation are defective. Further research would be needed to develop similar models for the mechanisms governing blood flow regulation in choroidal, retrobulbar, and ONH vascular beds.

## *Mathematical modeling of the relationship between hemodynamic alterations and OAG progression*

In order to study the relationship between hemodynamic alterations and OAG progression, it is necessary to combine the models describing mechanical and vascular factors, as discussed in steps 1, 2, and 3, with models describing metabolic factors and cellular functions. More precisely, the functionality and life cycle of retinal ganglion cells, as well as other cells involved in OAG pathophysiology such as astrocytes, should be modeled in relation to the availability of oxygen and other nutrients delivered to the tissue under conditions of functional or impaired blood flow regulation and under the action of physiologic or pathologic mechanical forces. Even though some metabolic models have been recently proposed to examine angiogenesis in the retina (56, 57) and choroid (58), the coupling of such models with mechanical and vascular factors constitutes another potential direction of research.

## *Reliability, limitations, and clinical relevance of mathematical model predictions*

The reliability of the predictions of a mathematical model strongly depends on the rationality of the assumptions on which the model is based, the precision of the parameter values involved in the model, and the accuracy with which the model solutions have been obtained. Thus, the development of a reliable mathematical model is a truly interdisciplinary endeavor. It requires active collaboration and continuous interaction between groups of theoretical and applied investigators. Mathematical modeling is certainly not a stand-alone investigative tool; it complements and synergistically combines with laboratory experiments and human or animal studies. Experimental and/or clinical data are critical for obtaining parameter values in the model. Moreover, the comparison between model predictions and

experimental/clinical data might unveil new phenomena to be studied with future experiments.

The use of mathematical modeling in conjunction with clinical research may also hold great potential in the exploration of racial and ethnic differences in the pathophysiology of OAG. Several studies have noted the increased incidence and prevalence of OAG in persons of African descent compared to those of European descent. In addition to the increased risk of developing glaucoma, persons of African descent also tend to develop OAG earlier, exhibit more severe disease, and experience more rapid disease progression than those of European descent (59). Several clinical and population-based studies have also reported anatomical differences in ocular structures among individuals of different ethnicities (60-70). Our work in mathematical modeling indicates that structural differences may induce significantly different hemodynamic responses of the retinal blood flow at a constant IOP. This may help to explain why certain individuals are more susceptible than others to ischemic damage in the optic nerve tissue even though they experience the same level of IOP. It might also help to explain some of the disparities in incidence and prevalence of ocular diseases between people of different ethnicities. Racial differences are a small subset of the many possible factors in disease pathology that could be effectively explored with the aid of modeling. Ultimately, the relationship between mathematical modeling and experimental and clinical work is dynamic, cyclic, and has the potential of establishing new developments in both the theoretical and applied sciences.

Address for correspondence:
Alon Harris, MS, PhD, FARVO
Lois Letzter Professor of Ophthalmology
Professor of Cellular and Integrative Physiology
Department of Ophthalmology
Eugene and Marilyn Glick Eye Institute
Indiana University School of Medicine
1160 W. Michigan St.
Indianapolis, IN 46202
USA
alharris@indiana.edu

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