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Ocular Blood Flow as It Relates to Race and Disease on Glaucoma

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Keywords

• Glaucoma • Ocular blood flow • Race • African descent • Modeling • Disparity • Artificial intelligence • Demographics

Key points

- In certain individuals, glaucoma involves, in part, an impaired blood supply to the retina and/or optic nerve head, contributing to glaucomatous damage.
- The vascular contribution to glaucoma pathogenesis and progression has been shown to play a more significant role in persons of African descent compared with European descent.
- Current research highlights the importance of considering demographics, including race, and the inclusion of vascular risk factors in the management of glaucoma.
- Artificial intelligence and mathematical modeling may provide the framework for a comprehensive glaucoma model inclusive of race, vascular biomarkers, and clinical outcomes to reduce disease disparities.

INTRODUCTION

Glaucoma, a progressive multifactorial optic neuropathy characterized by retinal ganglion cell and retinal nerve fiber layer (RNFL) degeneration, is the world's leading cause of irreversible blindness, accountable for approximately

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12% of global cases [1]. Although the pathophysiology of glaucoma is still not fully understood, primary open-angle glaucoma (OAG) has been historically attributed to elevated intraocular pressure (IOP). Currently, reduction of elevated IOP is considered the only approved modifiable risk factor (RF) to arrest the onset and progression of glaucoma. However, many patients develop and experience glaucoma progression without elevated IOP, whereas some patients with elevated IOP never experience glaucomatous vision loss. As a result, other RFs have been proposed, including vascular contributions to the glaucomatous disease process [2–4]. It has been demonstrated over many decades that OAG in certain individuals is, at least in part, the result of an impaired blood supply to the retina and/or optic nerve head (ONH; (Figs. 1 and 2). Over time, a strong association between ocular blood flow biomarkers and glaucoma has been established; however, it often is unclear whether vascular abnormalities are the primary insult of the disease or rather secondary to the disease process itself [2,4]. Rather than a singular RF, it is likely a combination of physiologic events, including elevated IOP, poor vascular health, lifestyle, and genetics and demographics, that combine to determine the overall risk for the onset and progression of glaucoma in a given individual.

Although glaucoma is a disease that universally affects all humans, significant OAG disease disparities exist within certain population groups, especially in persons of African descent (AD) [5,6]. Compared with their European descent (ED) counterparts, in persons of AD, OAG presents earlier, is more severe, and has a stronger ocular vascular component; in turn, AD populations also are known to have higher rates of systemic vascular disease [5–8]. As a result, researchers [2] have sought to understand not only to what extent hemodynamic mechanisms are involved in OAG but also how in part they might be responsible for the observed racial disparities seen in glaucoma.

Herein, the authors review the relationship between ocular blood flow and race and explore their potential involvement in the onset and progression of glaucoma. By summarizing key population-based and prospective studies, potential connections can be made between vascular health, glaucoma, and racial disparities of the disease. In addition, mathematical modeling and artificial intelligence applications that consider patient demographics and vascular biomarkers alongside clinical RFs may provide the framework to achieve individualized precision medicine and improved outcomes for vulnerable populations.

SIGNIFICANCE

Glaucoma is the single largest cause of irreversible blindness worldwide and is responsible for significant racial disparities and impact, especially in persons of AD [5,6]. Disease management is currently limited to IOP-modifying medications and surgical interventions, yet many treated patients continue to experience disease progression, whereas considerable proportions of glaucoma are represented by normal-tension glaucoma (NTG) [1]. Ocular vascular abnormalities involving biomarkers of perfusion, metabolism, and blood flow, along

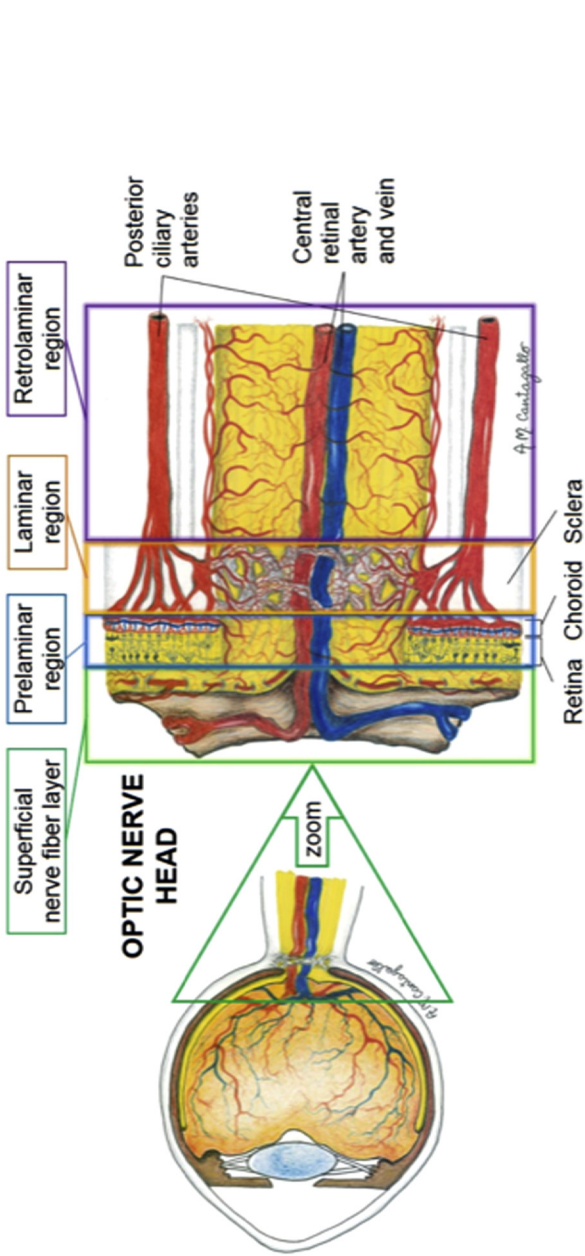

Fig. 1. Anatomy and vascular supply of the ONH. The ONH includes the superficial nerve fiber layer, the prelaminar region, the laminar region, and the retrolaminar region. (*From* Prada D, Harris A, Guidoboni G, Siesky B, Huang AM, Arciero J. Autoregulation and neurovascular coupling in the optic nerve head. Survey of Ophthalmology 2016 Mar 1;61(2):164 to 86; with permission.)

with optic disc hemorrhages, migraine, and nocturnal hyper/hypotension, also have been associated with OAG [2–4]. The extent to which IOP-induced mechanical damage versus vascular insult occurs in glaucoma, either separate or in combination, may be dependent on a person's overall vascular health, genetics, and ocular resiliency.

Racial disparities in glaucoma

Population-based studies have demonstrated significant racial differences in glaucoma onset and progression, suggesting genetics/demographics and especially race may be a particularly important RF to consider. Specifically, OAG disproportionately affects persons of AD when compared with those of ED, with approximately 6 times as many cases reported in AD populations [9]. In addition, AD populations have been shown to have earlier disease onset, more rapid glaucomatous progression, worse disease severity, and greater visual function and higher IOP compared with ED populations [5,6]. Glaucoma patients of AD have been shown to have increased visual field variability compared with patients of ED, possibly delaying detection of progression and effective treatment [10].

Across other populations groups, those of Asian descent and Latin American descent (LAD) have average prevalence rates of OAG that are greater than ED but less than AD, whereas the prevalence in Middle Eastern (ME) populations is estimated to be similar to that of Asian populations with relatively limited data available [11–15].

Mechanisms behind racial disparities in glaucoma

Although the underlying mechanisms explaining racial differences in OAG are not entirely clear, a variety of hypotheses have been suggested, including differences in aqueous humor dynamics, anatomic variation, such as differences in corneal thickness and optic disc area, oxidative stress, lamina cribrosa and scleral morphology, and vascular mechanisms [5,6,16]. Importantly, populations of AD tend to have a higher prevalence of systemic vascular conditions, including cardiovascular disease, diabetes mellitus, and associated RF, such as sedentary lifestyle and smoking, with resulting organ damage that generally is more severe and occurs earlier than in other populations [8]. Given the known differences in rates of systemic vascular disease in AD populations, the vascular cause of glaucoma may be particularly relevant when considering mechanisms behind racial disparities of glaucoma in persons of AD [6,17].

Ocular perfusion pressure

A key vascular biomarker associated with differential glaucoma outcomes in different racial populations is ocular perfusion pressure (OPP). OPP is an estimate of the pressure difference between arterial (estimated by mean arterial pressure [MAP]) and venous circulation (estimated by blood pressure [BP]-IOP) with various calculations for mean, systolic, and diastolic OPP measurements [2]. Many population-based studies have demonstrated a consistent relationship between estimates of OPP and glaucoma prevalence [2,4]. Specifically, in 2000, the

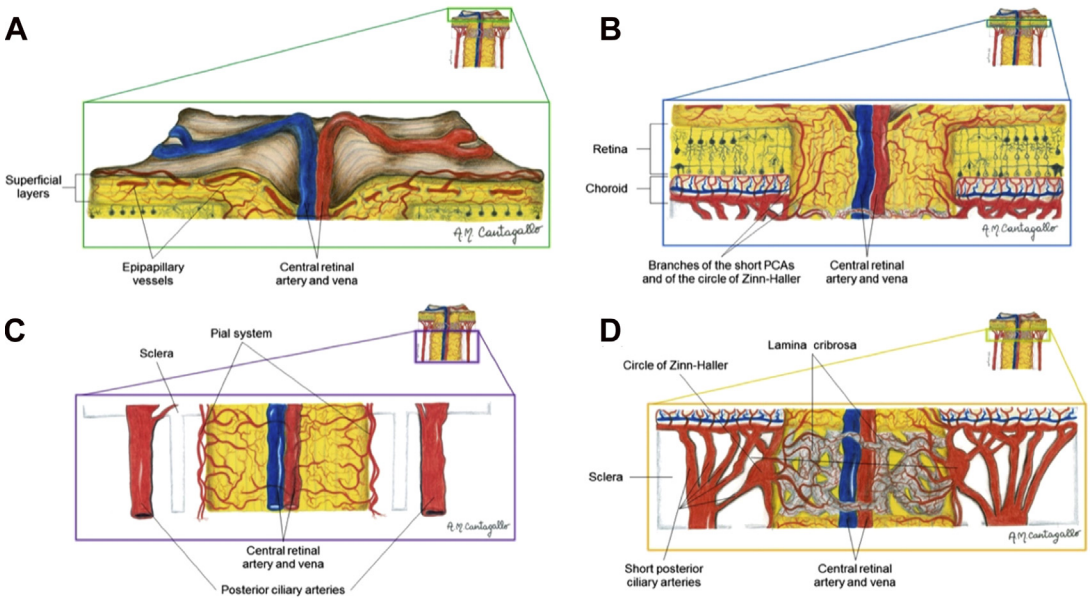

Fig. 2. Detailed views of the ONH regions. (*A*) Superficial nerve fiber layer (SNFL). The SNFL receives oxygenated blood primarily from retinal arterioles. These small vessels, called epipapillary vessels, originate in the peripapillary SNFL and run toward the center of the ONH. (*B*) Prelaminar region. The prelaminar region is mainly supplied by direct branches of the short 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. (*C*) Laminar region. Blood flow to the laminar region is provided by centripetal branches of the short PCAs. The centripetal branches arise either directly from the short PCAs or from the circle of Zinn-Haller. The lamina cribrosa is shown as a 3D network. (*D*) Retrolaminar region. The retrolaminar region is supplied by the CRA and the pial system. The pial system is an anastomosing network of capillaries located immediately within the pia mater. (*From* Prada D, Harris A, Guidoboni G, Siesky B, Huang AM, Arciero J. Autoregulation and neurovascular coupling in the optic nerve head. Survey of Ophthalmology 2016 Mar 1;61(2):164-86.; with permission.)

Egna-Neumarkt study demonstrated that lower levels of diastolic OPP (DOPP = diastolic BP − IOP) were associated with an increased prevalence of OAG in an ED population (DOPP < 68 mm Hg, odds ratio [OR]: 1; 68 to 78 mm Hg, OR: 0.33, 95% confidence interval [CI]: 0.14–0.58; $P<.001$) [18]. Similarly, the Barbados Eye Study demonstrated that the prevalence of OAG was associated with low DOPP in an AD population (DOPP < 52.3 mm Hg, OR: 3.29; CI: 2.06–5.28; $P<.05$) [19]. These results were confirmed by the Baltimore Eye Study, which found that both ED and AD patients with DOPP less than 30 mm Hg had a race-adjusted risk of OAG higher than patients with DOPP ≥50 mm Hg (OR: 6.22, CI: 2.15–17.94) [20]. Within LAD populations, the Proyecto Ver Study associated low OPP with OAG ($X^2 = 28.8$; $P = .001$, test for trend; age-adjusted OR: 0.96, CI: 0.94–0.99), whereas the Los Angeles Latino Eye Study associated low systolic OPP (SOPP = systolic BP − IOP) (OR: 2.5), DOPP (OR: 1.9), and mean OPP (MOPP = MAP − IOP) (OR: 3.6) with higher prevalence of OAG [12,21].

In Asian populations, the Singapore Malay Eye Study found glaucoma risk was higher for patients with low MOPP (OR: 1.73, CI: 1.05–3.15), whereas the Handan Eye Study showed that OAG patients had consistently lower SOPP, DOPP, and MOPP ($P<.05$) [22,23]. In addition, the Barbados Eye Study suggested that lower SOPP, DOPP, and MOPP were associated with increased glaucoma incidence in an AD population (relative risk [RR]: 0.66, CI: 0.54–0.80 per 10 mm Hg higher). Conversely, the Rotterdam Study found a nonstatistically significant association with incidence in an ED population (hazard ratio [HR]: 0.995 per mm Hg increase in MOPP; CI: 0.971–1.019) when adjusted for IOP [24,25]. Referencing the wealth of population-based data, in 2009, the World Glaucoma Association identified low OPP as an independent RF for OAG [4].

In addition to data on OAG prevalence and incidence, OPP has been identified as a possible biomarker for glaucoma progression. In 2007, the Early Manifest Glaucoma Trial identified low SOPP as a baseline predictor of structural glaucoma progression (≤160 mm Hg; HR: 1.42, CI: 1.04–1.94) [26]. Similarly, McGlynn and colleagues [27] identified MOPP as associated with structural progression measured by both RNFL thickness (OR: 0.3 per 10 mm Hg, CI: 0.08–0.8; $P<.02$) and by progressive parapapillary atrophy (OR: 0.4 per 10 mm Hg, CI: 0.2–0.9; $P<.02$) using flicker chronoscopy. A recent systemic review and meta-analysis suggested diurnal variability or fluctuation in OPP, as opposed to a single timepoint of OPP, may be more relevant to OAG progression especially in NTG patients [28].

Directly measured ocular blood flow biomarkers

Numerous directly assessed hemodynamic biomarkers from a wide variety of imaging modalities have been identified as being associated with OAG [2,4]. Imaging techniques used to quantify ocular vascular biomarkers include ultrasound Doppler imaging techniques, scanning laser Doppler modalities such as Heidelberg retinal flowmetry (HRF), laser speckle flowgraphy, optical

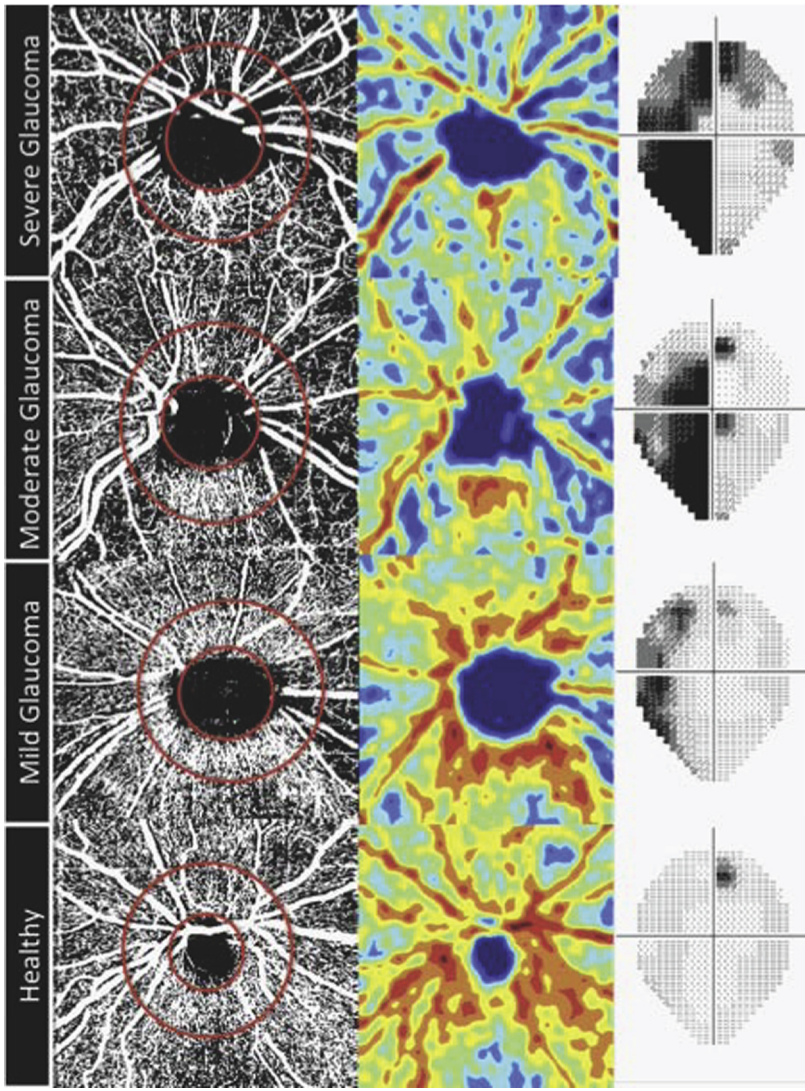

Fig. 3. OCTA images with corresponding visual fields. Correlation between vessel densities measured with OCT-A and visual field results, in both healthy controls and patients with glaucoma. Patients with glaucoma of several degrees have progressive peripapillary vessel deficits that correspond to greater relative visual field loss. This demonstrates a relationship between structural changes and functional changes. (*From* Yarmohammadi A, Zangwill LM, Diniz-Filho A, et al. Relationship between optical coherence tomography angiography vessel density and severity of visual field loss in glaucoma. Ophthalmology 2016 Dec;123(12):2498-2508; with permission.)

coherence tomography angiography (OCTA), and retinal photographic oximetry. It is important to note that there is no gold-standard imaging modality capable of assessing all relevant ocular vascular beds in glaucoma. In addition, hemodynamic biomarkers assessed by each different imaging technique have inherent limitations, require expertise, and generally are not interchangeable [2,29].

Many studies have routinely shown an association between retrobulbar blood flow and glaucomatous disease [2–4]. For example, Galassi and colleagues [30] conducted a longitudinal study on the association between retrobulbar blood flow and functional progression demonstrating a 6-fold increased risk of perimetric disease progression in patients with an elevated ophthalmic artery (OA) resistance. Similarly, Martínez and Sánchez [31] identified higher baseline OA and short posterior ciliary artery (PCA) resistance were predictive of functional disease progression. Calvo and colleagues [32] also found that patients who progressed structurally had a lower OA end-diastolic blood flow velocity and higher OA resistance. More recently, in 2017, Moore and colleagues [33] identified that lower baseline OA blood flow velocities and OA resistance were associated with both structural and functional glaucoma progression after 4 years.

In 2015, Siesky and colleagues [7] identified that OAG patients of AD had significantly lower retrobulbar blood flow biomarkers in the OA, central retinal artery (CRA), and short PCAs. Specifically, they found lower OA peak systolic (PSV) ($P = .0001$) and end-diastolic (EDV) ($P = .0008$) velocities, lower CRA PSV ($P = .01$), and lower temporal PCA PSV ($P = .0037$) and nasal PCA PSV ($P < .0001$) in OAG patients of AD. It is important to note that these lower blood flow velocities in AD OAG patients were independent of IOP and visual field differences, which were similar in AD and comparative ED cohorts [7]. In 2016, Siesky and colleagues [34] confirmed these findings in a prospective study over 4 years demonstrating PCA EDV and vascular resistance were more strongly correlated to glaucomatous changes in the ONH structure in AD patients when compared with ED patients. Importantly, Kaskan and colleagues [35] further identified lower retrobulbar blood flow biomarkers in non-glaucomatous AD eyes finding lower EDV in nasal PCAs ($P = .01$) and higher vascular resistance in the temporal PCA ($P = .01$) and CRA ($P = .04$). Together, these data suggest persons of AD may both be at an elevated risk for OAG development and have a higher risk of vascular involvement in the glaucomatous disease process.

OCTA modalities attempt to bridge the gap (in a single imaging device) of assessing proven clinical outcomes, such as RNFL, macular, and ONH structure, with vascular biomarkers in critical ocular tissues. Using laser light to generate high-resolution images, OCTA can quantify papillary and peripapillary vessel density (VD) and the ONH flow area at a specific point in time, allowing scientists to map the superficial vasculature. Initial studies using OCTA demonstrated that decreased VD was associated with glaucoma when compared with healthy eyes, whereas correlations between structural

parameters, such as RNFL thickness, ONH parameters, and ganglion cell complex thickness, have been correlated with decreases in VD [2,36]. Fig. 3 shows OCTA imaging of vascular biomarkers from both glaucomatous and healthy eyes.

In 2019, the African American Eye Disease Study found healthy AD eyes had lower peripapillary perfusion that was influenced by thin RNFL and longer axial lengths [37]. It is important to note a recent finding by Moghimi and colleagues [38], who found peripapillary capillary density parameters had good diagnostic accuracy for detecting glaucoma in patients of ED patients, but significantly worse diagnostic accuracy in patients of AD. Physiologic variability in age, sex, and systemic vascular health conditions, such as diabetes, also have been shown to influence OCTA vascular biomarkers in AD populations [39]. A recent small pilot study of 28 AD and 56 ED eyes found no significant differences in OCTA assessed peripapillary and macular microcirculation; however, both biomarkers were significantly correlated with disease severity in AD and ED [40].

Retinal capillary beds assessed with other imaging technologies, such as HRF, have shown reduced retinal capillary activity and vascular density in OAG patients of AD compared with ED. In 2014, Kanakamedala and colleagues [41] found that AD OAG patients had strong negative correlations between change in superior mean retinal capillary blood flow and cup/disc ratio (CDR) ($r = -0.78$; $P = .020$) and cup area ($r = -0.75$; $P = .0283$), and strong positive correlations with change in rim area ($r = 0.74$; $P = .0328$), with similar associations between inferior mean retinal blood flow and CDR (-0.88, $P = .0156$) and linear CDR ($r = -0.86$; $P = .0265$) over 3 years. When compared with ED OAG patients, the same correlations were weak and lacked statistical significance. Similarly, Siesky and colleagues [34] used customized HRF applications, finding a significantly larger increase in the avascular area of the inferior retina in patients of AD compared with ED that strongly correlated with reductions in macular thickness and that was independent of IOP.

Retinal oximetry is a photographic imaging technique that estimates blood oxygen saturation levels in retinal blood vessels. Generally, retinal oximetry has been used to note that glaucoma patients have higher oxygen saturation in retinal veins compared with healthy patients, whereas they have a lower arteriovenous saturation difference [2]. In consideration of race, Siesky and colleagues [42] found AD OAG patients had a significantly decreased arteriovenous difference (Fig. 4A, B) compared with OAG patients of ED (24.4% ± 9.3% vs 36.4% ± 14.1%; $P = .03$), with no significant difference in the mean oxygen saturation of retinal arteries ($P = .25$) nor veins ($P = .33$). This may be due to the lower vascular density described [34] in AD OAG patients, reduced capillary function in AD patients, and/or reduced functional oxygen utilization [2,42]. It is important to note, however, that differing levels of retinal pigment represent an unknown limitation when analyzing retinal oximetry across different population groups [2].

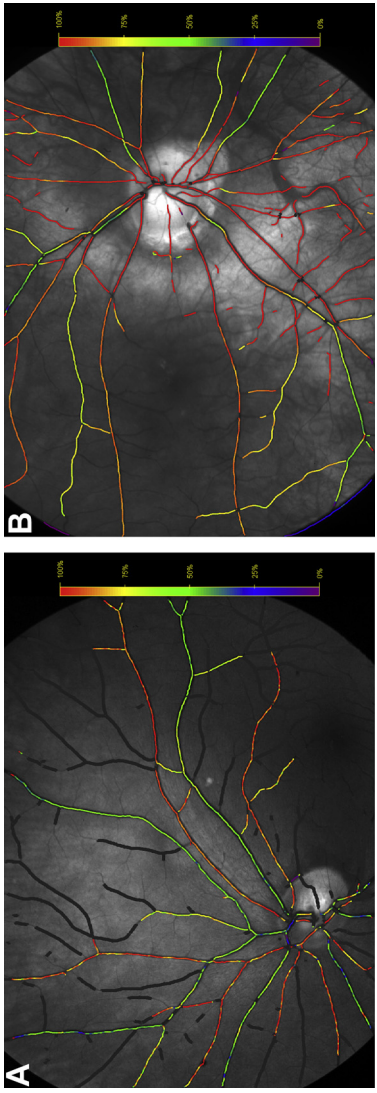

Fig. 4. (*A*) Retinal oximetry imaging from a glaucoma patient of ED. (*B*) Retinal oximetry imaging from a glaucoma patient of AD showing reduced arterial/venous difference in oxygen content of vessels.

Although some pilot data are available on ocular blood flow differences in OAG patients of AD and ED, little is known about other racial population clusters. In Asian populations, some studies have shown that systemic hypertension is associated with NTG, whereas others have shown evidence of vascular changes associated with glaucoma and independent of IOP [43,44]. Many studies suggest a higher level of vascular involvement in NTG, a condition frequent in Asian populations [2,4]. Studies of LAD populations have shown the association between glaucoma and low DOPP, but studies directly examining the vascular contributions to disease are severely lacking [12–14]. Currently, almost no information is available on ME glaucoma populations and its relationship to vascular health.

Current relevance and future avenues to consider or to investigate

Understanding the vascular contributions to glaucoma, as well as the interplay of race and individual susceptibilities, is a key factor to improving glaucoma management and patient outcomes. Alongside IOP, vascular involvement in the disease process has been well documented for many decades with recent pilot data suggesting a more significant contribution in persons of AD compared with ED. Other racial groups, including persons of Asian descent, LAD, and ME descent, lack available comparative data in the literature, rendering the understanding of mechanisms, including possible vascular causes, behind their disease disparity rates difficult to uncover [11–15]. This stresses the urgent need for data from large, population-based studies that are carefully designed to include and analyze OAG patients of different races.

Multidisciplinary research using mathematical modeling and artificial intelligence may help bridge the gap in available data to better understand racial, vascular, and demographic impact on glaucoma outcomes. This is an especially important approach to understand ocular hemodynamics and metabolism, as currently no gold standard exists for determining ocular vascular health with many ocular tissue beds relevant to glaucoma. Mathematical modeling techniques thus allow for a virtual laboratory where hypotheses surrounding retinal perfusion and tissue oxygenation changes can be built and tested in a controlled environment [2]. The benefits of mathematical approaches are especially relevant for modeling vascular contributions to glaucoma as well-understood hemodynamic laws, and principles can be built testing specific hypotheses that are unable to be directly visualized with imaging instrumentation.

Historically, mathematical modeling has been used to test everything from Newton's laws to Poiseuille's laws of hemodynamic flow. More recently, mathematical models have been developed to test the hypothesis of glaucomatous damage that is unable to be observed in real time. For instance, modeling has been used to investigate ocular biomechanics with regard to tissue strain and stress from IOP and cerebrospinal fluid pressure (CSFp), with more theoretic studies regarding circulation and oxygenation currently in development [2,45,46]. These mathematical models allow for hypotheses to consider the individual contributions of BP, IOP, vascular regulation, CSFp, and a variety of

hemodynamic biomarkers at once as opposed to multiple different clinical measurements assessed by standard statistical analysis. For example, in 2014, Guidoboni and colleagues [45] created the first mathematical model to account for retinal vascular blood flow, blood flow autoregulation, BP, and IOP by using an electric circuit analogy, as seen in Fig. 5. By modeling retinal vascular blood flow as an electric current, with resistors and capacitors to model vascular resistance and compliance, a model was developed that was able to clinically predict variance in hemodynamic outcomes in trabeculectomy patients [47]. As for the vascular theory of glaucoma, the model posits that as IOP shifts, a patient's plateau of vascular regulation similarly shifts, leading to possible blood flow reductions secondary to venous collapse in lower BP individuals, making these individuals more susceptible to ischemia [45].

Clinically, this suggests that in patients with low BP, an IOP greater than 21 mm Hg would lead to venous collapse at lower IOP values than patients with higher BP, findings that are reflective of known correlations with glaucoma and diurnal hypotension [2]. Interestingly, these findings were further corroborated when applied to data from the Singapore Epidemiology of Eye Diseases study, a population-based analysis of nearly 10,000 people from a multiethnic Asian population. When data from this study were applied to the mathematical model, individuals with high IOP ($\geq$21 mm Hg) and low systolic BP ($<$124 mm Hg) had a 1.69 times higher risk of glaucoma [48]. Perhaps the most relevant clinical takeaway from the Guidoboni and colleagues [45] model, however, is that a given IOP in an individual may not communicate higher risk for glaucoma alone; rather, IOP represents a complex clinical picture that is dependent on more comprehensive data. As modeling and artificial intelligence networks advance and become more inclusive of all RFs, race and demographic inputs will likely improve specificity of disease management and reduce the economic and quality-of-life impacts seen in glaucoma disparity, especially in persons of AD.

A comprehensive approach to understanding risk in OAG requires careful weighting of clinical markers, such as IOP and ONH structure, as well as consideration of demographics, including age, gender, and race, alongside vascular health and ocular hemodynamic biomarkers. A significant challenge exists in understanding the impact of a single variable, such as IOP or OPP, for a given individual. Individual variance in ocular structure and vascular networks lends complexity to a given biomarker's impact on the glaucoma disease process. Given the incredibly fine nature of the retinal and ONH microvascular network, modeling has used poroelasticity and structural viscoelasticity to describe the vasculature in ways previously unseen [2]. Clinically relevant outcomes of these models suggest that aging or other disease may lead to reductions in structural viscoelasticity, and, therefore, prevent ocular tissues from maintaining perfusion when affected by sudden changes in IOP. In fact, this suggests that physiologic sudden changes in IOP, such as from blinking or rubbing eyes, may in fact have pathologic consequences and induce glaucomatous change in the ONH [2]. Other mathematical models have built on these

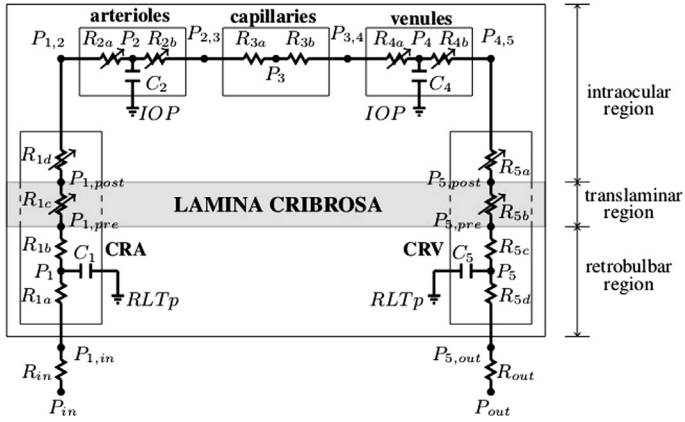

Fig. 5. Network model for the retinal vasculature. The vasculature is divided into 5 main compartments: the CRA, arterioles, capillaries, venules, and the central retinal vein (CRV). Each compartment includes resistances (*R*) and capacitances (*C*). The intraocular segments are exposed to the IOP; the retrobulbar segments are exposed to the retrolaminar tissue pressure (RLTp), and the translaminar segments are exposed to an external pressure that depends on the internal state of stress within the lamina cribrosa (*gray shaded area*). Diameters of venules and intraocular and translaminar segments of the CRA and CRV are assumed to vary passively with IOP, whereas arterioles are assumed to be vasoactive. (*From* Guidoboni G, Harris A, Cassani S, et al. Intraocular pressure, blood pressure, and retinal blood flow autoregulation: a mathematical model to clarify their relationship and clinical relevance [published correction appears in Invest Ophthalmol Vis Sci. 2015 Oct;56(11):6247]. Invest Ophthalmol Vis Sci. 2014;*55*(7):4105-4118; with permission.)

findings, as well as explored the interplay between hemodynamics and oxygen transport in order to explore the impact of hypoxia on ocular tissues [2].

Mathematical models based on the principles of physics and physiology have the potential of being translatable across studies in different populations, thereby yielding an opportunity to provide a mechanistic understanding of differences in glaucoma pathogenesis and progression in different races. The future of these approaches may allow individualized demographic characteristics, such as age, gender, race, and other confounding disease states, such as diabetes, to be incorporated into a comprehensive model to provide evidence-based individualized glaucoma management plans [49]. The future inclusion of clinical and vascular data from specific ethnic cohorts into established models of glaucoma damage may help identify the underlying mechanisms for racial disparities in glaucoma that currently remain enigmatic. For example, according to Guidoboni and colleagues [45], racial differences have been detected in a variety of ocular tissues, including the geometric properties of the cornea. Given the influence these tissues have on IOP and optic nerve tissues, it is possible that the complex interplay between biomechanics and ocular tissues could explain racial disparities in glaucoma. As for hemodynamics, the

individual variations of ocular tissues seen in populations of different races may lead some to be more prone to vascular insult, and mathematical modeling will allow for a better understanding of the mechanisms of these hemodynamic variations [17]. Currently, many more factors are observed to vary among individuals of different races than those that can be accounted for in principle-based mathematical modeling; yet principles of physics and physiology are translatable across races and yield hope to identify differences in RFs and disease mechanisms. In recent years, artificial intelligence techniques show great promise to bridge the gap between the rigor of principle-based modeling and the variety of real data [50].

SUMMARY

Glaucoma is the worldwide leading cause of irreversible blindness, with significant disease disparities in the AD population. Current treatments remain limited to reduction of IOP, and modern therapies have failed to fully arrest the disease in many individuals. Vascular insult and hemodynamic contributions to the glaucomatous disease process are well established in certain patient groups, especially in persons of AD. A lack of available ocular hemodynamic data from certain population groups, including persons of LAD, ME descent, and Asian populations, limits the current understanding of racial differences in OAG pathologic condition. Glaucoma is likely a disease initiated by a multifactorial collection of RFs that include IOP, ocular structure, ocular circulatory health, and demographics, including age, gender, and race. These RFs may interact in synergistic ways that elevate risk yet are unseen and unaccounted for during normal clinical examinations.

Mathematical modeling and artificial intelligence applications may help better understand the unseen forces acting in glaucoma pathogenesis. Current modeling is limited by availability of data, especially directly assessed vascular biomarkers in differing racial groups. As these models expand and undergo rigorous testing, and more robust data can be incorporated, a comprehensive model of glaucoma may be finally realized. This will require, however, integration of individual patient characteristics with proven clinical outcomes, such as IOP and retinal and ONH structures, alongside biomarkers of vascular structure and oxygen transport efficiency.

At the base level of these complications and complexities, however, is the fact that glaucoma itself is a complex, heterogeneous disease. Glaucoma pathogenesis and progression are difficult to study, requiring longitudinal data collection that is complicated by aging processes, medication regimens, and other chronic disease. In addition, because populations of AD are most impacted by glaucoma, there may be a resource allocation challenge inherent to the studies required to fully understand glaucoma RFs. Other population clusters, such as persons of LAD and ME, remain significantly understudied in regard to ocular blood flow and glaucoma.

Despite these challenges, a wealth of research points to a bright future with improved understanding of glaucoma, particularly as it relates to vascular

involvement in racial disparities. Currently, an urgent need exists for large, carefully designed prospective trials to advance the understanding of vascular involvement in glaucoma, especially in vulnerable patient populations. Technological limitations in imaging modalities may be mitigated by modeling approaches that provide mechanistic understanding of vascular insult in combination with elevated IOP, or through IOP-independent pathways. Going forward, reducing racial disparities in glaucoma remains an important goal for clinicians and researchers alike. Designing future prospective studies in collaboration with mathematical modeling and artificial intelligence approaches may uncover previously unseen synergies of clinical RFs, vascular health, and patient demographics. Advancing knowledge of glaucoma RFs specific to high-risk population groups will ultimately culminate in reduced racial disparities through improved diagnosis and disease management.

CLINICAL CARE POINTS

- Glaucoma is a multifactorial disease with high variation in risk factors and a cause that affects each person differently.
- Reductions in ocular blood flow and/or faulty vascular regulatory function are involved in the onset and progression of glaucoma in certain individuals.
- Persons of African descent are at elevated risk for glaucoma and have higher levels of vascular involvement in the disease process.
- Understanding of vascular contributions to the glaucomatous disease process is hindered by methodological limitations and a lack of sufficient longitudinal data.
- Mathematical modeling of risk factors inclusive of clinical, vascular, and demographic considerations may improve diagnosis and disease management.

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