

Biomechanics of glaucoma: factors influencing the intraocular pressure

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Abstract

We present a simple biomechanical model, based on the works of Collins *et al.* [1,2,3], which describes volume and pressure changes within the eye as functions of measurable ocular properties. We suppose that the rate of the volume change of the whole ocular is the sum of the rate of volume change of the ocular arterial bed and the rate of volume change of the aqueous humor. The mechanical characteristics of the cornea and sclera are expressed throughout by the so-called ocular rigidity function. Blood flow circulation within the eye is represented as if from an equivalent vessel, that is, a single cylindrical vessel represents the whole vascular bed. The aqueous humor dynamics are predisposed by the difference between production and outflow. Finally, an ordinary differential equation was derived for the intraocular pressure. In this equation, the rigidity of the corneoscleral envelope and the blood vessels, the production, critical pressure and outflow of aqueous humor remain constant. The variation of their values over the suitable physiological range elucidates the interdependence of the intraocular pressure (IOP) on those parameters.

The results of the parametric study can be summarized as follows: 1) The arterial blood pressure in the ocular bed practically does not affect the IOP; 2) The increased rigidity of the corneoscleral envelope increases IOP slightly; 3) The parameters describing the aqueous humor production can either increase or diminish IOP significantly; 4) The resistance to aqueous outflow plays a determining role in increasing the IOP.

Keywords: Glaucoma, intraocular pressure, mathematical model

1. Introduction

Glaucoma is the most common cause of blindness, affecting approximately 70 million people in the world, of whom more than 7 million are blind. About 70 thousand Bulgarian citizens suffer from glaucoma [4]. In the vast majority of such cases, the intraocular pressure (IOP) is higher than normal and therefore, the hypothesis that elevation of IOP causes optic nerve damage and hence visual impairment is generally accepted. There are different mathematical and experimental models in the literature specifying the factors which influence the IOP. Some authors assume that the elevated IOP is caused by an increased resistance to the outflow of aqueous humor from the eye either through the conventional outflow pathway or that the combined resistance of the trabecular meshwork filled with biopolymer together with the inner lining of Schlemm's canal is estimated to be sufficient to be the primary source of resistance to the outflow of aqueous humor in healthy humans. Thus the observed increase in IOP during glaucoma could partially result from faulty caliber regulation in Schlemm's canal, but does not result from the collapse of the inner wall of Schlemm's canal [5,6]. Other authors connect the IOP-induced stresses and strains in the optical nerve head with the mechanical failure of the connective tissues of the *lamina cribrosa*, scleral canal wall, and peripapillary sclera [7]. Finally, a large number of authors suggest that altered corneal viscoelastic/elastic properties and vascular dysregulation may contribute to the development of glaucoma in patients with elevated IOP [8-11].

The purpose of this paper is to analyze which parameters of the ocular biomechanics and haemodynamics are sensitive to the elevation of the IOP and to assess their importance. For this purpose we apply the Collins model [1,2,3]. In the next section we briefly outline the essence of the model. Later we present the results of the parametric study and discuss future implementations of the model.

2. Biomechanical model of the IOP

The figure 1 below depicts the relationships between the various parameters of the eye that can affect the intraocular pressure IOP. From the influence diagram it is evident that the parameters are inter-related; that is for example, the IOP affects and is affected by the intraocular volume and venous pressure.

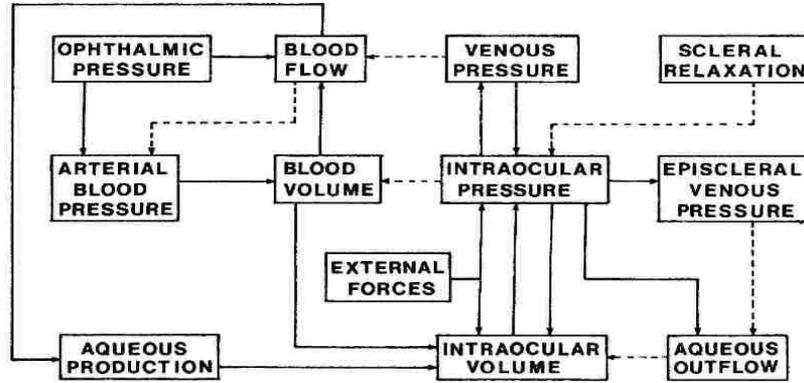


Fig. 1. Influences on intraocular pressure. The arrows denote the direction of influence; dashed lines indicate a negative relationship (e.g. an increase in venous pressure causes a decrease in blood flow). (Extracted from [1])

The intraocular pressure changes in response to variations in the internal volume of the ocular. The interior of the eye comprises solids (iris, lens, retina, vitreous, and vascular structure) and liquids (aqueous and blood). The volumes of solids and of vitreous vary on a slow time scale, i.e. month or years. This means that the short time intraocular volume changes are due to alterations in blood or aqueous volumes. Thus

$$(1) \quad \frac{dV}{dt} = \frac{dV_a}{dt} + \frac{dV_{aq}}{dt} + \frac{dV_{ext}}{dt}$$

where $\frac{dV}{dt}$ is the rate of the volume change of the ocular, namely corneoscleral envelope, $\frac{dV_a}{dt}$ is the rate of the volume change of the ocular arterial bed, $\frac{dV_{aq}}{dt}$ is the rate of volume change of the aqueous humor, and $\frac{dV_{ext}}{dt}$ is the rate of the external volume changes imposed e.g. by tonometric probes on the cornea. In this work, the last term of Eq. (1), i.e. external volume changes, is not taken into account here.

2.1. Ocular pressure-volume relationship

As the intraocular pressure changes in response to variations in the internal volume of the ocular, the corneo-scleral envelope will expand and relax accordingly. The motion of this envelope is associated with the mechanical characteristics of both cornea and sclera and is expressed throughout by the so-called *ocular rigidity function* which is basic to the eye's performance. The ocular rigidity relates the IOP change ΔP to the corresponding volume change ΔV . McEwen and St. Helen [12] proposed the following exponential relation as the ocular rigidity function for small limit deformations

$$(2) \quad \Delta V = \frac{1}{a} \ln \left\{ \frac{P + \frac{b}{a}}{P_0 + \frac{b}{a}} \right\}$$

where a and b are constants and P_0 is initial, or average, IOP taken here as 15.6 mmHg. Collins & Van der Werff [1] summarized their results for *post mortem* human eyes to obtain averaged values of $a = 0.022 \mu l^{-1}$ and $b = 0.208 \text{ mmHg}/\mu l$. Supposing that $b = 0$, then Eq. 2 takes the formulation of Friedenwald [13].

$$(3) \quad \Delta V = \frac{1}{\alpha} \ln \left\{ \frac{P}{P_0} \right\}$$

Another non-linear approximation of the ocular pressure—volume relationship was proposed by McBain [14] in the form

$$(4) \quad \Delta V = 21.4 \{ P^{0.356} - P_0^{0.356} \}$$

After differentiating Eqs. (2) and (4) with respect to time, the rate of volume change of the ocular is obtained as

$$(5) \quad \frac{dV}{dt} = \frac{1}{\alpha P + b} \frac{dP}{dt} \text{ in McEwen and St. Helen [12] and } \frac{dV}{dt} = 10.46 P^{-0.644} \text{ in McBain [14]}$$

formulations.

2.2. Pressure – volume relation for the vascular bed

The intraocular blood vessels are of different types (artery, capillary, and vein), of different sizes, of different compositions and elastic properties, and subjected to different transmural pressures, because of the drop in the pressure along the vascular bed. Therefore we adopt the idea of the so-called *equivalent vessel*; that is, a single cylindrical vessel representing the whole vascular bed. The vessel deforms under the action of arterial pressure P_a and intraocular pressure P , or that of the transmural pressure which equals $(P_a - P)$. We suppose that the volume changes of the equivalent vessel are proportional to the transmural pressure

$$(6) \quad P_a - P = k_\alpha \frac{\Delta V_\alpha}{V_\alpha}$$

where V_α is the blood content inside the equivalent vessel and ΔV_α is the variation of V_α under the influence of the transmural pressure. Following the linear theory of elasticity, the coefficient k_α can be expressed as

$$(7) \quad k_\alpha = \frac{E_\alpha h_0}{2(1-\theta^2)r_0}$$

where h_0 and r_0 are the initial (undeformed) thickness and radius of the equivalent vessel respectively, ν is the Poisson ratio, and E_α is the elastic modulus which is not a constant but depends upon the state of stress - characterizing the collagen structures [15]

$$(8) \quad E_\alpha = k(P_a - P)^\alpha$$

with $k = 2.5$ and $\alpha = 1.6$. If we put Eqs. (5) and (6) into (4), and after differentiation with respect to time, the rate of volume change of the equivalent vessel can be represented as

$$(9) \quad \frac{dV_\alpha}{dt} = \frac{V_\alpha (1-\alpha)}{k_\alpha (P_a - P)^\alpha} \left\{ \frac{dP_a}{dt} - \frac{dP}{dt} \right\}$$

where k_α is a constant, equal to

$$(10) \quad k_\alpha = \frac{h_0}{2(1-\theta^2)r_0}$$

2.3. Aqueous humor dynamics

We follow the hypothesis that aqueous humor is formed both by secretion within the cells of the ciliary epithelium in a manner similar to that of the secretory cells of the kidney and by ultrafiltration. The most important factor controlling the secretion of aqueous humor appears to be IOP itself. Experiments have shown that the formation rate of the aqueous humor falls as the IOP is raised, ceasing entirely when

the pressure approaches the so-called *cutoff pressure* P_c . This suggests the following linear relationship between the production of aqueous humor S_p and the intraocular pressure IOP

$$(11) \quad S_p = C_p(P_c - P)$$

where P_c is the cutoff pressure and C_p is a constant. The cutoff pressure P_c is the filtration pressure required to counteract the secretory component of the aqueous production. The constant C_p is called the *facility of aqueous production*.

The aqueous outflow process is essentially mechanical. Most of the resistance to aqueous outflow is encountered in the trabecular network. The flow of aqueous humor through the trabecular matrix can be compared to fluid flow through a porous medium, which is described by Darcy's equation. Solving that equation, it was shown in [16] that the aqueous outflow rate is linearly proportional to the net pressure drop between the anterior chamber and the episcleral venous plexus; that is

$$(12) \quad S_0 = C_f(P - P_v)$$

where S_0 is the total outflow of aqueous through Schlemm's canal, P is the intraocular pressure in the anterior chamber, P_v is the episcleral venous pressure, and C_f - an ocular constant known as the *outflow facility*. The reciprocal of C_f is R_f , the *resistance to outflow*. The outflow facility depends on the IOP by the following formula [17]

$$(13) \quad C_f = \frac{1}{a_1 P + a_2}$$

where a_1 and a_2 are constants.

The episcleral venous pressure P_v itself is a function of IOP of the form

$$(14) \quad P_v = a_3 P + a_4$$

Incorporating Eqs (14), (13) and (12) into Eq. (11), and keeping in mind that

$$(15) \quad \frac{dV_{aq}}{dt} = S_p - S_0,$$

we obtain

$$(16) \quad \frac{dV_{aq}}{dt} = C_p(P_c - P) - \frac{(1-a_3)P - a_4}{a_1 P + a_2}$$

Finally, inserting Eqs (5), (9) and (16) into Eq. (1), and supposing that P_a is constant; that is, $\frac{dP_a}{dt} = 0$, yields an ordinary differential equation for the intraocular pressure P .

$$(17) \quad \frac{dP}{dt} = \left\{ C_p(P_c - P) - \frac{(1-a_3)P - a_4}{a_1 P + a_2} \right\} / \left\{ \frac{1}{aP + b} + \frac{V_a(1-\alpha)}{k_\alpha(P_a - P)^\alpha} \right\}$$

In this equation, the values of the rigidity of the corneoscleral envelope a , b and the blood vessels k_α ; the production C_p , critical pressure P_c and outflow a_2 of aqueous humor all remain constant. The variations of their values over a suitable physiological range could elucidate the interdependence of the IOP on those parameters.

3. Results

A parametric study of Eq. (17) was performed with the following constants as reported in [1] for the normal human eye: $C_p = 0.046 \mu\text{l}/\text{min}/\text{mmHg}$, $P_c = 90 \text{ mmHg}$, $a_1 = 0.005 \text{ l}/\mu\text{l}/\text{min}$, $a_2 = 1.05$

$mmHg/\mu l/min$, $a_3 = 0.5$, $a_4 = 3.95 mmHg$, $a = 0.022 l/\mu l$, $b = 0.208 mmHg/\mu l$, $k_a = 1.166$, $\alpha = 1.6$, $Pa = 55 mmHg$. It should be noted that some values were slightly changed in order to reproduce IOP equal to $15.6 mmHg$.

Figure 2 illustrates a characteristic feature of the differential equations; that is, the solution is sensitive to the initial value of the IOP. Indeed, when starting at $P = 10 mmHg$, the IOP increases and after approximately 15 minutes it reaches a steady or equilibrium state of $15.6 mmHg$. The opposite process happens when the starting point is $20 mmHg$. Therefore, for all further simulations, the initial value of IOP was taken equal to $15 mmHg$.

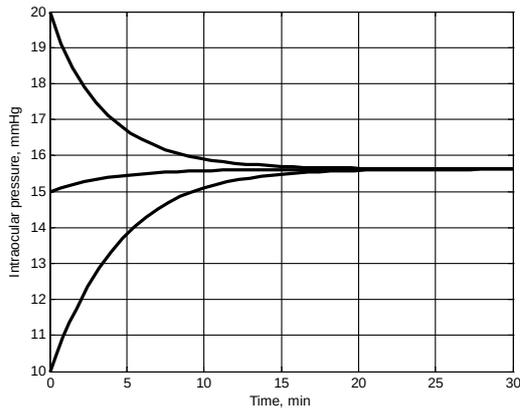


Fig. 2. Variation of the vascular pressure over time. Normal eye.

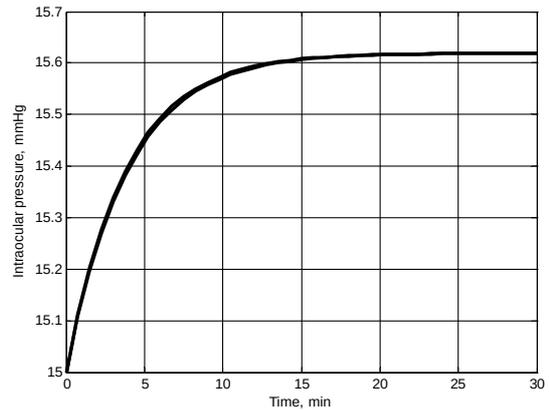


Fig. 3. Influence of the vascular pressure Pa on IOP. Pa : $35 mmHg$ (continuous line); $75 mmHg$ (dotted line)

Figure 3 presents the influence of the ocular arterial pressure Pa , whose physiological variations are between 35 and $75 mmHg$, on the IOP. As is evident, the variations of the ocular arterial pressure practically do not affect the IOP. For that reason, the ocular arterial pressure was kept in our further simulations at its mean value of $Pa = 55 mmHg$.

The influence of the arterial bed rigidity on IOP can be assessed as negligible. Indeed, a ten-fold change in the parameter k_α (dotted curve, Figure 4) leads to small changes only in the transitional phase of the IOP time behavior. This result does not seem strange since the elasticity of the blood vessels is important in large vessels like the aorta where the dotted blood flow from the heart is subsequently transformed into continuous flow.

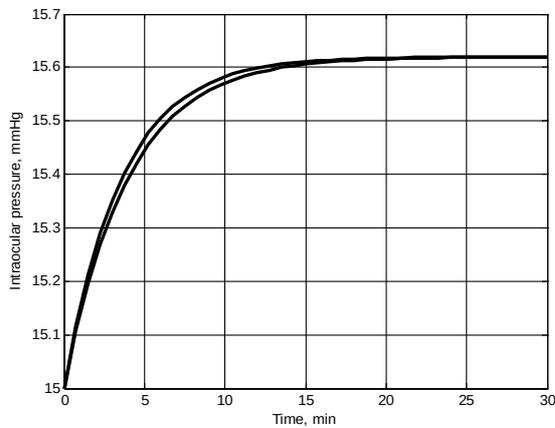


Fig. 4. Influence on IOP of the arterial bed rigidity: $k_\alpha = 0.166$, $\alpha = 1.6$ (continuous line); $k_\alpha = 1.166$, $\alpha = 2.6$ (dotted line)

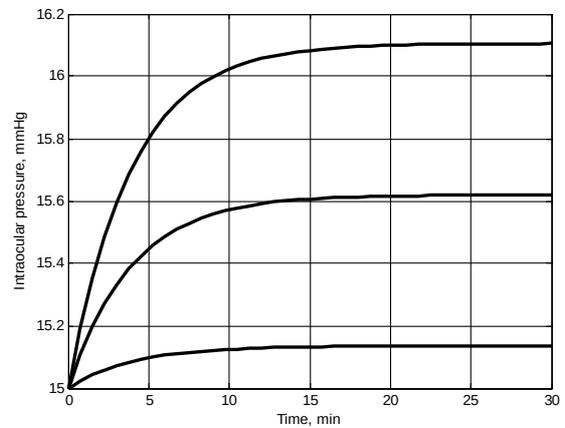


Fig. 5. Influence on IOP of the cutoff pressure: $Pc = 85 mmHg$ (dotted line), $Pc = 90 mmHg$ (continuous line), $Pc = 95 mmHg$ (dotted line)

Our results show that the parameters governing the aqueous humor dynamics play a decisive role in IOP changes. The influence of the cutoff pressure P_c on IOP is relatively minor in comparison. Figure 5 shows that the change of P_c from 85 to 95 mmHg increases IOP from 15.1 to 16.1 mmHg. Such values are within the physiologically acceptable range.

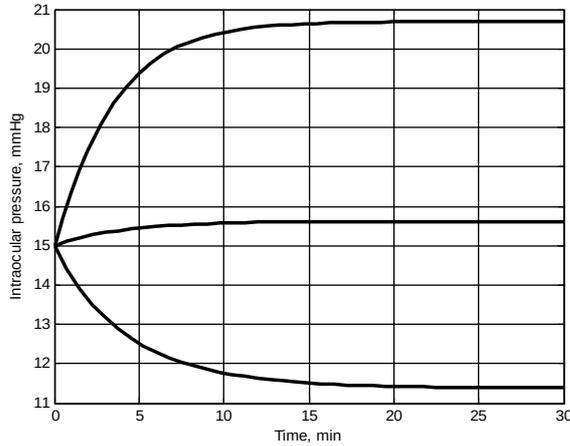


Fig. 6. Influence on IOP of the aqueous humor production: $C_p = 0.02 \mu\text{l}/\text{min}/\text{mmHg}$ (dotted line), $C_p = 0.046 \mu\text{l}/\text{min}/\text{mmHg}$ (continuous line), $C_p = 0.08 \mu\text{l}/\text{min}/\text{mmHg}$ (dotted line)

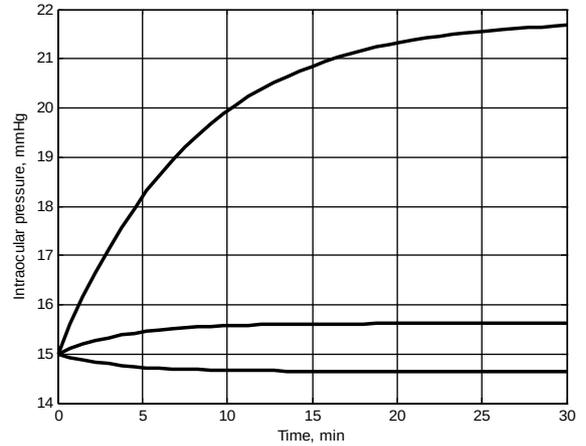


Fig. 7. Influence on IOP of the outflow resistance: $a_1 = 0.0051/\mu\text{l}/\text{min}$, $a_2 = 0.9 \text{ mmHg}/\mu\text{l}/\text{min}$ (dotted line); $a_1 = 0.005 \text{ l}/\mu\text{l}/\text{min}$, $a_2 = 1.05 \text{ mmHg}/\mu\text{l}/\text{min}$ (continuous line); $a_1 = 0.05 \text{ l}/\mu\text{l}/\text{min}$, $a_2 = 1.125 \text{ mmHg}/\mu\text{l}/\text{min}$ (dotted line)

The influences on IOP of the aqueous humor production parameter C_p are more pronounced as seen in Figure 6. For example, a two-fold decrease in C_p (dotted curve) diminishes the IOP to 11.5 mmHg, while a two-fold increase in C_p value increases IOP to 20.8 mmHg.

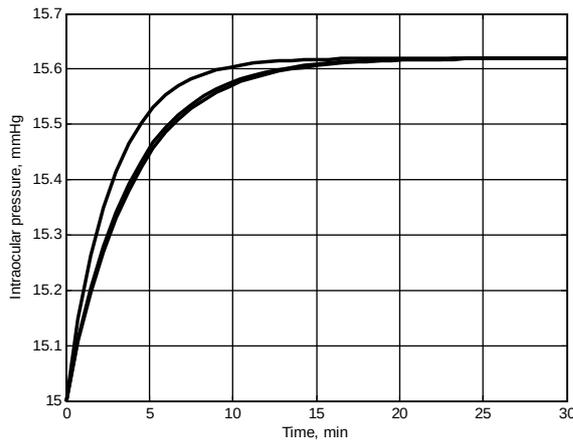


Fig. 8. Influence on ocular pressure-volume estimations: McEwen & St. Helen approximation [12] (continuous curve); Friedenwald approximation [14] (dotted curve); McBain approximation [13] (broken curve)

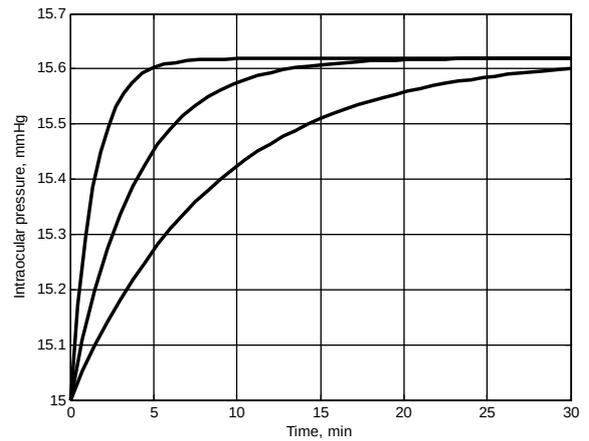


Fig. 9. Influence on IOP of ocular rigidity: $a = 0.022 \text{ l}/\mu\text{l}$ (continuous line); $a = 0.08 \text{ l}/\mu\text{l}$ (dotted line); $a = 0.0022 \text{ l}/\mu\text{l}$ (broken line)

The outflow resistance parameters a_1 and a_2 change IOP (Figure 7) the most sensitively and in a non-linear manner. Indeed, a 10% decrease in a_2 from its normal value decreases IOP by approximately 1 *mmHg*, while a same increase in a_2 increases IOP by approximately 6 *mmHg*.

Figure 8 illustrates the influences of the pressure-volume relations of the McEwen & St. Helen approximation (continuous curve), Friedenwald approximation (dotted curve), and McBain approximation (broken curve) of IOP. It is evident that none of them changes the IOP in the steady phase.

As mentioned before, our model comprises the rigidity of the whole body of the eye; that is, the combined sclera and cornea. Figure 9 indicates only a small influence of the ocular rigidity on IOP; i.e. the increased rigidity due to age or some pathological condition increases IOP to some degree. Keeping in mind that the area of the cornea is small compared to that of the retina, their separate contributions must be studied in further detail.

4. Discussion

As noted at the beginning of this article, glaucoma is the most common cause of blindness, affecting approximately 70 million people in the world, of whom more than 7 million are blind. Glaucoma is a group of eye diseases that can lead to blindness by damaging the optic nerve. The eye continuously produces a fluid called the aqueous humor, which must drain from the eye to maintain healthy eye pressure.

In the most common type of glaucoma, Primary Open Angle Glaucoma, the eye's drainage canals become blocked, and the fluid accumulation causes pressure to build within the eye. This pressure can cause damage to the optic nerve, which transmits information from the eye to the brain. Glaucoma results in peripheral (or side) vision loss initially, and the effect can be like looking through a tube or into a narrow tunnel. This "tunnel vision" effect makes it difficult to walk without bumping into objects that are off to the side, near the head, or at foot level. Glaucoma is an especially dangerous eye condition because most people do not experience any symptoms or early warning signs at the onset of glaucoma. This is why glaucoma is often called "the sneak thief of sight."

Glaucoma can be treated, but it is not curable. The damage to the optic nerve from glaucoma cannot be reversed. However, lowering the pressure in the eye can help prevent further damage to the optic nerve and further peripheral vision loss. Early detection, appropriate and ongoing treatment, and the availability of specialized [low vision](#) and [vision rehabilitation services](#) can help people with glaucoma live productive and satisfying lives.

Corneal hysteresis appears to provide a measurement of intraocular pressure which may help manage glaucoma clinically, offering valuable information regarding which patients are more at risk of progression and which patients will respond more to topical medications.

Corneal thickness is important because it can mask an accurate reading of eye pressure, causing doctors to treat for a condition that may not really exist or to treat unnecessarily when the patient is actually normal. Actual IOP may be underestimated in patients with a thinner cornea and overestimated with a thicker one.

One important difference between hysteresis and corneal thickness is that corneal thickness is almost always very similar, if not identical, between the two eyes; it does not change markedly with intraocular pressure. In contrast, hysteresis will often vary when IOP changes. For example, corneal hysteresis is lower when intraocular pressure is higher. Corneal hysteresis is therefore not an inherent property of a cornea. The fact that IOP and corneal hysteresis interact may be both potentially helpful and harmful from a clinical standpoint.

Obviously, all of this raises some important questions. What's happening in the cornea that produces a high or low hysteresis measurement? And how does the level of hysteresis increase or decrease the risk of glaucomatous progression? Currently, we have no clear answers.

It was shown in one study [18] that when IOP was elevated, the optic nerve in patients with a high corneal hysteresis bowed back more than the optic nerve in people with lower corneal hysteresis. This behavior may actually reduce damage at the cellular level if the nerve and cornea accommodate pressure by moving, rather than remaining rigid.

The interplay between corneal hysteresis and medication response is also very useful clinically. Knowledge of a patient's corneal hysteresis may indicate how much of a pressure drop an eye will achieve

on a new medication. Corneal hysteresis is also important when managing normal-tension glaucoma patients, whose apparent normal IOP may be fallacious if not corrected for corneal hysteresis, thus altering the diagnosis and risk factors.

It has been shown in this article that relatively straightforward mathematical modelling of the quantitative influences of glaucoma on the intraocular pressure can serve as a useful clinical indicator for the detection of underlying mechanisms responsible for deteriorating quality of vision in affected patients, leading to a more focused clinical approach for effective treatment of such debilitating diseases.

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