EXPERT REVIEWS

Ocular rigidity

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Ocular rigidity is a macroscopic parameter characterizing the relationship between pressure and volume changes in the human eye. Ocular rigidity depends on the architecture and material properties of the globe. Measurements of ocular rigidity have mainly been performed by means of invasive manometric devices or paired Schiotz tonometry. These measurements pertain to the injection (or displacement) of a given volume in the eye and measurement of the associated intraocular pressure change. Ocular volume, age, intraocular pressure, arterial pressure and ocular blood volume have all been suggested to influence ocular rigidity. Moreover, rigidity has been shown to be altered in patients with glaucoma and age-related macular degeneration. The significance of an accurate assessment of this parameter is apparent in tonometry, tonography and pulsatile ocular blood flow measurements, while its possible role in the pathogenesis of ocular disease remains to be elucidated.

Keywords: age-related macular degeneration • elasticity • glaucoma • intraocular pressure • ocular rigidity • sclera

At the beginning of the 20th Century, the identification of the role of intraocular pressure (IOP) measurement in clinical practice created the need for accurate tonometer calibration, leading to the recognition of the relationship between the indentation tonometer reading and the resistance of the ocular wall to deformation, as well as to the actual increase of the IOP associated with the displacement of aqueous volume during indentation.

In principle, it is possible to calculate the pressure–volume relationship for any eye using parameters such as the Young's modulus and the Poisson's ratio for each of the materials of the globe, as well as the exact geometry and thickness distribution of the ocular wall [1,2]. However, as these parameters (material properties and geometry) are not generally available with the required precision *in vivo*, such calculations do not have a practical application in the living eye [3]. For most clinical purposes, empiric equations and parameters that relate volume changes to pressure changes are used. The parameters that numerically determine the pressure–volume relationship express the combined geometric and material properties of the eye. Ocular rigidity, as described by Friedenwald, is a measure of the resistance that the eye exerts to distending forces [4]. This parameter is derived from experimental data and describes the elasticity of the ocular shell, especially the sclera, cornea and the compressibility of the choroid, assuming that the other ocular compartments are practically incompressible.

The concept of ocular rigidity is fundamental to the theory and practice of tonometry [4]. Moreover, ocular rigidity is an important parameter involved in the estimation of outflow facility from tonography [5–7] and pulsatile ocular blood flow from real-time IOP recordings [8,9], where intraocular volume changes are computed from IOP changes.

Measurement techniques

Several measurement techniques have been suggested throughout the years in order to quantify the pressure–volume relationship, each having its advantages and disadvantages.

The first measurements of the pressure–volume relationship were performed using a manometric system and injecting the eye with known volumes of saline (cannulation of the vitreous cavity or anterior chamber) in animals and cadaver eyes (either enucleated or *in situ*), followed by investigations in living human eyes scheduled for enucleation [10–13]. Pallikaris and colleagues presented a series of direct manometric measurements performed before cataract surgery in human eyes under retrobulbar anesthesia [14]. The mean ocular rigidity coefficient,

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according to Friedenwald's equation [4], was found to be 0.0126 μl^{-1} (95% CI: 0.0112–0.0149) and the coefficient of repeatability was 0.0023 μl^{-1}. In a series of manometric measurements in eyes under anesthesia (with drops) with a device capable of more accurate IOP recordings, the pressure–volume relationship was approximated with an exponential fit, whereas the coefficient of ocular rigidity was estimated to be 0.0224 μl^{-1} (standard deviation: 0.0049) (Figure 1) [15]. Nevertheless, the invasive nature of the technique restricts its clinical use. Sources of error due to irritation of the eye by the presence of the cannula are meant to be minimal when the measurements' length of time is kept brief.

Friedenwald introduced the method of paired Schiotz tonometry, in which the ocular rigidity coefficient may be calculated from two readings with different weights (preferably 5.5- and 10-g weights), by referring to nomograms that relate IOP with the tonometer resting on the cornea to volume of indentation [4]. On application of the Schiotz tonometer a series of events occur, including a distortion of the ocular wall, expulsion of blood from the eye and increased aqueous outflow. The mean ocular rigidity coefficient in Friedenwald's set of measurements in normal human eyes in individuals under the age of 50 years and with small refractive errors was 0.021 μl^{-1} [4]. In general, the pressure–volume relationship and values for the coefficient of ocular rigidity from manometric investigations in living eyes are lower than those reported by Friedenwald. In most studies in the literature, differential tonometry is used, either with the aforementioned method or with the use of two tonometry readings, one with Schiotz and one with Goldmann tonometry. Although the flaws and inaccurracies inherent in Schiotz tonometry affect both methods [16], leading to a large variability in the measurement of the ocular rigidity ocefficient [17,18], the second technique is thought to induce larger errors [19].

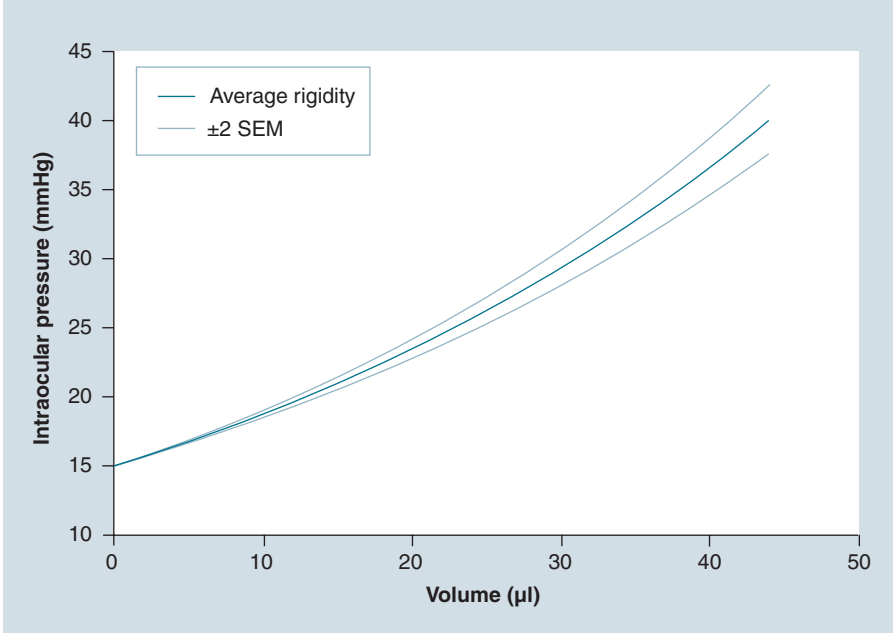

Figure 1. The pressure–volume relationship in the living human eye.
SEM: Standard error of mean.
Replotted from [15].

Different approaches have also been recently suggested. Ocular pulse amplitude measured with pneumotonometry and fundus pulsation amplitude assessed by laser interferometry may be used as pressure and respective volume, producing a new parameter that could be used as an ocular rigidity parameter [20,21], whereas in another study, choroidal blood volume measured with laser Doppler flowmetry is used to approximate volume change [22].

A minimally invasive device that is currently being validated has also been proposed to assess ocular rigidity *in vivo* [23,24]. The device, called an 'elastometer', consists of an optoelectronic applanation sensor featuring a convex surface that displaces aqueous volume, and a force sensor. From the combined measurements of displaced volume, area of contact and force required to achieve this volume dispacement, the pressure–volume relationship is calculated.

It must be kept in mind that ocular rigidity is essentially a macroscopic parameter referring to pseudostatic pressure–volume changes. This means that (relatively) fast changes (such as those occuring during the cardiac cycle or indentation by an air jet) may be characterized by a different pressure–volume relationship where the viscoelastic properties of the ocular wall should be taken into account. It remains to be elucidated whether or not this error is important in practice. Moreover, aqueous outflow during measurements is another source of error. However, this error is more straightforward to take into account using simple calculations.

Mathematical formulations

With the first attempts to quantify ocular rigidity [25,26], the nonlinearity of the pressure–volume relationship was recognized. The dependence of ocular rigidity (the rate of pressure change $[IOP_2–IOP_1]$ to volume change ΔV) on the IOP led Friedenwald to the introduction of a measurement independent of IOP, the ocular rigidity coefficient K, based on a logarithmic equation [4]:

$$K = \frac{(\log IOP_2 - \log IOP_1)}{DV}$$

The constant K arises from the more fundamental constant k, and is inversely proportional to ocular volume. Equation 1 implies an exponential pressure–volume relationship for the human eye:

$$P = P_0 \cdot e^{KV}$$

where K is Friedenwald's rigidity coefficient. This equation in differential form is also summarized in Table 1.

Several authors have suggested different formulae to describe the pressure–volume relationship in the eye based on investigations with manometry and tonometry in both living and postmortem eyes. Their measurements suggest a decrease in the

Table 1. Synopsis of different formulae to approximate the pressure–volume relationship in the eye.

Author/study (year)	Equation	Ref.
Friedenwald (1937)	$\frac{dV}{dP} = \frac{k}{V}P = KP$	[4]
McBain (1958)	$\frac{dV}{dP} = aP^n$	[33]
Holland *et al.* (1960)	$\frac{dV}{dP} = a(P-c)^n$	[34]
McEwen *et al.* (1965)	$\frac{dV}{dP} = aP + b$	[35]
Woo *et al.* (1972)	$\frac{dV}{dP} = 0.016P + 0.13$	[36]
Hibbard *et al.* (1970)	$\frac{dV}{dP} = 0.02P + 0.24$	[37]
van der Werff (1981)	$\frac{dV}{dP} = 3KP^{\frac{2}{3}}$	[38]
Silver *et al.* (2000)	$DV = V(C + C_0 \ln P + C_1 P)$	[39]

ocular rigidity coefficient with increasing IOP [7,10,17,27], an initial increase followed by a decrease [28], an increase [29], or no change [11,30–32], which is of relevance when ocular rigidity is measured from two pressure–volume pairs. Moreover, in an investigation in human postmortem eyes (enucleated and *in situ*) [7], the values for the coefficient of ocular rigidity reported were found to be lower than those reported by Friedenwald [4].

The formula proposed by Friedenwald (Equation 1) based on experiments in cadaver eyes is the one most widely used. A set of different mathematical approximations to fit the experimental data has been proposed thereafter (Table 1) [33–38]. McEwen and Helen developed a more generalized two-parameter formula than Friedenwald's equation to fit the available data, based on their experiments on scleral segments [35]. Recently, Silver and Geyer suggested a new mathematical description that may be more appropriate for *in vivo* measurements, based on an analysis of the pressure–volume data available in the literature on living human eyes [39].

Factors affecting ocular rigidity

Ocular volume

Friedenwald's coefficient of ocular rigidity is inversely proportional to ocular volume, resulting in a high correlation between ocular rigidity and refraction found in his set of measurements in young individuals [4]. Moreover, ocular volume is an important parameter in the pressure–volume relationship in the rigidity equation proposed by Silver [39]. A high dependence of the ocular rigidity coefficient on axial length has also been reported in a manometric study in a large number of human eyes [40]. The aforementioned considerations are of importance when pulsatile ocular blood flow (POBF) assessed with pneumotonometry is measured in eyes with different axial lengths. In all studies addressing the hypothesis that POBF is in fact decreased in myopia, ocular rigidity is the main confounding factor in interpreting the results [41–43]. Furthermore, the relationship between ocular volume and rigidity underlies the difference in the pressure spikes observed after an intravitreal injection in eyes with different axial lengths [44].

Moreover, the relationship between ocular rigidity and ocular volume may suggest an alteration in the compliance of the sclera in myopic eyes. Abnormalities in the scleral distensibility and thickness [45–48], and choroidal thickness and blood flow [46,47,49–51] are involved in myopia pathogenesis, with stretching and thinning of the choroid and sclera as observed with ocular enlargement. In addition, in a study investigating the biomechanics of weakened sclera during myopia development, the role of cellular and matrix factors including myofibroblasts and reduced collagen content has been highlighted, relating these changes in scleral properties to the process of eye elongation [45].

However, in a study in enucleated eyes 1–16 days postmortem, no evidence of abnormal distensibility and difference in the biomechanical properties of the sclera was reported in the eyes tested after controlling for their ocular volume, and the decreased ocular rigidity in myopic eyes was thought to be primarily a consequence of their larger ocular volume [52].

Finally, when comparing enucleated eyes before and after scleral buckling, a decrease in ocular rigidity was manifested after the buckling procedure, suggesting that an alteration in ocular shape and a resultant change in stress distribution influences ocular rigidity [53]. Moreover, it should be noted that the buckling material also plays a large role in the resulting decrease in ocular rigidity, as is suggested in a study comparing silicone and metal buckling materials in enucleated eyes [54].

Age

An increase in the ocular rigidity coefficient with increasing age was first reported by Friedenwald in a large series of human eyes [4]. In more recent studies performed with paired identation tonometry [55,56] and manometry in living [14] and enucleated eyes [52], an increase in ocular rigidity with age was observed. An increase in stiffness and decrease in thickness of the peripapillary and posterior sclera with age has also been reported in primates [57], while measurements in human scleral segments also indicate a relationship between age and elasticity of the

sclera [58]. The relationship between age and ocular rigidity is of importance as it may underlie the susceptibility to age-related ocular disease [59].

Arterial pressure & ocular blood volume

In measurements performed in cadaver eyes, inevitable postmortem changes, lack of blood supply and temperature control, as well as the conditions of the experiments, and control of 'leak' and stress relaxation, are parameters that may have affected existing data from different investigators in various ways, and emphasize the need for *in vivo* measurements. Vascular rigidity, as a parameter characterizing the resistance of the choroidal vessels to blood expulsion from the eye through the vortex veins, is also mentioned in the work of Friedenwald as a source of variation in the value of the ocular rigidity coefficient when discussing his findings on the effect of drugs and the presence of glaucoma [4].

When comparing data *in vivo* and *ex vivo*, ocular rigidity in the same IOP level appears to be higher in enucleated eyes [10,13]. The pressure–volume curves of the living and dead eye coincide when blood perfusion in the living eye is stopped at an IOP that exceeds the arterial blood pressure [10,60], suggesting that vascular blood supply may play a role in the value of the ocular rigidity coefficient. This 'cushioning' effect is estimated to be of small magnitude [10], whereas in another study considerable blood volume changes, comparable to corneal volume changes, were reported during indentation tonometry [13]. Moreover, from animal studies using carotid compression a measure of vascular rigidity can be obtained and ocular rigidity was found to increase when ocular blood volume is decreased [13,61].

In his experimental studies in rabbits, Kiel investigated the effect of changing mean arterial pressure on the pressure–volume relationship [60]. Kiel concluded that systemic arterial pressure influences ocular rigidity by altering blood volume and choroidal blood flow. The initial part of the pressure–volume curve is indeed influenced by the degree of choroidal autoregulation, which accounts for the arterial pressure dependence of choroidal volume [62], whereas in higher IOPs and lower perfusion pressures, blood expulsion from the eye is the main source of discrepancy between the rigidity curves in the living and dead eye. When intraocular blood volume is expelled, the pressure–volume relationship becomes independent of mean arterial pressure. However, in a study in living human eyes, the relationship between ocular rigidity and mean arterial pressure was not significant in the range of clinically encountered systemic blood pressures and IOPs [15].

Thickness of the cornea & sclera

Apart from the dimensions of the globe, it may be assumed that the thickness of the cornea and sclera may also play a role in ocular rigidity. Moreover, central corneal pachymetry (CCT) can easily be assessed in everyday clinical practice. However, in the few studies addressing this hypothesis, no relationship was reported between rigidity and CCT [14] or scleral thickness [52].

The effect of corneal refractive surgery on ocular rigidity has also been investigated. In an experimental manometric study in rabbits, no difference in rigidity was found before and after a large decrease in CCT induced with photorefractive keratectomy [63], whereas in another report in human eyes LASIK was found to influence ocular rigidity measured with differential tonometry [64]. However, it must be kept in mind that tonometric techniques are more susceptible to error pertaining to the local mechanical stiffness of the cornea, a parameter that is affected by refractive surgery.

Experimental studies have shown that the stiffness of the cornea is increased compared with that of the sclera [65–67], and that the distensibility of the sclera was higher than that of the cornea in enucleated rabbit [65] and human eyes [66], up to an IOP of at least 50 mmHg. In another study in porcine eyes, the cornea modulus of elasticity was measured to be higher than that of the sclera [67], suggesting that the cornea offers more resistance to deformation than the sclera. Furthermore, a change in the scleral and not the corneal curvature [68–69] along with an increase in axial length [70] with increasing IOP is reported. The scleral modulus of elasticity, on the other hand, appears to be higher than that of the choroid [58]. However, in an experimental study in animal cadaver eyes, the IOP change resulting from an acute volume change was increased compared with baseline after an induced corneal stiffening with glutaraldehyde cross-linking [71]. Therefore, corneal rigidity is a factor in the ocular rigidity [71,72], but of a rather decreased significance as to the manifest macroscopic resistance of the globe in the range of clinically encountered IOPs.

Ocular rigidity & ocular disease

Age-related macular degeneration

Ocular rigidity has been suggested by Friedman to play a role in the pathogenesis of age-related macular degeneration (AMD) [59,73]. According to the model proposed, diet and age may be associated with a lipoid infiltration and decreased compliance of the sclera, the retinal pigment epithelium (RPE) and vessel walls, leading to an increased resistance to blood flow, impaired perfusion and elevated choriocapillary pressure. Eventually the series of events result in decreased RPE transport, the formation of drusen, RPE detachment and neovascular membranes (i.e., the dry and exudative forms of the disease). Another point towards this theory is the increased incidence of AMD in hyperopic eyes [74–76], along with the relationship between ocular rigidity and volume.

Pallikaris *et al.* investigated this hypothesis using a manometric device and found that eyes with neovascular AMD treated with photodynamic therapy exhibited increased ocular rigidity compared with eyes with the dry form of the disease and control subjects [77].

Glaucoma

The theories relating material properties and geometry of the optic nerve and scleral wall, and the resulting level of IOP-related stress and strain with the pathogenesis and progression of glaucomatous optic neuropathy and susceptibility to

damage [78–82] are supported in various histomorphometry and finite element modeling studies that aim to characterize the biomechanics of the lamina cribrosa and posterior sclera [57,83–85]. Although the stiffness of the sclera has been proposed as a major determinant of optic nerve head biomechanics [83,86], it is also the interaction between geometry and mechanical factors that is suggested to influence IOP-related stress and strain [87]. In this context, ocular rigidity, as a macroscopic parameter characterizing the distensibility of the globe, may also be altered in glaucoma.

Friedenwald reported that ocular rigidity was highly variable in acute glaucoma and increased in untreated chronic glaucoma, usually returning to normal after surgical or pharmaceutical treatment [4]. The aforementioned results may be confounded by a dependence of the ocular rigidity coefficient on IOP. In a study in glaucoma patients under miotic therapy [88], a decreased ocular rigidity coefficient has been reported using indentation tonometry. In the study by Hommer and colleagues, primary open-angle glaucoma patients taking antiglaucoma medications were compared with normal subjects, and a higher rigidity factor, calculated as the product of ocular pulse amplitude measured with pneumotonometry and fundus pulsation amplitude assessed by laser interferometry, was found in the glaucoma group [21]. However, fundus pulsation amplitude, used as a respective index of volume change, corresponds to the corneo–retinal distance change and does not estimate the scleral outward movement during the cardiac cycle [89]. In another study, measurements were performed with dynamic contour tonometry, and axial length was measured with partial coherence laser interferometry before and after a reduction in IOP with acetazolamide [90]. Glaucoma patients again exhibited a higher ocular rigidity parameter, although baseline IOP was higher in the glaucoma patients and the axial length change was near the resolution limit of the device used, as mentioned by the authors. Moreover, an increase in the ocular rigidity coefficient in living and dead rabbit eyes that had been subjected to raised IOP has been reported [18]. However, a lower rigidity parameter computed from dynamic contour tonometry and laser Doppler flowmetry has also been found in open-angle glaucoma patients compared with normal subjects and ocular hypertensives [22].

Keratoconus, uveitis, osteogenesis imperfecta, hormones & drugs

Alterations to the biomechanical properties of the cornea [91], stretching without tissue mass loss [92], intra-lamellar displacement and slippage [93] are involved in the pathogenesis of keratoconus. Keratoconus patients exhibit lower ocular rigidity coefficients compared with normal controls [94], measured with Schiotz tonometry, and corneal thinning was found to correlate with ocular rigidity in these patients [95]. In the same study, ocular rigidity was found to return to normal after corneal transplantation.

In Friedenwald's studies, ocular rigidity was found to be altered in uveitis patients [4]. Uveitis is associated with ocular vessel congestion, alterations in aqueous flow and changes in IOP. Friedenwald hypothesized that in uveitis ocular rigidity would be decreased, at least in eyes with IOPs in the normal range. However, measurements showed that it was in fact increased irrespective of the level of IOP [4]. In the same study, measurements in eyes under treatment with pilocarpine and epinephrine showed that drugs acting as vasodilators and vasoconstrictors result in a decrease and increase in ocular rigidity, respectively.

In another study in a series of patients with osteogenesis imperfecta, ocular rigidity was reported to be lower compared with controls [96], and an inverse relationship was found between the blueness of the sclera and ocular rigidity [97]. Ocular rigidity was found to be decreased in eyes with thyrotropic endocrine exophthalmos [98] and after retinal detachment surgery [99,100]. Finally, no difference was observed in ocular rigidity values during the menstrual cycle [101].

Expert commentary

Although the concept of ocular rigidity and the ocular pressure–volume relationship spans over a century, our knowledge on this parameter remains limited. An apparent explanation is the lack of an accurate, noninvasive measurement technique. The invasive nature of manometry, as well as the inaccuracies of paired indentation tonometry, posed limitations as to the number of eyes studied as well as to the conclusions drawn from existing studies.

The pressure–volume relationship is the manifestation of a complex series of different phenomena occuring in the eye as a response to a volume change. Ocular volume and shape, thickness of the ocular wall, choroidal blood volume and age have all been shown to influence ocular rigidity. Moreover, there is evidence that ocular rigidity is increased in patients suffering from glaucoma and neovascular AMD, whereas the relationship between ocular rigidity and the pathogenesis of myopia remains controversial. These initial findings have yet to be confirmed.

Five-year view

A key point in the characterization of ocular rigidity is the development of an accurate and noninvasive instrument for clinical use. Measurement devices such as the elastometer, which is currently being evaluated, are promising [23,24]. The measurement of the pressure–volume relationship in a clinically significant range of IOPs with this instrument is important for our understanding of the biomechanics of the human eye. Moreover, other approaches have already been used to assess parameters of ocular rigidity [21,22]. One of the main difficulties in measuring ocular rigidity has been the quantification of ocular volume changes. Heart rate-related distance changes between the cornea and different preselected reflecting layers in the eye, measured with a device based on the principle of low coherence tissue interferometry [102], may be used as a surrogate for ocular volume changes. However, as mentioned by the authors, the measurement of the relative movement of the anterior surface of the cornea and the submacular sclera may be problematic owing to scattering and absorption owing to the choroid's rich vascularity. In addition, the ocular response

analyzer is suggested to measure corneal viscoelastic properties [103] and the parameters that can be quantified with this device are being characterized in ongoing studies. However, the relationship of these parameters to the macroscopic index of ocular rigidity is unknown to date.

The role of the biomechanical properties of the ocular shell in glaucoma and AMD is another prominent objective. According to Friedman's theory [59,72], eyes with decreased ocular elasticity are predisposed to the development of AMD, a hypothesis that has been supported from manometric measurements [77]. Moreover, studies in glaucoma patients have provided initial evidence for an increased ocular rigidity in those patients [21,90].

In this context, possible therapeutic approaches that aim to reduce ocular rigidity need to be evaluated. Surgical methods could pertain to one or more of the following: localized reduction of the ocular wall stiffness, a deformation (e.g., indentation) of the ocular wall, and a compressible implant inserted into the eye, or even placed in contact with the eye. In this context, in an experimental model the rigidity of the eye was decreased after the insertion of an intraocular bubble, which, being more compressible, increased the manifest elasticity of the eye [104].

Further *in vivo* studies assessing the factors influencing ocular rigidity are warranted. In addition, measurements of ocular rigidity may enhance the accuracy of tonography and pulsatile ocular blood flow measurements. Finally, whether this parameter is involved in the pathogenesis of ocular disease or is secondary to the disease process remains to be elucidated.

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Key issues

- Ocular rigidity is a measure of the material and geometrical properties of the eye.
- The pressure–volume relationship in the living human eye is nonlinear (the slope depends on the intraocular pressure [IOP]).
- The ocular rigidity coefficient is a measure of the stiffness of the eye, based on a logarithmic pressure–volume relationship and is assumed to be independent of IOP.
- The pressure–volume relationship differs in the living and postmortem eye, indicating that tissue necrosis and choroidal blood volume affect ocular rigidity. Therefore, *in vivo* ocular rigidity estimates should be employed in tonography and pulsatile ocular blood flow studies.
- The main factors that influence ocular rigidity are IOP, ocular volume, age, ocular blood volume and arterial pressure, and properties of the cornea and sclera (i.e., thickness, elasticity).
- Ocular rigidity is reported to be altered in glaucoma and age-related macular degeneration. Further studies in this direction are warranted.

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