tvst

https://doi.org/10.1167/tvst.8.5.10

Article

Characterization of Corneal Biomechanical Properties and Determination of Natural Intraocular Pressure Using CID-GAT

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Received: 23 May 2019
Accepted: 13 July 2019
Published: 11 September 2019

Keywords: intraocular pressure; biomechanical properties; corneal modulus; confounding factors; porcine eyes

Citation: Lu S-H, Chong IT, Leung SYY, Lam DCC. Characterization of corneal biomechanical properties and determination of natural intraocular pressure using CID-GAT. Trans Vis Sci Tech. 2019;8(5):10, https://doi.org/10.1167/tvst.8.5.10

Purpose: The intraocular pressure (IOP) measured using Goldmann Applanation Tonometry (GAT) is confounded by individual corneal properties. We investigated a modified method that removes the confoundment by incorporating corneal properties into the Imbert-Fick's law is investigated.

Method: Porcine eyes were pressurized between 10 and 40 mm Hg using a manometer. The eyes were indented using a flat cylindrical indenter. A modified corneal indentation device (CID) procedure was used to obtain the corneal moduli E_{qs}. The calculated IOP_{NC} from the Imbert-Fick's Law using the corneal moduli E_{qs} was compared to the natural IOP_N, measured using pressure sensor inserted into the eye.

Results: Test results showed that IOP-dependent corneal modulus E_{qs} is a primary confounding factor in IOP calculation. The average elastic modulus E_{qs} is 0.173 $\pm$ 0.018 MPa at 20 mm Hg, and increases with IOP at a linear rate of 0.0066 MPa per mm Hg ($r = 0.997$, $P < 0.001$). Incorporation of individual E_{qs} into IOP_{NC} calculation showed that IOP_{NC} are in good agreement with reference IOP_N (slope = 0.999, $r = 0.939$, $P < 0.001$).

Conclusions: The IOP-dependent corneal modulus E_{qs} is a primary confounding factor in IOP calculation. A modified CID-GAT procedure to obtain natural cornea-independent IOP_{NC} is developed and verified in this study. The CID-GAT IOP modification may be used in place of conventional GAT when the confounding effects in eyes with atypical cornea (e.g., laser-assisted in situ keratomileusis [LASIK] thinned) are significant.

Translational Relevance: Confoundment from corneal properties results in IOP measurement errors. The study showed that the CID-GAT method can significantly reduce the confounding corneal errors.

Introduction

The accuracy of Goldmann applanation tonometry (GAT) is confounded by individual variations, such as central corneal thickness (CCT), corneal radius of curvature, and elastic modulus.[1–9] Confoundment by these parameters leads to >3 mm Hg error in the measurement.[9–13] The majority of the geometric parameters, including CCT and curvature, can be measured in vivo, and methodologies to account for these geometric parameters in GAT intraocular pressure (IOP) have been developed.[9] Despite these advances, a gap between the GAT and natural (IOP_N) IOP in the eye remains because of the inability to account for individual biomechanical properties in the GAT IOP.

GAT measures the corneal applanation load at a fixed area A and calculates the IOP using the Imbert-Fick's law.[14] During applanation, the applanation force F is opposed by the surface tension s from the tear film, upward corneal resistance b, and outward IOP. The force balance is given as Equation 1.

$$\mathrm{IOP} = \frac{F + s - b}{A}. \quad (1)$$

The method is valid only when the corneal

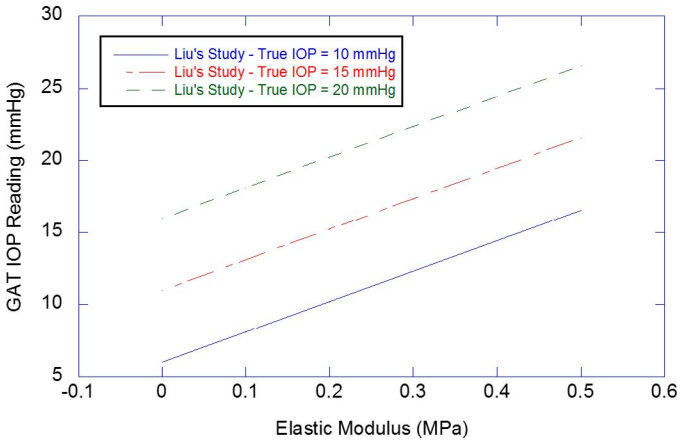

Figure 1. Theoretical prediction of the influence of corneal biomechanics on IOP measurement by Liu et al.[8]

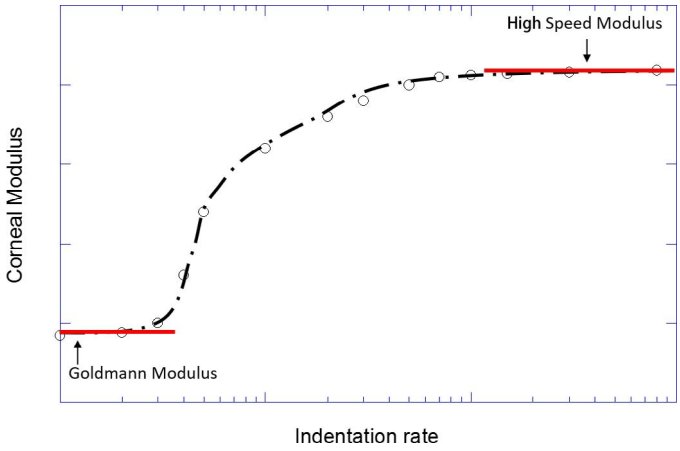

Figure 2. Corneal tangent modulus as a function of indentation rate for a porcine eye.[16]

resistance b cancels out the corneal surface tension s. Mechanics analysis[15,16] showed that the individual corneal resistance b is not a constant, but is a function of the corneal thickness t, anterior cornea curvature R_c, indentation depth δ, geometric parameter a, Poisson's ratio v, and Goldmann quasistatic elastic modulus E_{GAT}, given as:

$$b = \frac{E_{GAT} t^2}{a(R_c - t/2)\sqrt{1 - v^2}} \delta. \quad (2)$$

Goldmann and Schmidt[14] examined the corneal applanation behavior on a group of patients. The study determined that the population-averaged b is counterbalanced by s at the GAT applanation contact area $A_{GAT} = 7.35$ mm^2 (applanation diameter of 3.06 mm) such that,

$$\mathrm{IOP}_{GAT} = \frac{F}{A_{GAT}}. \quad (3)$$

The simplification is acceptable when the corneal resistance of the subject is the same as assumed in the formulation, but IOP measurement on subjects with corneal properties different from that assumed in GAT will lead to measurement errors.[4] The error has been theoretically examined by Liu et al.[8] They showed that when the elastic modulus is halved or doubled, up to 5 mm Hg of error may occur (Fig. 1). In further work by others,[16–18] the corneal behavior is shown to be nonlinear viscoelastic, such that the effective elastic modulus is dependent on the IOP and loading rate (Fig. 2). In Goldmann applanation, the load is measured after the applanation is stabilized. Under this quasistatic condition, the E_{GAT} measured in GAT is a quasistatic property. Estimates in the literature showed that corneal property is a confounding factor that could result in IOP error of up to 5.35 mm Hg[4] in GAT.

In this study, a new method to measure the corneal properties of test eyes and an analysis method to determine the corneal-independent IOP_N are developed and tested using porcine eyes.

Methods

In prior studies, indentation methodologies were developed to characterize high-speed indentation behavior of the eyes.[16–18] The instrumented corneal indentation was used to characterize load-displacement data at high speed for eyes pressurized between 20 mm Hg and 40 mm Hg. The procedure was tested on porcine eyes ex vivo and rabbit eyes in vivo. The corneal indentation device (CID, Fig. 3) was developed from these earlier studies and was designed to indent the cornea using a flat punch indenter; the

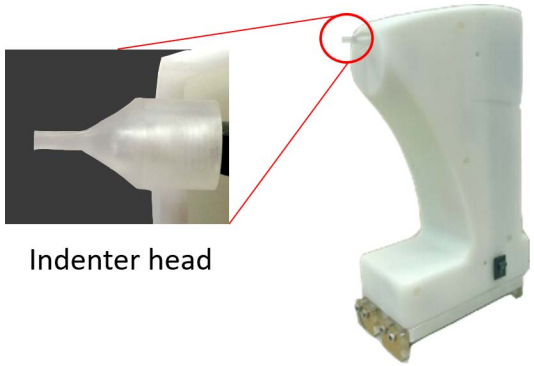

Figure 3. Corneal indention device and corneal indenter (US Patent WO2012163080 A, 2012).

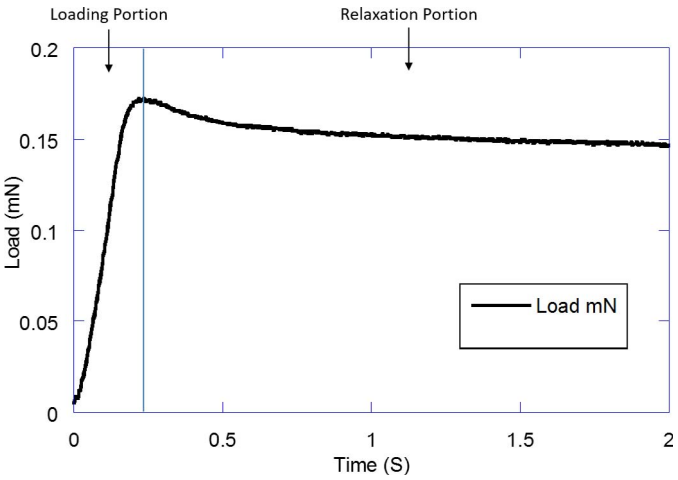

Figure 4. Fast indentation loading and relaxation of indented load on porcine eyes.

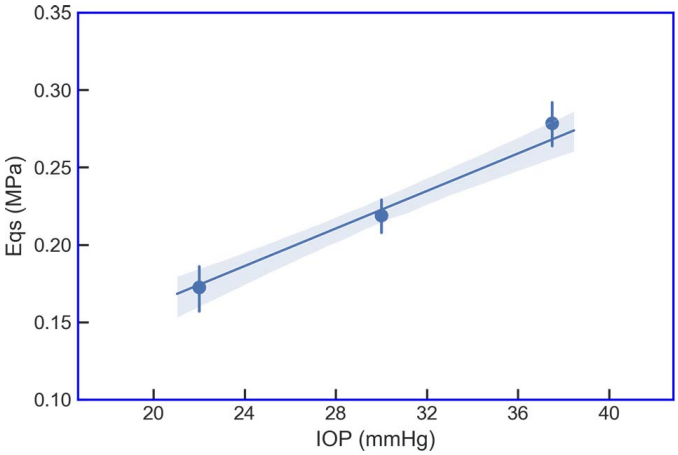

Figure 6. Goldmann tangent modulus in the function IOP on porcine eyes.

loads and displacements are recorded during corneal indentation. The CID was deployed successfully in clinical trials to characterize the in vivo corneal tangent modulus[16–18] in humans. In CID tests on porcine eyes, the indentation load becomes stable at fixed displacement after the displacement is held for 2 or more seconds (Fig. 4). The stabilized CID quasistatic load is fully relaxed, and the load measured under this condition corresponds directly with the quasistatic load in GAT. The quasistatic stiffness of the eye then is the change in quasistatic load per unit indent depth. The procedure to characterize the quasistatic stiffness as a function of IOP under the quasistatic Goldmann condition is detailed below.

We tested 15 fresh ex vivo porcine eyes in indentation tests in this study. Porcine eyes were obtained from a local abattoir, and kept moist and cold using an insulated bucket with refrigerants. All experiments were conducted within 12 hours of the animals being killed.

Before testing, the porcine eye with muscle and adipose tissue attached was placed on a support cup fixture. A hypodermic needle, connected to a manometer, was inserted into the anterior chamber of the eye. The pressure P_m was adjusted between 10 and 40 mm Hg by adjusting the liquid level in the manometer and calculated using,

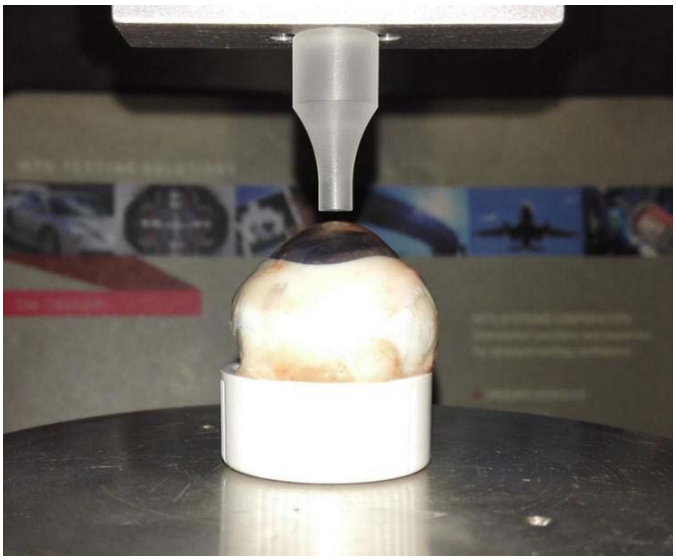

Figure 5. Experimental setups on porcine eyes.

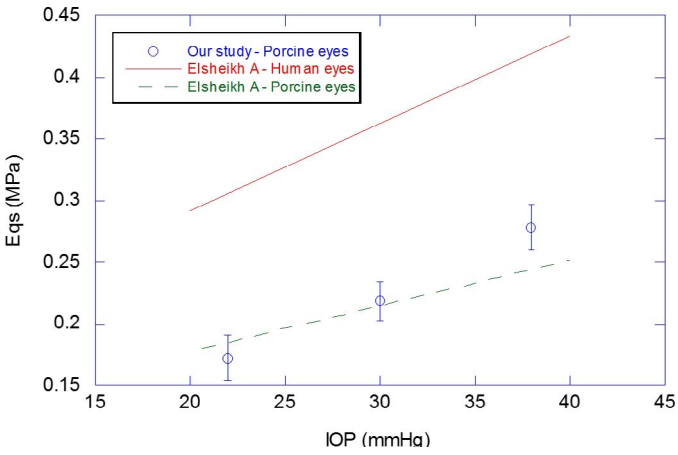

Figure 7. Comparison of quasistatic tangent modulus with Elsheikh's study.[3]

Table 1. Determination of the Coefficient: The Empirical Geometry Coefficient a can be Determined From the Look-Up Table Using the Value of Indentation Geometry Constant μ (Equation 7)

μ	0	0.1	0.2	0.4	0.6	0.8	1.0	1.2	1.4
a	0.443	0.431	0.425	0.408	0.386	0.362	0.337	0.311	0.286

$$P_m = \rho g h, \tag{4}$$

where ρ is the density of the fluid (water) in the manometer, g is the gravitational acceleration, and h is the height difference between the hypodermic needle and liquid level in the manometer. A needle pressure sensor was inserted into the anterior chamber to monitor the reference IOP_N in the chamber synchronously as feedback.

The pressurized porcine eyes were indented using the CID with a 3.5 mm flat punch indenter (Fig. 5). The eyes were indented to full contact by the 3.5 mm flat punch at a rate of 12 mm/s to set depths of $\delta_p =$ 0.4 and 0.6 mm, respectively. The displacements were held for four seconds at each set depth until the load became steady (Fig. 4). The load-displacement and time data were captured at a sampling rate of 333 Hz (1 sampling point/0.003 second) by the CID and stored.

In indentation tests, the cornea is deformed by the indentation load and IOP. At full indenter contact, the indentation resistance is described by Equation 2, and the force balance on the indenter can be modeled using the Imbert-Fick's law (Equation 1). Rearranging,

$$E|_{IOP} = \frac{dF/d\delta|_{IOP}}{K_g} = \frac{s|_{IOP}}{K_g}, \tag{5}$$

the indentation modulus at constant IOP as $E|_{IOP}$ can be derived from the corneal stiffness, $s|_{IOP}$ is the corneal stiffness. K_g is,

$$K_g = \frac{t^2}{a(R_c - t/2)\sqrt{1-\nu^2}} \tag{6}$$

where R_c is the anterior corneal radius of curvature (outermost surface), t is the central corneal thickness, ν is the Poisson's ratio of the cornea ($\nu \sim 0.5$[19]), and a is the empirical geometry coefficient, determined from indentation geometry constant μ and Table 1,[15]

$$\mu = r_0 \left[\frac{12(1-\nu^2)}{(R - t/2)^2 t^2}\right]^{1/4}, \tag{7}$$

where r_0 is the radius of the contact area between the indenter and cornea.

After complete relaxation at the two displacements $\delta_{p,1}$ and $\delta_{p,2}$, the individual E_{GAT} were determined from the two stabilized loads and displacements using,

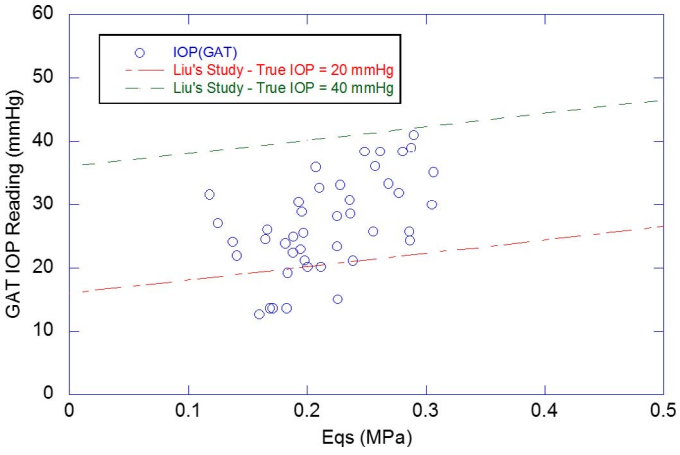

Figure 8. Comparison of GAT IOP readings in the function of Goldmann quasistatic modulus with Liu's study.[8]

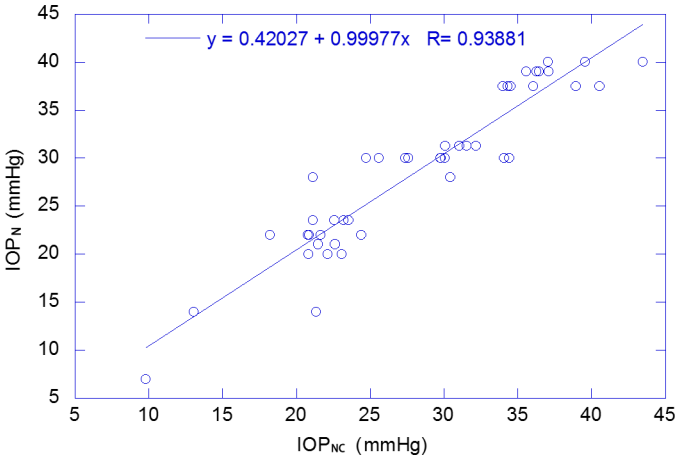

Figure 9. Correlation of modified IOP versus controlled IOP on porcine eyes.

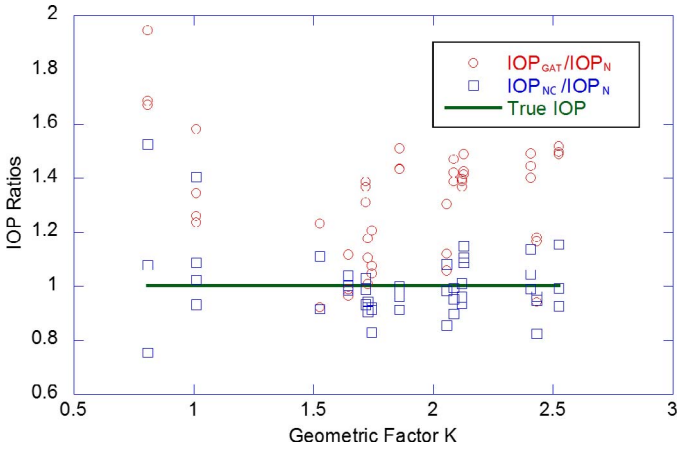

Figure 10. Measured IOP/true IOP ratio in the function of geometric factor K_g.

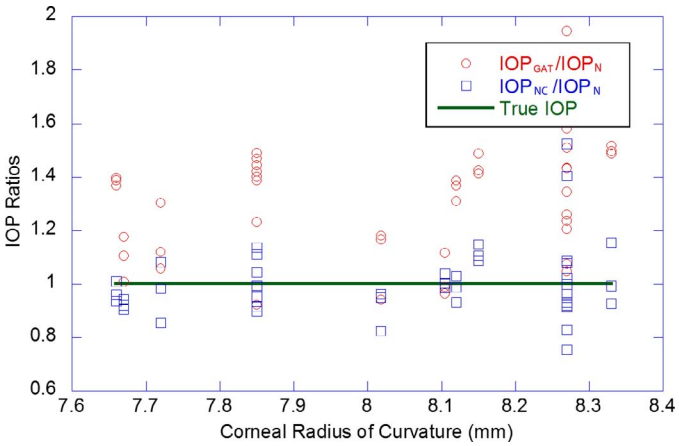

Figure 12. Measured IOP/true IOP ratio in the function of corneal radius of curvature.

$$E_{\mathrm{GAT}} = \frac{dF/d\delta|_{\mathrm{GAT}}}{K_g} = \frac{F_{p,1} - F_{p,2}}{\delta_{p,1} - \delta_{p,2}} / K_g. \qquad (8)$$

The corneal bending resistance then is determined by substituting Equation 8 into Equation 2. The specific surface tension s can be determined by the diameter of the contact area between the indenter and the cornea,

$$s = s_{\mathrm{GAT}} \frac{D}{D_{\mathrm{GAT}}}, \qquad (9)$$

where s_{GAT} is the tear surface tension at $A_{\mathrm{GAT}} = 7.35$ mm^2 ($s_{\mathrm{GAT}} \approx 0.00407115$N[2,8]), D is the diameter of the indenter, and D_{GAT} is 3.06 mm.

$\mathrm{IOP_{NC}}$ is computed using the Imbert-Fick's law in Equation 1 while the GAT IOP was determined by Equation 3 where the applanation area was set to 3.06 mm^2. The corneal dependence of IOP was examined by comparing $\mathrm{IOP_{NC}}$ with the reference $\mathrm{IOP_N}$.

Results

The Goldmann elastic modulus from the quasistatic stiffness in Equation 5 is shown in Figure 6. The average elastic modulus E_{qs} is 0.173 ± 0.018 MPa at IOP of 20 mm Hg. The magnitudes are comparable with Elsheikh's study using the inflation test where corneas also were loaded in a quasistatic manner (Fig. 7).[3,8] The Figures show the E_{qs} varied linearly with IOP such that an increment of each mm Hg in IOP results in an E_{qs} change of 0.0066 MPa ($r = 0.997$, $P < 0.001$). The quasistatic corneal modulus E_{qs} doubles if the IOP is increased by 25 mm Hg. The results are in agreement with the theoretical estimates reported in the study by

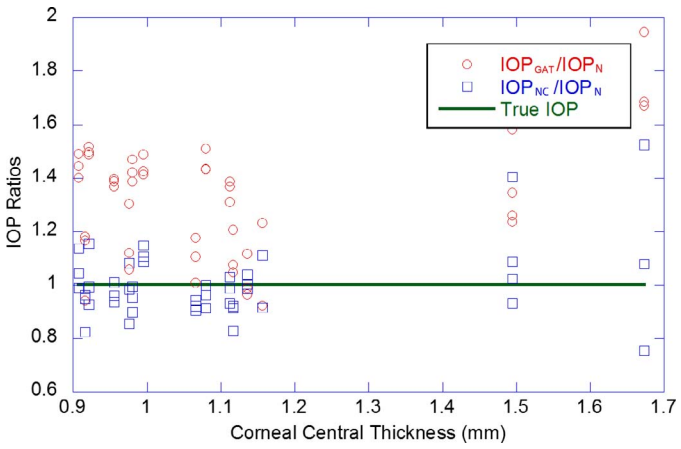

Figure 11. Measured IOP/true IOP ratio in the function of corneal central thickness.

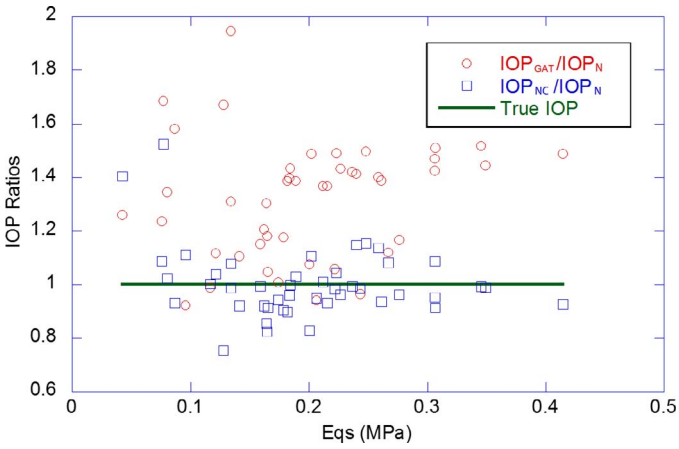

Figure 13. Measured IOP/true IOP ratio in the function of Goldmann elastic modulus E_{qs}.

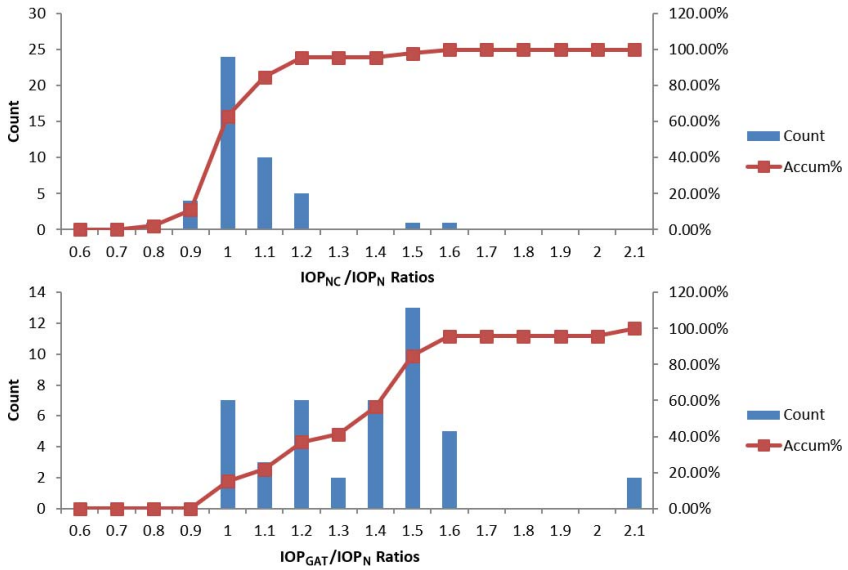

Figure 14. Comparison of corneal-independent IOP and GAT IOP measurement.

Liu et al.[8] (Fig. 8). Comparison of IOP_{NC}, calculated using individual E_{qs}, with reference IOP_N is plotted in Figure 9. Analysis showed that IOP_{NC} is in good agreement with IOP_N ($n = 15$, $r = 0.94$, $P < 0.001$). This shows that the CID-GAT procedure and the modified calculation method successfully removed the confounding effect from the cornea from IOP_{NC}.

Discussion

The good agreement between IOP_{NC} and reference IOP_N is dependent on the ability of the CID to characterize the quasistatic E_{qs} of the cornea. Asejczyk-Widlicka et al.[20] reported a corneal elastic modulus of 0.05 to 0.24 MPa in the IOP range from 12 to 25 mm Hg on porcine eyes ex vivo.[20] Inflation tests were conducted in their study, but the rates were not specified. Elsheikh et al.[3] performed inflation tests on human and porcine eyes. In their tests, the eyes were quasistatically loaded to set pressure and with similar loading conditions to our study. The corneal quasistatic tangent moduli determined in their inflation tests of porcine eyes (dashed line) are in the same range of results as the present study shown in Figure 7.

The confounding effects of corneal properties in GAT IOP measurement were examined quantitatively by Liu et al.[8] They investigated the IOP elevation in porcine eyes after glutaraldehyde treatment and found that the corneal modulus increased 1 MPa for every 5 mm Hg change in IOP.[21] Our results are in line with their model over the tested range of pressure (Fig. 8).

The confounding effect of the geometric factor K_g, corneal center thickness, corneal radius, and E_{qs} on IOP are shown in Figures 10 to 13, respectively. The variation between the IOP_N and IOP_{GAT} indicates the dependencies of GAT measurement on these corneal properties. Comparison (Fig. 14) showed that the standard deviation (SD = 0.11) of IOP_{NC} from IOP_N was significantly smaller than that (SD = 0.32) of the IOP_{GAT} from IOP_N. More than 80% of IOP_{NC} were within 10% error of IOP_N while IOP_{GAT} generally deviated from IOP_N by 50%.

The CID-GAT method was designed to characterize the IOP_N by accounting for the effects of individual-specific corneal biomechanical properties and corneal geometries on IOP_N. Changes in corneal curvature (R_c), thickness (t), and corneal elastic properties (E_{qs}) were accounted for in Equation 6. The corneal elastic properties (i.e., the elastic modulus of the tissue) are known to increase with aging and IOP.[22–25] The curvature and corneal modulus may change in subjects with keratoconus, and the corneal thickness may increase in subjects with edematous corneas. These confounding effects from aging or illnesses are readily accounted for by the CID-GAT method in Equation 6.

In conclusion, the confounding effect of corneal properties has a great impact on GAT IOP measurement. The effect can be reduced significantly using the CID-GAT method with an updated treatment for corneal resistance in the Imbert-Fick's Law. The

updated calculation of IOP_{NC} using corneal modulus obtained from the CID showed good agreement with IOP_N, the natural IOP of the eye. The CID-GAT method to calculate IOP_N may be of particular relevance and use for subjects with corneas having abnormal biomechanical properties (e.g., aging effects, refractive surgeries, swelling, keratoconus, and so forth).

Acknowledgments

Disclosure: **S.-H. Lu**, None; **I.T. Chong**, None; **S.Y.Y. Leung**, None; **D.C.C. Lam**, None

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