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Partial Contact Indentation Tonometry for Measurement of Corneal Properties-Independent Intraocular Pressure

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Abstract: Inter-individual differences in corneal properties are ignored in existing methods for measuring intraocular pressure *IOP*, a primary parameter used in screening and monitoring of glaucoma. The differences in the corneal stiffness between individuals can be more than double and this difference would lead to *IOP* measurement errors up to 10 mmHg. In this study, an instrumented partial-contact indentation measurement and analysis method that can account for inter-individual corneal difference in stiffness is developed. The method was tested on 12 porcine eyes *ex vivo* and 7 rabbit eyes *in vivo*, and the results were compared to the controlled *IOPs* to determine the method's validity. Analyses showed that without corneal stiffness correction, up to 10 mmHg of measurement error was found between the existing approach and the controlled *IOP*. With the instrumented indentation and analysis method, less than 2 mmHg of differences were founded between the measured *IOP* and the controlled *IOP*. These results showed that instrumented partial-contact indentation can effectively account for inter-individual corneal variations in *IOP* measurement.

Keywords: Intraocular pressure, corneal stiffness, cornea, indentation, glaucoma

1 Introduction

Intraocular pressure (*IOP*) of the eye is the primary risk factor in the pathogenesis of glaucoma, diagnosis and management of glaucoma [Quigley and Addicks (1980); Costa and Wilson (2002); Gupta (2004); Sit and Liu (2009)]. Techniques such as the Goldmann Applanation Tonometry (*GAT*) are available to measure individual's *IOP*. In the classical Goldmann Applanation Tonometry [Goldmann and

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Schmidt (1957)], the *IOP* is determined from the force balance between the applied force, corneal membrane resistance, the intraocular pressure and the surface tension (Imbert-Fick Law). The force balance of these forces is (Figure 1) [Ethier and Simmons (2007)],

$$F + s = A \cdot IOP + b, \tag{1}$$

where *IOP* is the intraocular pressure, *F* is the indentation load, *A* is the indentation

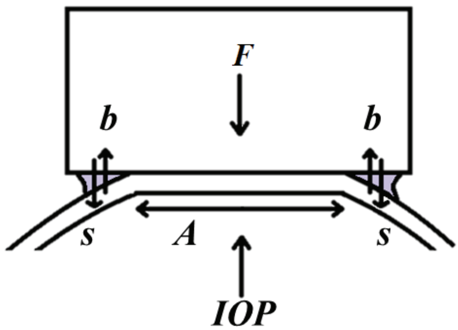

Figure 1: The force balance of the cornea under the indenter.

contact area, *s* is the tear surface tension pulling the indenter toward the cornea, and *b* is the upward resistance generated by the corneal membrane. For *GAT*, the applanation area is fixed at d = 3.06 mm; A = 7.35 mm^2 such that *b* is assumed to be equal to *s* [Goldmann and Schmidt (1957)]. Given this standing assumption in *GAT*, the variation in *b* is ignored so that the *GAT* measured *IOP* (IOP_G) can be determined simply via,

$$IOP_G = \frac{F}{A}. \tag{2}$$

The corneal resistance *b* is directly proportional to the corneal stiffness (S_{cn}). Study in the literature showed that the corneal stiffness (S_{cn}) varies with *IOP* and with individuals (Figure 2) [Kurita, Kempf, Iida, Okude, Kaneko, Mishima, Tsukamoto, Sugimoto, Katakura and Kobayashi (2008)]. This implies that *b* is not constant as is assumed in the original GAT formulation above. Variation in S_{cn} from individual to individual would lead to variation in *b* and measurement error in IOP_G. The IOP_G measurement error from variation of S_{cn} between 0 and 0.1 N/mm can be estimated (Appendix I for calculation details). For normal population mean eye geometries and *IOP* of 15 mmHg, the variation in S_{cn} may lead to IOP_G measurement error up to 10 mmHg (Figure 3).

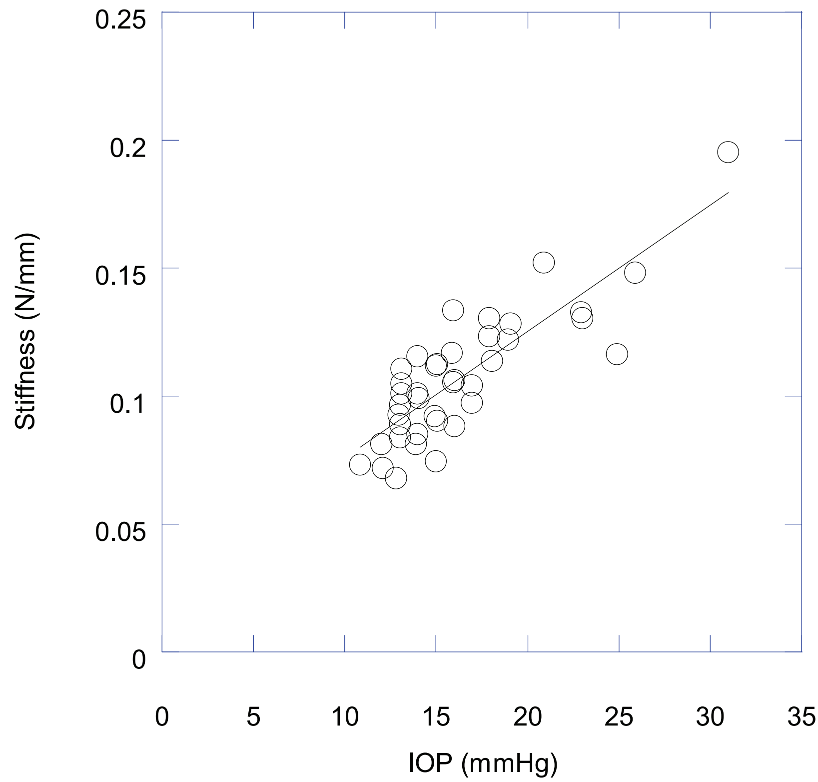

Figure 2: Correlation between human eye stiffness and *IOP* from Kurita et al. [Kurita, Kempf, Iida, Okude, Kaneko, Mishima, Tsukamoto, Sugimoto, Katakura and Kobayashi (2008)].

Other than the corneal stiffness, the central corneal thickness (*CCT*) and corneal radius of curvature (R_{cn}) also affect the IOP_G measurement [Whitacre and Stein (1993); Ku, Danesh-Meyer, Craig, Gamble and McGhee (2005); Schneider and Grehn (2006); Francis, Hsieh, Lai, Chopra, Pena, Azen and Varma (2007); Medeiros, Sample and Weinreb (2007); Ceruti, Morbio, Marraffa and Marchini (2008); Kwon, Ghaboussi, Pecknold and Hashash (2008); Hsu, Sheu, Hsu, Wu, Yeh, Tien and Tsai (2009); Oh, Yoo, Kim, Kim and Song (2009); Realini, Weinreb and Hobbs (2009)]. Studies showed that the IOP_G underestimates the true intraocular pressure (IOP_T), when the *CCT* is thick and/or when the R_{cn} is large (Figure 4 and Figure 5).

To remove the corneal thickness and the corneal radius dependences in the measurement, the cornea can be forced to conform to a rigid contour. This approach was used in Dynamic Contour Tonometry (*DCT*) to minimize the bending and tan-

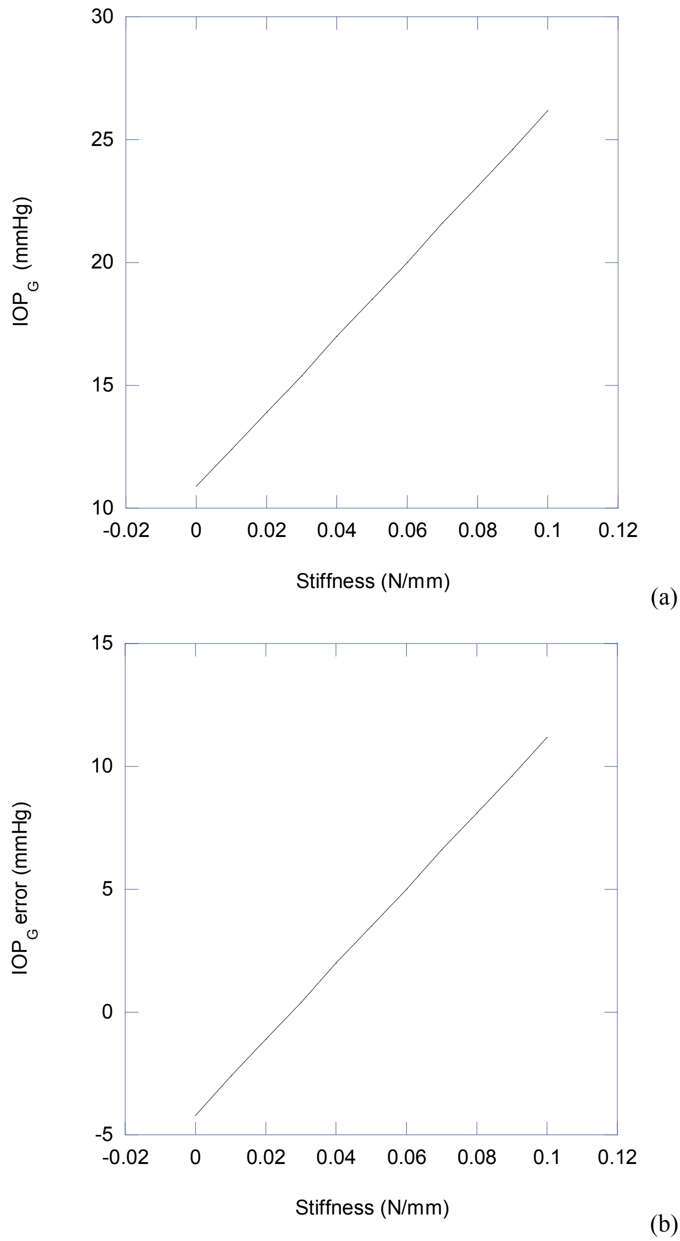

Figure 3: (a) IOP_G measurement as a function of corneal stiffness. (b) Variation of IOP_G measurement error (IOP_G - IOP_T) as a function of corneal stiffness. The data were calculated using equation (A4) at IOP_T = 15 mmHg and corneal radius of curvature (7.8 mm).

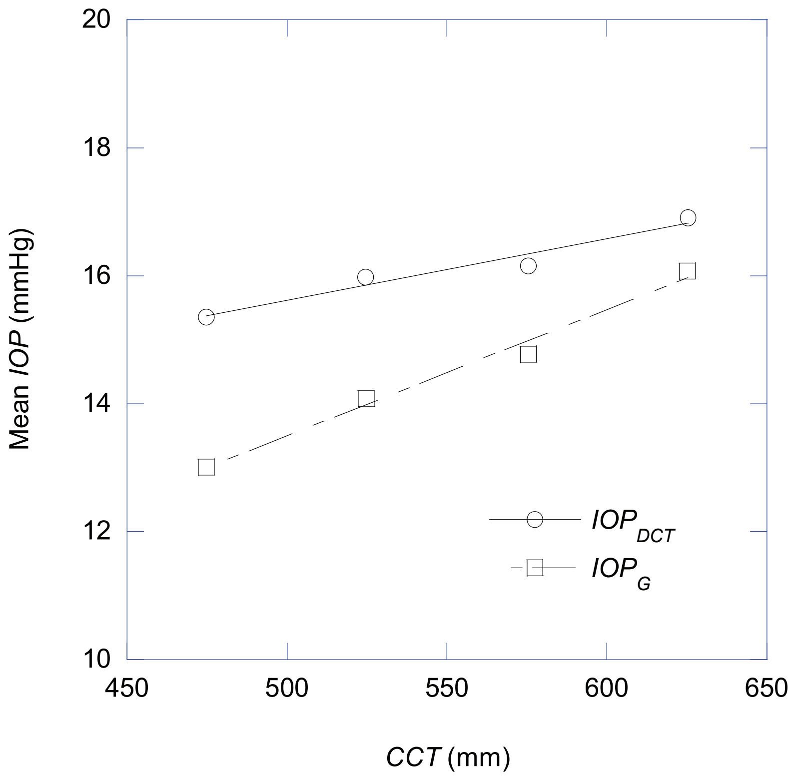

Figure 4: Effect of central corneal thickness *CCT* on IOP_G and IOP_{DCT}. Data adapted from Francis et al. [Francis, Hsieh, Lai, Chopra, Pena, Azen and Varma (2007)].

gential forces acting on the area of the cornea-tip contact [Kanngiesser, Kniestedt and Robert (2005)]. However, study in the literature showed that the corneal radius dependence was not eliminated, and variations of *DCT IOP* with R_{cn} and *CCT* remain significant. (Figure 4 and Figure 5) [Francis, Hsieh, Lai, Chopra, Pena, Azen and Varma (2007)]

The corneal stiffness of an individual is affected by the corneal curvature and central corneal thickness and the stiffness variations would induce *IOP* measurement error [Liu and Roberts (2005)]. In this study, a new instrumented indentation method that accounts for individual corneal stiffness in *IOP* measurement is developed (US Provisional Patent Application (US 61/675,835)). The methodology was tested on pressure-controlled porcine eyes *ex vivo* and rabbit eyes *in vivo*. The *IOPs* calculated with and without correction of the individual corneal variations

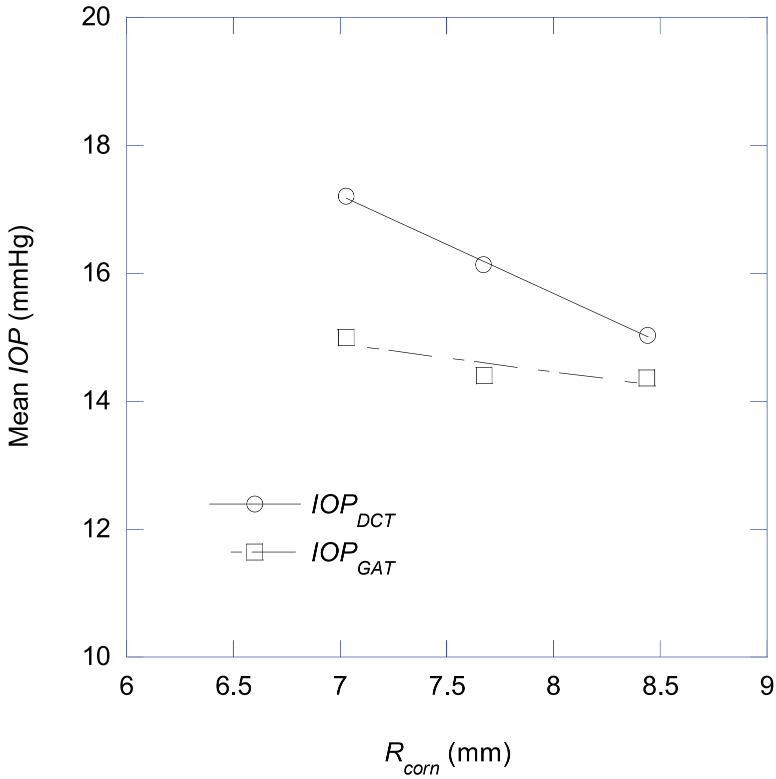

Figure 5: Effect of corneal radius of curvature R_{cn} on IOP_G and IOP_{DCT}. Data adapted from Francis et al. [Francis, Hsieh, Lai, Chopra, Pena, Azen and Varma (2007)].

were then compared with the controlled intraocular pressure to examine the effectiveness of the proposed method.

2 Methods and materials

2.1 Indentation test

The corneal membrane bending force b is dependent on the corneal radius of curvature R_{cn}, the central corneal thickness CCT, the Poisson's ratio of the cornea ν, corneal geometry coefficient a, and indentation depth δ via [Young (1989)]

$$b = \frac{E \cdot CCT^2}{a(\delta)(R_{cn} - CCT/2)\sqrt{1-\nu^2}}\delta, \tag{3}$$

where

$$M = \frac{E \cdot CCT^2}{(R_{cn} - CCT/2)\sqrt{1-\nu^2}}, \tag{4}$$

is a function of the geometries of cornea and the corneal biomechanical properties. Substituting M into equation (3) gives,

$$b = M\frac{\delta}{a(\delta)}. \tag{5}$$

Introducing a factor α to account for the asphericity of the cornea, and incorporating b in equation (5) into the force balance in equation (1) gives

$$F + s = \alpha A \cdot IOP + M\frac{\delta}{a(\delta)}. \tag{6}$$

For a partially-contacted cornea, the applanation contact area A is given as

$$A = 2\pi R_{cn}\delta, \tag{7}$$

and the surface tension s is

$$s = 2\pi r S_c, \tag{8}$$

where

$$r = \sqrt{2R_{cn}\delta}, \tag{9}$$

is the applanation contact radius, and S_c is the surface tension of water (72 mN/m). Substituting equations (3), (7), (8) and (9) into equation (6), and rearranging gives,

$$F = \alpha \cdot 2\pi R_{cn}\delta \cdot IOP + M\frac{\delta}{a(\delta)} - 2\pi\sqrt{2R_{cn}\delta}S_c. \tag{10}$$

Differentiating F with respect to the corneal indentation displacement δ gives the corneal stiffness (S_{cn}= $dF/d\delta|_{IOP}$) as,

$$\left.\frac{dF}{d\delta}\right|_{IOP} = \alpha \cdot 2\pi R_{cn} IOP + \frac{1}{\beta a(\delta)}M - \frac{\sqrt{2R_{cn}}\pi S_c}{\sqrt{\delta}}, \tag{11}$$

where

$$\beta = \frac{a(\delta)}{a(\delta) - \delta\frac{da(\delta)}{d\delta}}. \tag{12}$$

Substituting equation (11) back into equation (10) and rearranging, gives the indentation *IOP* relation as,

$$IOP_{in} = \frac{\beta\delta \frac{dF}{d\delta}\big|_{IOP} - F + (\beta - 2)\sqrt{2R_{cn}\delta}\pi S_c}{\alpha(\beta - 1)\cdot 2\pi R_{cn}\delta}. \tag{13}$$

In this form, the corneal and eye-specific biomechanical properties parameters are embedded inside the experimental corneal stiffness of the eye ($dF/d\delta|_{IOP}$). $dF/d\delta|_{IOP}$ can be determined directly from the experimental load-displacement (F-δ) data of the individual. S_c, α and β are constants, and the only major geometric parameter needed to determine *IOP* is R_{cn}, which can be measured independently for each eye. To test this method, the equation was experimentally tested in porcine eyes *ex vivo* and rabbit eyes *in vivo*.

2.1.1 Experimental procedures

In this study, 12 fresh porcine eyes *ex vivo* and 7 rabbit eyes *in vivo* were tested. The porcine eyes were obtained from a local abattoir. Experiments were conducted within 12 hours of the animals being killed and were kept cold and moist using an insulated bucket with refrigerants. The rabbits (New Zealand white rabbit) were obtained from APCF (Animal and Plant Care Facility, HKUST). All rabbits were >6 months old and weighted >4kg. The rabbits were anesthetized using ketamine (35 mg/kg), xylazine (5 mg/kg) and acepromazine (1 mg/kg). The central corneal thickness *CCT* and corneal radius of curvature R_{cn} of each eye were measured using anterior segment optical coherence tomography (Visante OCT, Carl Zeiss Meditec, Dublin, CA). The mean central corneal thickness of the porcine corneas (n = 12) and rabbit corneas (n = 7) were 1.04 ± 0.12 mm and 0.40 ± 0.03 mm, respectively; the radius of curvature of the porcine corneas and rabbit corneas were 7.2 ± 0.8 mm and 6.8 ± 1.5 mm, respectively. In the test, the porcine eye with the muscle and adipose tissue attached was placed in a cup fixture for support. A manometer-connected hypodermic needle was inserted into the anterior chamber of the eye (Figure 6), and the *IOP* was controlled by adjusting the bottle height h in the manometer. The controlled *IOP* was calculated using,

$$IOP_T = \rho g h, \tag{14}$$

where IOP_T is the manometer controlled *IOP*, ρ is the density of the liquid in the manometer and g is the gravitational acceleration. The IOP_T was varied from 12 to 40 mmHg for porcine eyes, and 5 to 40 mmHg and rabbit eyes, respectively. Three cycles of loading and unloading between 5 to 50 mmHg were applied to condition the tissue and stabilize its behavior before actual testing. At each pressure setting, the pressure was stabilized for more than 10 minutes before each indentation.

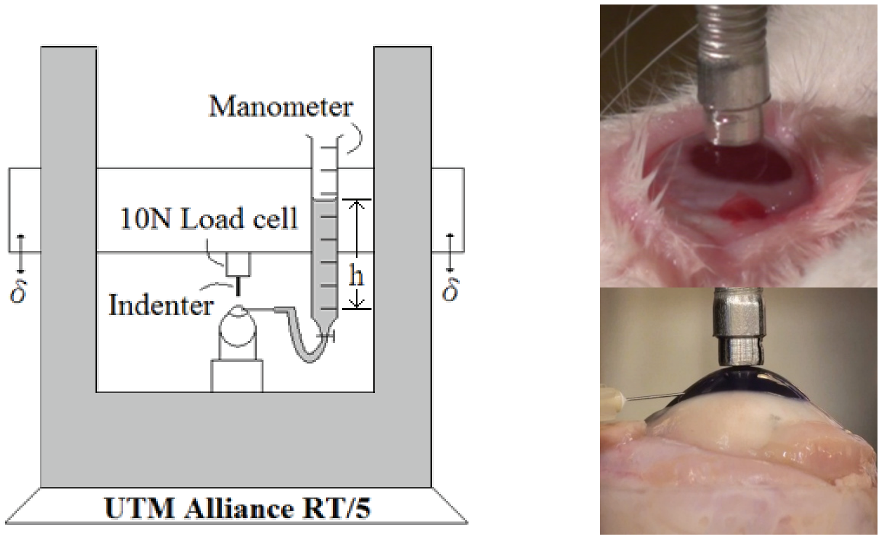

Figure 6: Schematic of indentation experimental setup for porcine eyes *ex vivo* (right - bottom) and rabbit eyes *in vivo* (right - top).

Indentations of the pressurized cornea were conducted on a universal testing machine (Alliance RT/5, MTS Corporation, Eden Prairie, Minnesota, USA) with the maximum indentation depth set at 1 mm for porcine eyes and 0.5 mm for rabbit eyes respectively to prevent damage of the cornea. A 5 mm diameter cylindrical indenter was screw-mounted onto a 10 N load cell (MTS 100-090-795, load resolution 0.0001 N) that was further screw-mounted onto the crosshead of the UTM. Indentations were conducted at 20 mm/min to minimize the viscoelastic effect [Ko, Leung, Lam and Leung (2012)].

3 Results

The typical load-displacement (F-δ) behaviors of rabbit eyes are shown in Figure 7. Figure 7 showed that the experimental load-displacement curves varied from individual to individual at the same *IOP*. The effect of pressure on the load-displacement (F-δ) curve for a single rabbit is shown in Figure 8. The plot showed that the slope of the curve ($dF/d\delta$), i.e., the indentation stiffness S_{cn} increased with *IOP*. Similar inter-individual and pressure variations were also observed for porcine eyes *ex vivo*. Using the experimental $dF/d\delta$ for the tested eyes, the indentation *IOPs* (IOP_{in}) were calculated and the results are plotted in Figure 9 and Figure 10. The results showed that the deviation of IOP_{in} from IOP_T is 1.0 ± 0.8 mmHg for the 12 porcine eyes (R^2 = 0.987) and 0.8 ± 0.5 mmHg for the 7 rabbit eyes (R^2 =

0.988) tested, respectively. The small variation of IOP_{in} from IOP_T showed that the indentation methodology is accurate.

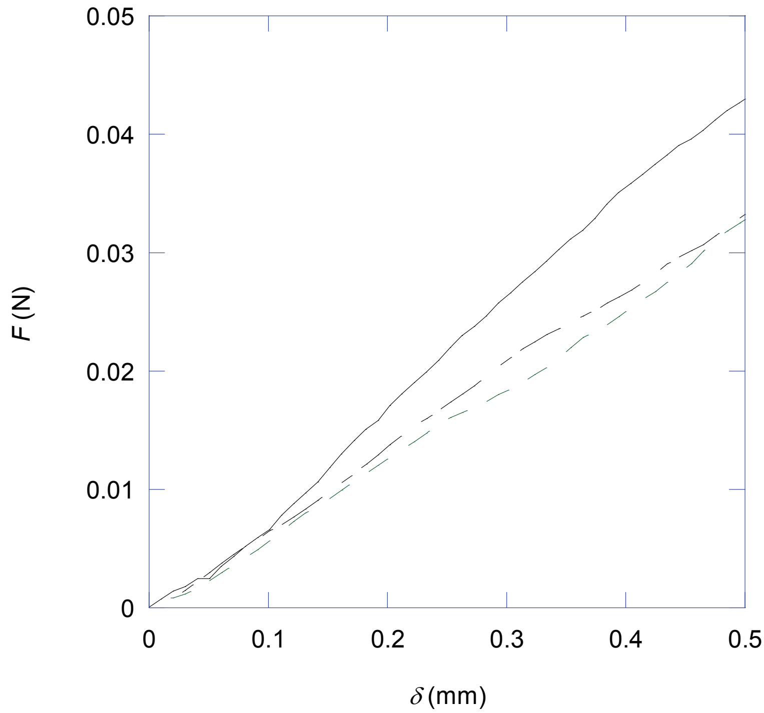

Figure 7: Load-displacement (F-δ) behavior of three rabbit eyes (IOP_T = 17 mmHg)

4 Discussions

4.1 Effect of corneal stiffness

The IOP for healthy human eyes ranges from 10 – 21 mmHg and the IOP for glaucomatous eyes can reach up to 40mmHg. An IOP reduction of 1 mmHg can lead to a 10% reduction in the risk of visual field deterioration [Leske, Heijl, Hussein, Bengtsson, Hyman and Komaroff (2003)]. In IOP_G measurements, inter-individual variations of the corneal stiffness were generally ignored. Study showed that measurement errors up to 17 mmHg can result from the variations in the corneal biomechanical properties [Liu and Roberts (2005)]. Such errors can greatly mislead clinicians in the diagnosis and management of glaucoma.

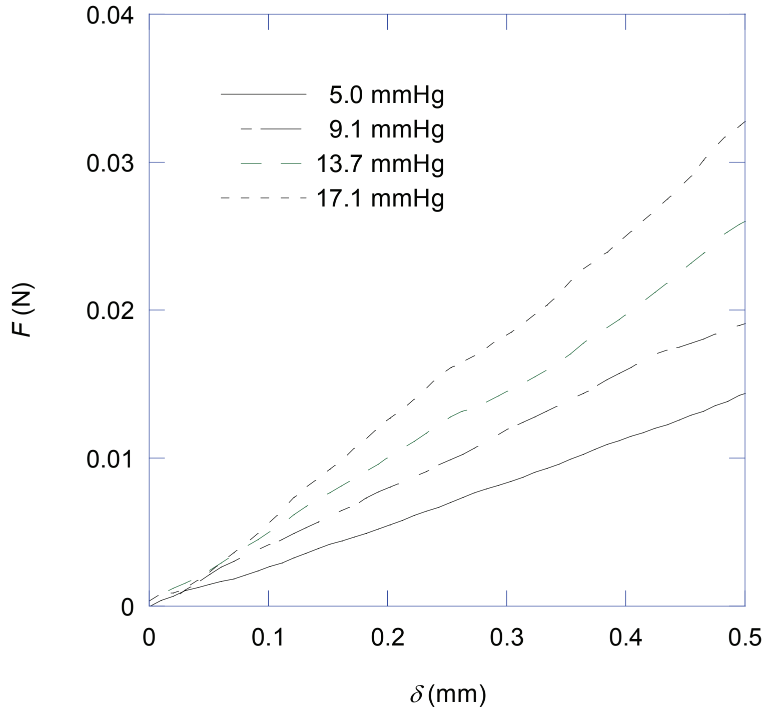

Figure 8: Variation of F-δ as a function of IOP_T for a single rabbit. (R_{cn} = 7.5 mm and CCT = 0.45 mm).

The IOP_G calculated using the equation (2) with load at fixed Goldmann applanation area of A = 7.35 mm^2 are plotted as a function of IOP_T in Figure 11. The plot showed that the IOP_G underestimated the IOP_T by an average of 7.08 $\pm$ 3.52 mmHg in rabbit eyes *in vivo*. The deviation of measured IOP from controlled pressure IOP_Tcan reach up to 10 mmHg depending on the pressure and individual. Similar underestimation of IOP_G = 4.01 $\pm$ 1.76 mmHg was reported by Kniestedt *et.al* on human cadaver eyes [Kniestedt, Nee and Stamper (2004)] (Figure 12). These results confirmed that inter-individual differences and pressure dependences are non-negligible in IOP_G measurement. In comparison, deviation of IOP_{in} from IOP_T was 1.0 $\pm$ 0.8 mmHg for the 12 porcine eyes tested (Figure 9) and 0.8 $\pm$ 0.5 mmHg for 7 rabbit eyes tested (Figure 10). This showed that the developed method successfully accounted for inter-individual variations and can dramatically improve IOP measurement *in vivo*.

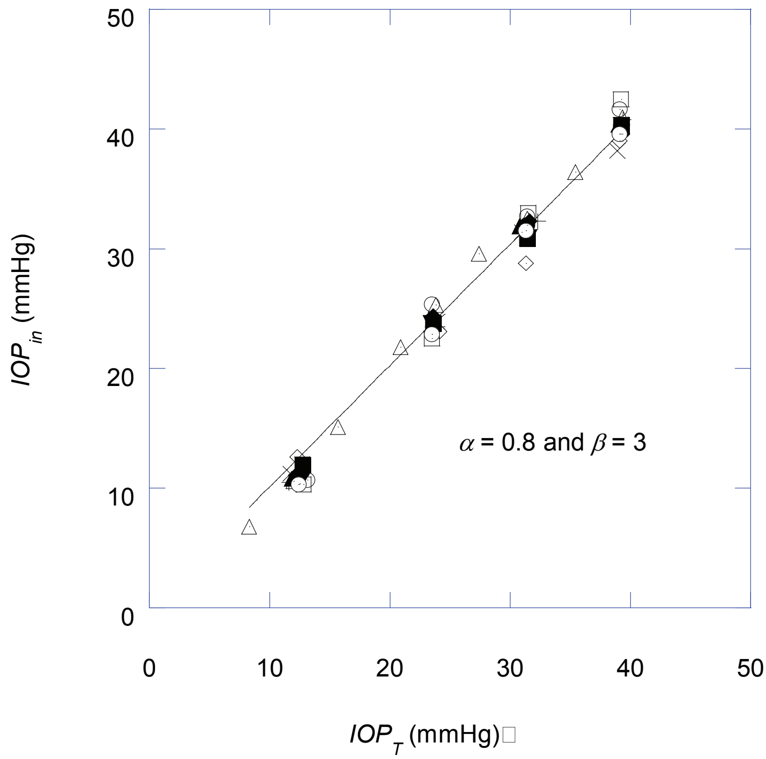

Figure 9: Calculated IOP_{in} as a function of IOP_T for porcine eyes (n = 12) with porcine geometric constants α = 0.8 and β = 3. Different symbols represent different porcine eyes tests. The coefficient of determination (R^2) of the fitted line is 0.987.

5 Conclusions

Goldmann Applanation Tonometry ignored individual variations of the corneal geometries and pressure dependent corneal properties. This may lead to significant errors in the *IOP* measurement, which may adversely mislead diagnosis. By accounting for the individual corneal variations, the partial-contact indentation measurement method was shown to be able to accurately measure the *IOP* with less than 2 mmHg error in rabbit *in vivo*. *IOPs* of individuals with age-stiffened cornea such as the elderlies, LASIK patients with altered corneal stiffness and patients with pressure-stiffened cornea can be accurately measured using this method. The method can also be used in public health glaucoma screening to reduce screening errors arising from individual corneal variations.

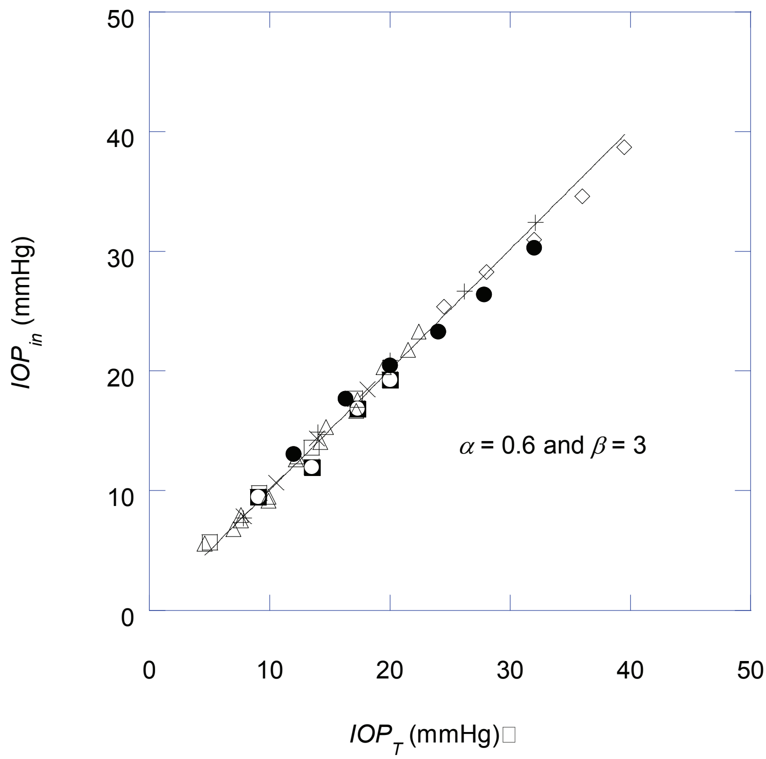

Figure 10: Calculated IOP_{in} as a function of IOP_T for rabbit eyes (n = 7) with rabbit geometric constants $\alpha = 0.6$ and $\beta = 3$. The coefficient of determination (R^2) of the fitted line is 0.988.

Appendix I: The influence of corneal stiffness on IOP$_G$ measurement

To estimate the effect of the corneal properties on *GAT* measurement error, Liu et al. [Liu and Roberts (2005)] proposed a mathematical model to quantify the IOP_G measurement error.

$$P = IOP_G + S - IOP_T, \tag{A1}$$

where P is the resultant pressure, IOP_G is the Goldmann applanation pressure, IOP_T is the true intraocular pressure and S is the pressure caused by the surface tension of the tear film. Defining the applanation stiffness S_{cn} of the cornea as,

$$S_{cn} = \frac{P \cdot A}{\delta}, \tag{A2}$$

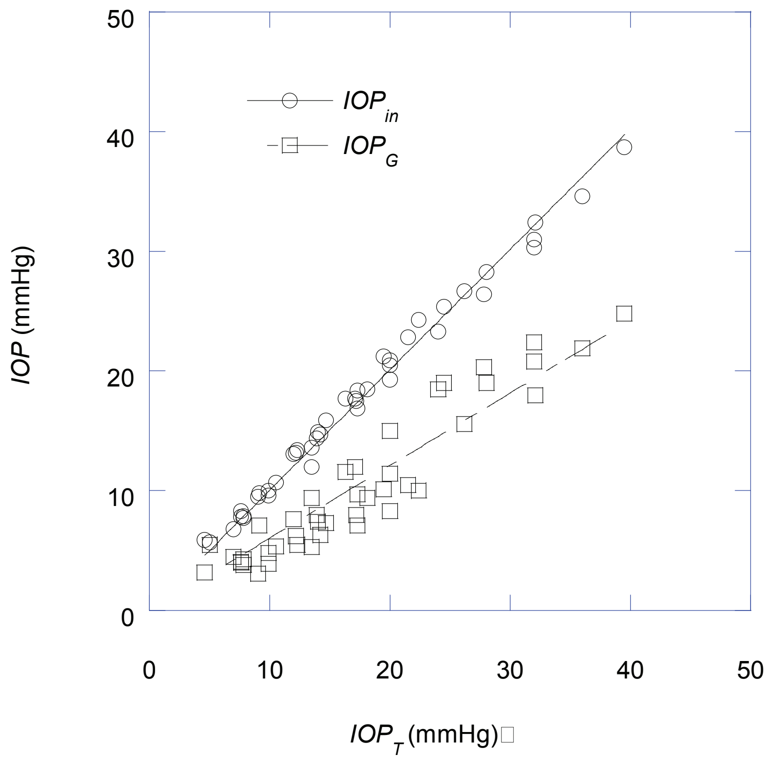

Figure 11: Plots of IOP_G (open squares) and IOP_{in} (open circles) versus the IOP_T for rabbit eyes *in vivo* (n = 7).

where A is the Goldmann applanation contact area, PA is the applanation force and δ is the applanation depth. The tear films caused an approximately 0.415 gram force on the tonometer tip and the amount of force which corresponds to a pressure S equal to 4.15 mmHg [Damji, Muni and Munger (2003)]. Multiplying equation (A1) by A and dividing by δ gives,

$$S_{cn} = P \cdot \frac{A}{\delta} = (IOP_G + 4.15 - IOP_T) \cdot \frac{A}{\delta}. \tag{A3}$$

Further rearranging and writing as a function of IOP_G gives,

$$IOP_G = IOP_T + \frac{S_{cn} \cdot \delta}{A} - 4.15, \tag{A4}$$

$$\delta \approx \frac{d^2}{8R_{cn}}, \tag{A5}$$

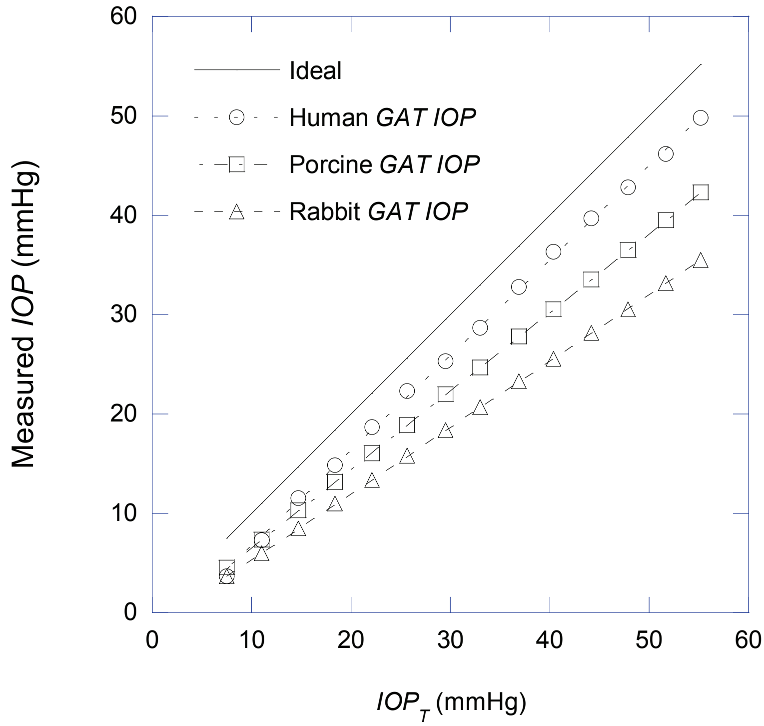

Figure 12: Comparison of measured *IOP* versus IOP_T for porcine eyes (open squares) and rabbit eyes (open triangles) from current study, and human cadaver eyes from Kniestedt el. at. (open circles). The solid line represents ideal error-free behavior.

where d is the *GAT* set applanation diameter (3.06 mm) and R_{cn} is the corneal radius of curvature.

In this form, the IOP_G and the IOP_G measurement error from the variation of S_{cn} can be obtained using the equation (A4) by setting IOP_T equal to 15 mmHg, A equal to 7.35 mm^2 and d equal to 3.06 mm.

Appendix II: Constancy of S$_c$, α and β

S_c, α and β are constants and are assumed to be independent from individual variations. S_c is the surface tension of water (72 mN/m) and is a physical constant. The correction factors α and β are geometric constants of the eye. The validity check of the assumption is shown in Figure 9 ($\alpha = 0.8$; $\beta = 3$) for porcine eyes and in Figure 10 ($\alpha = 0.6$; $\beta = 3$) for rabbits. The plots showed that the constancy is unchanged for different eyes.

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