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ABSTRACT

Primary objective: This study uses numerical analysis and validation against clinical data to develop a method to correct intraocular pressure (IOP) measurements obtained using the Corvis Tonometer for the effects of central corneal thickness (CCT), and age.

Materials and Methods: Finite element analysis was conducted to simulate the effect of tonometric air pressure on the intact eye globe. The analyses considered eyes with wide variations in IOP (10–30 mm Hg), CCT (445–645 microns), *R* (7.2–8.4 mm), shape factor, *P* (0.6–1) and age (30–90 years). In each case, corneal deformation was predicted and used to estimate the IOP measurement by Corvis (CVS-IOP). Analysis of the results led to an algorithm relating estimates of true IOP as a function of CVS-IOP, CCT and age. All other parameters had negligible effect on CVS-IOP and have therefore been omitted from the algorithm. Predictions of corrected CVS-IOP, as obtained by applying the algorithm to a clinical data-set involving 634 eyes, were assessed for their association with the cornea stiffness parameters; CCT and age.

Results: Analysis of CVS-IOP measurements within the 634-large clinical data-set showed strong correlation with CCT (3.06 mm Hg/100 microns, r^2 = 0.204) and weaker correlation with age (0.24 mm Hg/decade, r^2 = 0.009). Applying the algorithm to IOP measurements resulted in IOP estimations that became less correlated with both CCT (0.04 mm Hg/100 microns, r^2 = 0.005) and age (0.09 mm Hg/decade, r^2 = 0.002).

Conclusions: The IOP correction process developed in this study was successful in reducing reliance of IOP measurements on both corneal thickness and age in a healthy European population.

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Tonometry; cornea; Corvis ST; ocular biomechanics; intraocular pressure

Introduction

Glaucoma is a group of diseases that can lead to optic nerve damage and irreversible loss of vision. Sixty million people worldwide are affected by glaucoma; the second most common cause of blindness (Quigley & Broman 2006). The diseases are associated with an elevated intraocular pressure (IOP), the accurate determination of which is important for the effective management of glaucoma. The most commonly used method to measure IOP, and the reference standard in tonometry, is the Goldmann applanation tonometer (GAT) (ISO8612, 2001). The method, which determines IOP by measuring the force required to applanate a certain area of the central cornea, has been found to be affected by corneal stiffness parameters including the central corneal thickness (CCT), the mechanical properties of corneal tissue and corneal curvature (Ehlers & Bramsen 1975; Shimmyo et al. 2003; Kotecha et al. 2005; Liu & Roberts 2005). As a result, several correction equations have been developed to compensate for the effect of stiffness and hence obtain a more accurate estimate of the true IOP (Stodtmeister 1998; Ko et al. 2005; Kotecha et al. 2005; Elsheikh et al. 2011).

Over the past five decades several other tonometers have been developed including those that still rely on contact techniques (most notably the rebound tonometer and the dynamic contour tonometer) and non-contact techniques that use an air puff to indent the cornea. The advantages of non-contact tonometers over contact tonometers include their relative ease of use and less-invasive operation. However, non-contact tonometers, which are similar to contact tonometers in that they apply a mechanical force and correlate the resulting deformation to the value of IOP, have also been found to be influenced by corneal stiffness parameters, and in particular corneal thickness, curvature and mechanical properties (Tonnu et al. 2005; Kotecha et al. 2006; Elsheikh et al. 2009). Additionally, as non-contact tonometers have traditionally been known to

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be less reliable than contact methods, their use has been mainly in clinics, leaving hospital applications to be dominated by contact tonometers.

However, this trend is changing with the emergence of reliable non-contact tonometers such as the ocular response analyzer, which has been shown to provide close results to GAT and other contact devices such as the dynamic contour tonometer. More recently, a non-contact tonometer, the Corvis ST (corneal visualisation scheimpflug technology), has been developed by OCULUS Optikgeräte, Inc. (Wetzlar, Germany) (Ambrosio et al. 2011). The Corvis relies on high-precision, ultra high-speed, Scheimpflug technology to monitor corneal deformation under air puff and produce a wide range of tomography and deformation parameters, which have the potential to enable accurate estimates of both corneal stiffness and IOP. This paper is intended to exploit this potential and enable the development of IOP estimates that are significantly less affected by the natural changes in the cornea's stiffness parameters.

Materials and methods

The paper presents a parametric study of the Corvis procedure to determine the effect of the main stiffness parameters; corneal thickness, curvature, shape factor and the tissue's material properties, on IOP measurements. The study uses nonlinear finite element simulations of the air pressure application on the eye as applied by the Corvis. Analysis of the results allowed development of a closed-form algorithm providing estimates of IOP with significantly reduced correlation with the stiffness parameters. Successful validation of the equation has been carried out using a clinical dataset of 634 healthy eyes.

Numerical analysis

The finite element (FE) software ABAQUS 6.13 (Dassault Systèmes Simulia Corp., Rhode Island, USA) was used to simulate the Corvis ST testing procedure on models of the human eye. The models included the eye's outer tunic (cornea and sclera) and internal fluids (aqueous and vitreous), but excluding other components of the orbit. In order to ensure accurate representation of *in vivo* conditions, the FE models adopted the following features from previous work (Elsheikh 2010; Elsheikh, Geraghty et al. 2010; Elsheikh et al. 2013):

- Consideration of cornea's and sclera's thickness variation;
- Stress-free form of the eye globe (under zero IOP);
- Regional variation of sclera's mechanical properties; and
- Dynamic representation of the Corvis air pressure.

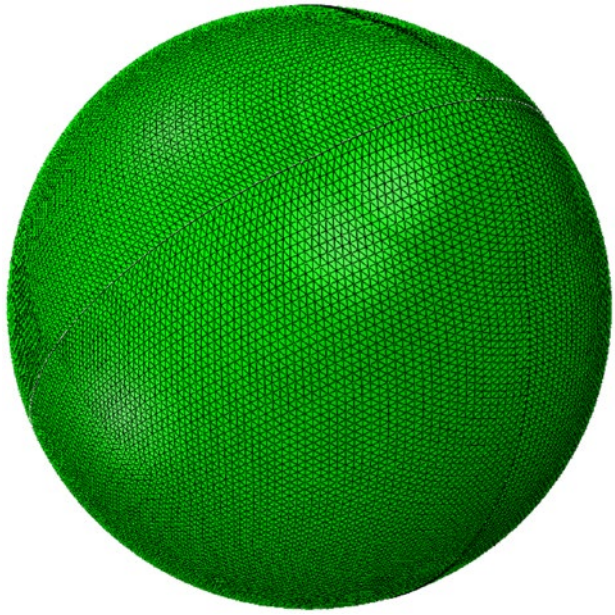

Figure 1. Computational mesh of the whole eye model.

The models employed 10952 15-noded elements organised in 25 element rings in the cornea, 124 element rings in the sclera and 1 element layer (Figure 1). This high mesh density allowed smooth representation of ocular topography and thickness variation. Third-order, hyperelastic Ogden models were used to represent the ocular tissue's mechanical behaviour and its variation with age (Elsheikh, Geraghty, Rama et al. 2010; Geraghty et al. 2012). Scleral regional variation in stiffness and its gradual reduction from the limbus towards the optic nerve was incorporated in the models (Elsheikh, Geraghty et al. 2010).

To prevent the models from rigid body motion, all nodes along the equator were restrained in the anterior–posterior direction (z-direction), and corneal apex and posterior pole nodes were restrained in both the superior–inferior and temporal–nasal directions. To account for the aqueous' and vitreous' incompressible behaviour, the ocular globe models were filled with an incompressible fluid with a density of 1000 kg/m^3 (Villamarin et al. 2012).

Before conducting the study, the stress-free configuration for each model was obtained while following an iterative procedure explained in (Elsheikh et al. 2013). Two subsequent steps were then adopted in the simulations. First, the models started from their stress-free configurations and the IOP was applied gradually as a pressure increase in the internal incompressible fluid up to the desired level. In the second step, space- and time-varying external air pressure was applied on the anterior surface of the cornea. The spatial distribution of the air pressure (Figure 2(a)) was obtained from (Elsheikh et al. 2009) and the time variation was obtained from data acquired from the device manufacturers (Figure 2(b)). The maximum air pressure that Corvis produces is about 180 mm Hg

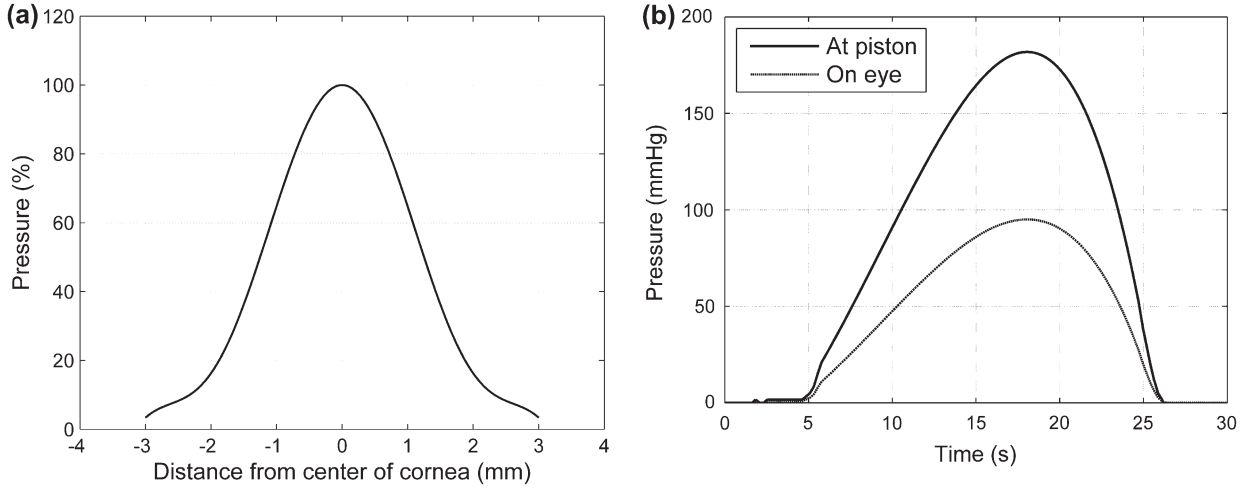

Figure 2. Spatial distribution (a) and time variation (b) of air pressure on the cornea's surface. Note: In (b) thick black line represents air puff produced at the device piston and grey line represents the pressure acting on the cornea's surface.

and that was found by the manufacturer to be reduced by approximately 50% as the air puff reached the cornea's anterior surface.

In the Corvis device, successive images are taken by the device's Scheimpflug camera during the 30 ms duration of the air puff. The images are analysed by an integrated computer to determine IOP and several other parameters including corneal pachymetry, apical deformation, first and second applanation time (A1, A2-time), first and second applanation length (A1, A2 length), velocity of corneal apex at first and second applanation (A1, A2 velocity), highest concavity time (HC time), and the distance between the two peaks at the point of highest concavity (Figure 3). The IOP is measured in Corvis (CVS-IOP) as a function of the time to the first applanation event (A1-time), or when the cornea starts to change its shape from convex to concave. Once the A1-time is known, the external pressure acting on the cornea at that time (AP1) is measured and the IOP estimate is calculated as a function of AP1. This process was replicated in the analysis of the FE model results to determine AP1 and hence estimate CVS-IOP.

Parametric study

The numerical models were used in a parametric study to quantify the effect of parameters with potential considerable influence on CVS-IOP measurements. The parameters included the true IOP in addition to the main stiffness parameters of the cornea, namely the thickness, curvature and shape factor. Age was introduced for its known effect on the stress–strain behaviour of the tissue, and it was therefore used as a parameter controlling the mechanical stiffness of both the cornea and sclera (Pallikaris et al. 2005; Geraghty et al. 2012; Elsheikh et al. 2007). In the study, IOP was varied from 10 to 30 mm Hg in steps of 5 mm Hg, CCT from 445 to 645 μm in steps of 50 μm, age from 30 to 90 years in steps of 10 years, central radius of anterior curvature (R) from 7.2 to 8.4 mm in steps of 0.3 mm and corneal anterior shape factors (P) of 0.6, 0.71, 0.82 and 1. These values were compatible with the ranges of variation reported in earlier clinical studies (Douthwaite et al. 1999; Gatinel et al. 2001; Douthwaite 2003; Shimmyo & Orloff 2005; Yildirim et al. 2007).

The total number of models in the parametric study was 3500, allowing 5 variations in true IOP, 5 in CCT, 7 in age, 5 in R and 4 in P. In each model specific values of CCT, R, P, age and IOP were used. The analysis step of the air puff application was dynamic and consisted of 300 pressure increments (time step = 0.0001 s) covering the 0.03 s of the Corvis procedure. The coordinates of corneal anterior nodes were extracted at each time step using a Python code, and a MATLAB code (MathWorks, MA) was used to determine the point of applanation (A1-time), the external pressure at this point (AP1) and hence IOP estimate (CVS-IOP) as a product of AP1 and a calibration factor provided by Oculus.

The results of the parametric study were used to analyse the effect of CCT, R, P and age on the CVS-IOP estimates, and to develop an algorithm relating estimates of true IOP to both the measured CVS-IOP and the cornea's stiffness parameters.

Clinical validation of numerical results

The numerical results have been validated twice against clinical data. First, the match between the outputs of four FE models specifically created to represent four randomly

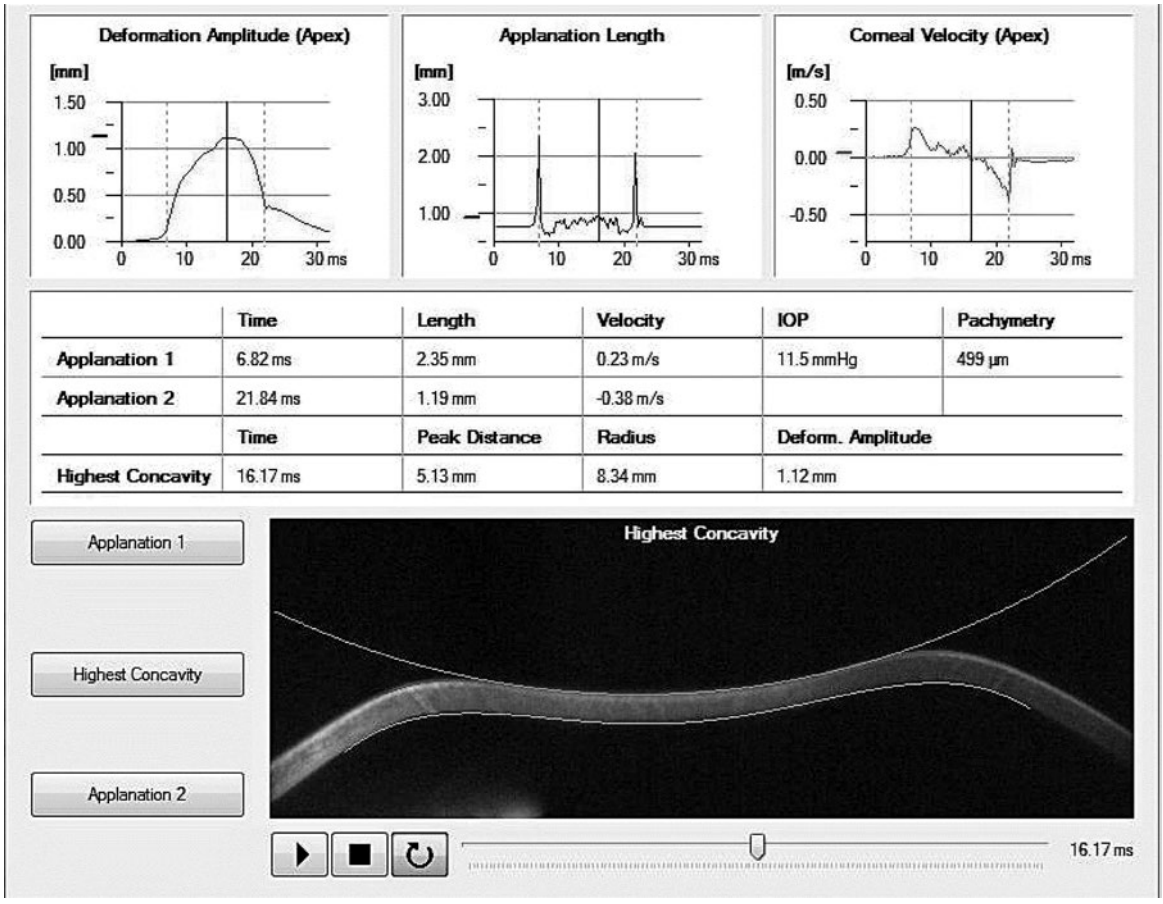

Figure 3. Example of a Corvis measurement showing the deformed cornea at the highest concavity.

Table 1. Details of the clinical data-set.

Parameter	CCT (µm)	CVS-IOP (mm Hg)	Age (years)
Mean ± SD	537.3 ± 41.8	14.5 ± 2.8	40.0 ± 11.6
Range	404–650	6.5–35.5	21–83

selected eyes with wide variations in IOP, CCT and age was assessed in detail against the Corvis output for the four eyes. The comparisons covered a wide range of Corvis output parameters including the cornea's apical deformation and the first applanation time. With this validation step successfully conducted, the IOP algorithm produced in the parametric study was then validated in a clinical data-set by testing its effectiveness in reducing the strength of association between IOP estimates and the stiffness parameters considered.

Validation clinical data-set

A clinical data-set was collected at Smile Eyes Clinics in Munich, Germany, and used in exercises to validate the numerical results of the study. The data-set involved 634 eyes of 317 healthy participants with no pathological conditions. All patients signed a written informed consent form. The study was approved by the local institutional review board and adhered to the tenets of the Declaration of Helsinki. For each participant, CCT, IOP, apical deformation, A1 time and AP1 were measured by the Corvis. All measurements were performed by the same investigator (SM). Mean, standard deviation and range of measurements are presented in Table 1.

Results

Parametric study

The numerical results illustrated a clear effect of increased CCT (from 445 to 645 µm) in decreasing maximum apical displacement by 37% and increasing A1-time by 14% on average, Figure 4(a). Similarly, an increase in age from 30 to 90 years (and hence increased material stiffness) was associated with an average decrease in corneal displacement of 27% and a slight increase in A1-time of 4%, Figure 4(b). Moreover, an increase in true IOP from 10 to 30 mm Hg led to an average reduction in apical displacement of 47% and an average increase in A1-time of 48% (Figure 4(c)). Changes in corneal curvature and shape factor within the considered range led to only slight changes in corneal deformation and A1-time that were <3% as shown in Figures 4 (d) and (e).

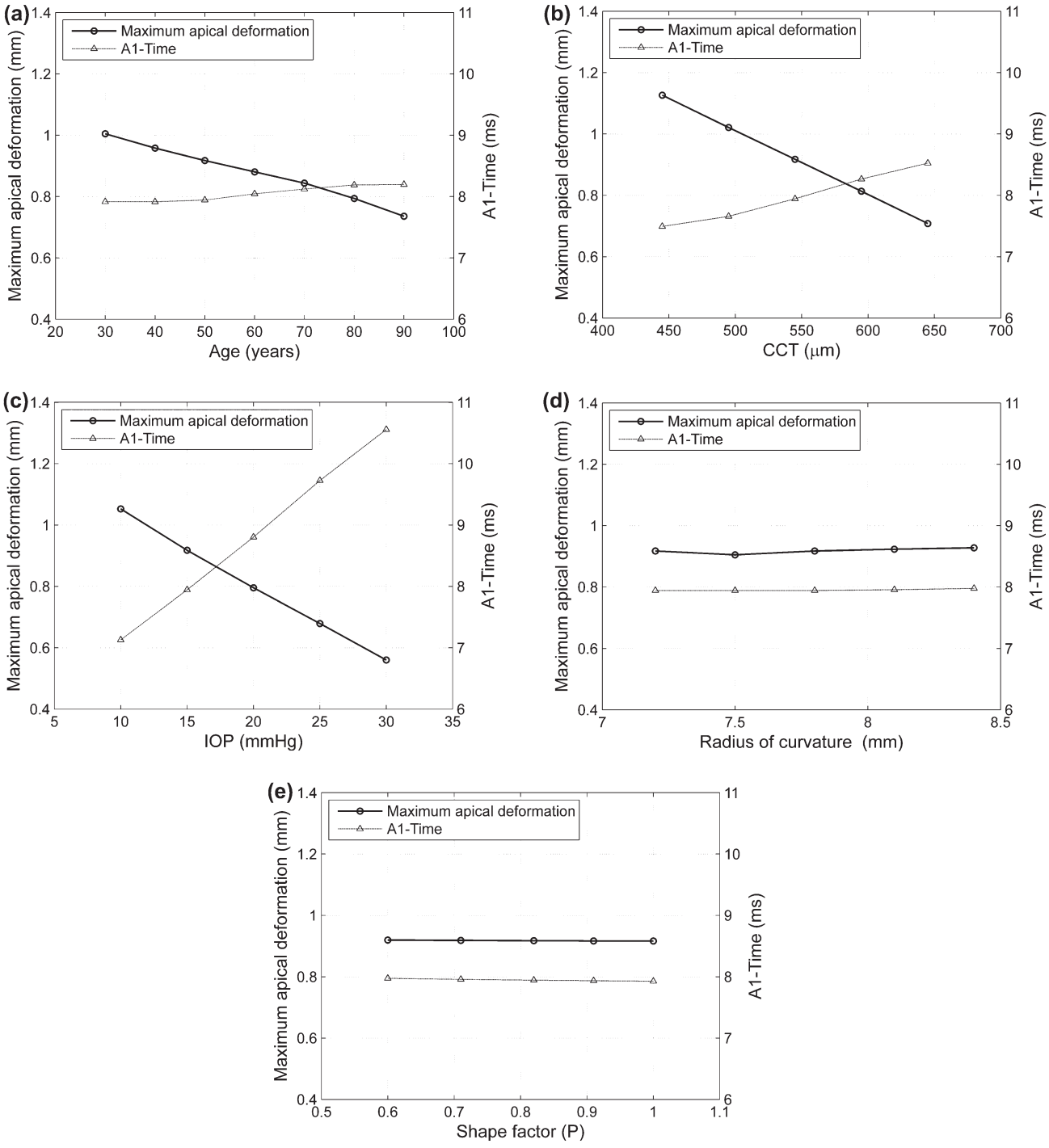

Figure 4. Relationships between maximum apical deformation and A1-time and (a) age, (b) CCT, (c) true IOP, (d) radius of curvature (R) and (e) shape factor (P).

The results show that the apical deformation and applanation time are associated with changes in CCT, IOP and age, while variations in corneal curvature parameters (*R* and *P*) have only negligible effects on corneal deformation behaviour.

Further, the influence of true IOP, CCT, age, *R* and *P* on estimated CVS-IOP is presented in Figure 5(a)–(d). The results demonstrate that CVS-IOP is strongly associated with (or strongly influenced by) CCT, correlated with age but with weaker association, while it is almost independent of variations in *R* and *P*. These results illustrate that for the IOP to be estimated with reduced influence of corneal stiffness, consideration must be made of variations in CCT and age.

IOP correction algorithm

The parametric study predictions of CVS-IOP and the input parameters of true IOP, CCT and age were used to develop Equation (1) linking the four parameters

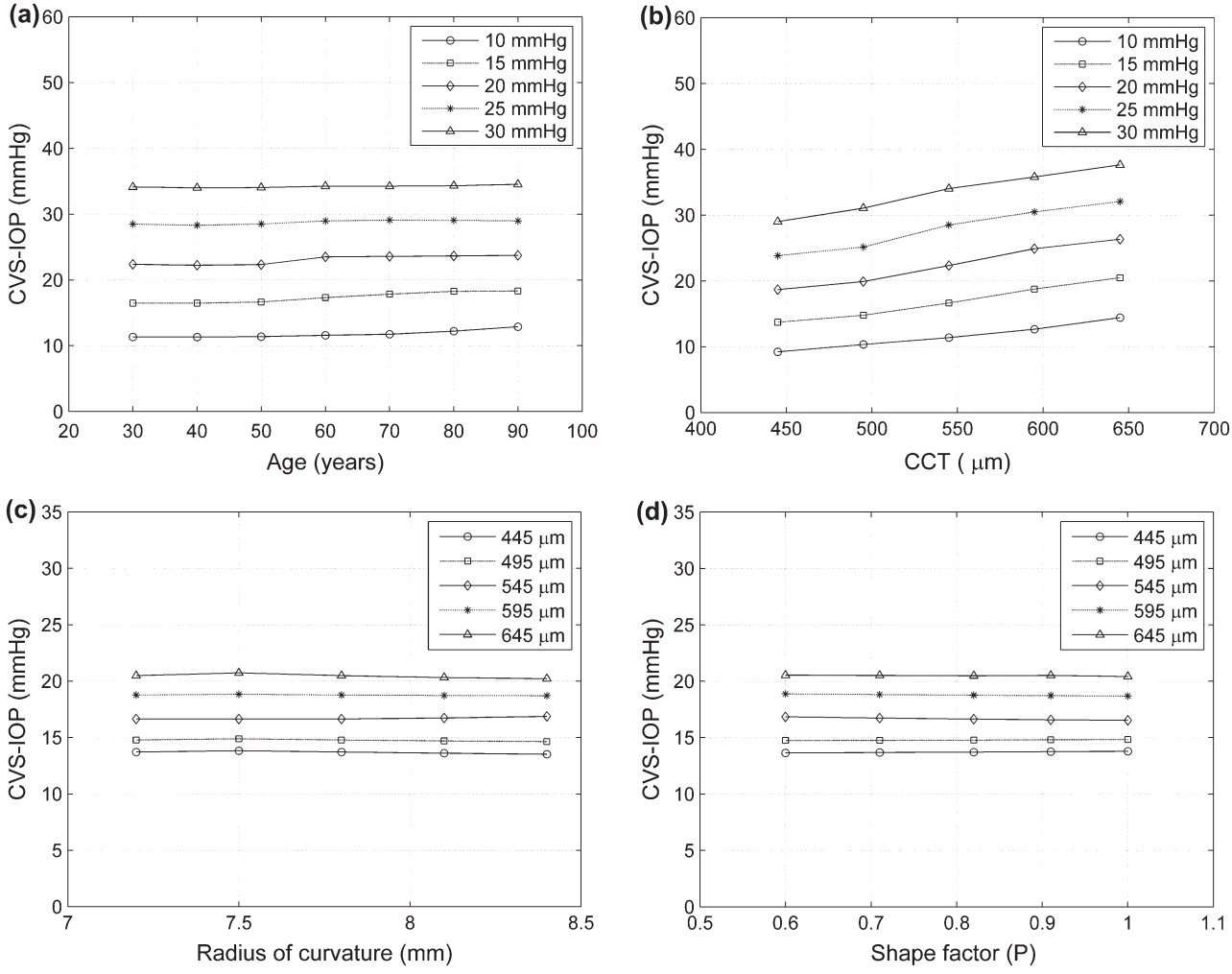

Figure 5. CVS-IOP as a function (a) age, (b) CCT, (c) radius of curvature (R) and (d) shape factor (P).

together and providing estimates of IOP that were less affected by the stiffness parameters than CVS-IOP. Values of the equation's parameters were obtained using the least squares method by minimising the sum of squared errors between corrected and true IOP ($\Sigma(\text{IOP}_{\text{FEM}} - \text{true IOP})^2$). In this equation, IOP_{FEM} represents the corrected IOP values, which are based on the FEM parameteric study. The resulting equation has the form:

$$\text{IOP}_{\text{FEM}} = \left(C_{\text{CCT1}} \times C_{\text{CVS-IOP}} + C_{\text{CCT2}}\right) \times C_{\text{age}} \quad (1)$$

where C_{CCT1} and C_{CCT2} are parameters representing the effect of variation in CCT (mm);

$$C_{\text{CCT1}} = 4.67 \times 10^{-7} \times \text{CCT}^2 - 7.8 \times 10^{-4} \times \text{CCT} + 0.63$$

$$C_{\text{CCT2}} = -1.73 \times 10^{-5} \times \text{CCT}^2 + 2.02 \times 10^{-3} \times \text{CCT} - 0.97$$

$C_{\text{CVS-IOP}}$ represents effect of variation in measured CVS-IOP (mm Hg) = 10 + (CVS-IOP + 1.16)/0.389.

C_{age} denotes effect of variation in age (years) = $-2.01 \times 10^{-5} \times \text{age}^2 + 1.3 \times 10^{-3} \times \text{age} + 1.00$.

Figure 6(a) shows the difference between the corrected IOP and CVS-IOP increasing mainly with CCT, but also with CVS-IOP and age. Without compensating for CCT and age variation, CVS-IOP had a predicted measurement error as high as 10 mm Hg when CCT = 645 μm and age > 60 years. After IOP correction, the error in IOP reduced in most cases to below 1 mm Hg (Figure 6(b)).

Validation of numerical results against clinical data

Validation using four random clinical points

In order to validate the numerical simulations of the Corvis procedure, the numerical results of four models specifically created to represent four randomly selected eyes with wide variations in IOP, CCT, *R* and age were considered in detail. Table 2 shows part of the Corvis output for the four eyes where the mean values of three clinical measurements are presented.

An eye-specific model was generated for each eye based on the CCT and *R* values, and the material properties for the cornea and sclera were assumed to follow

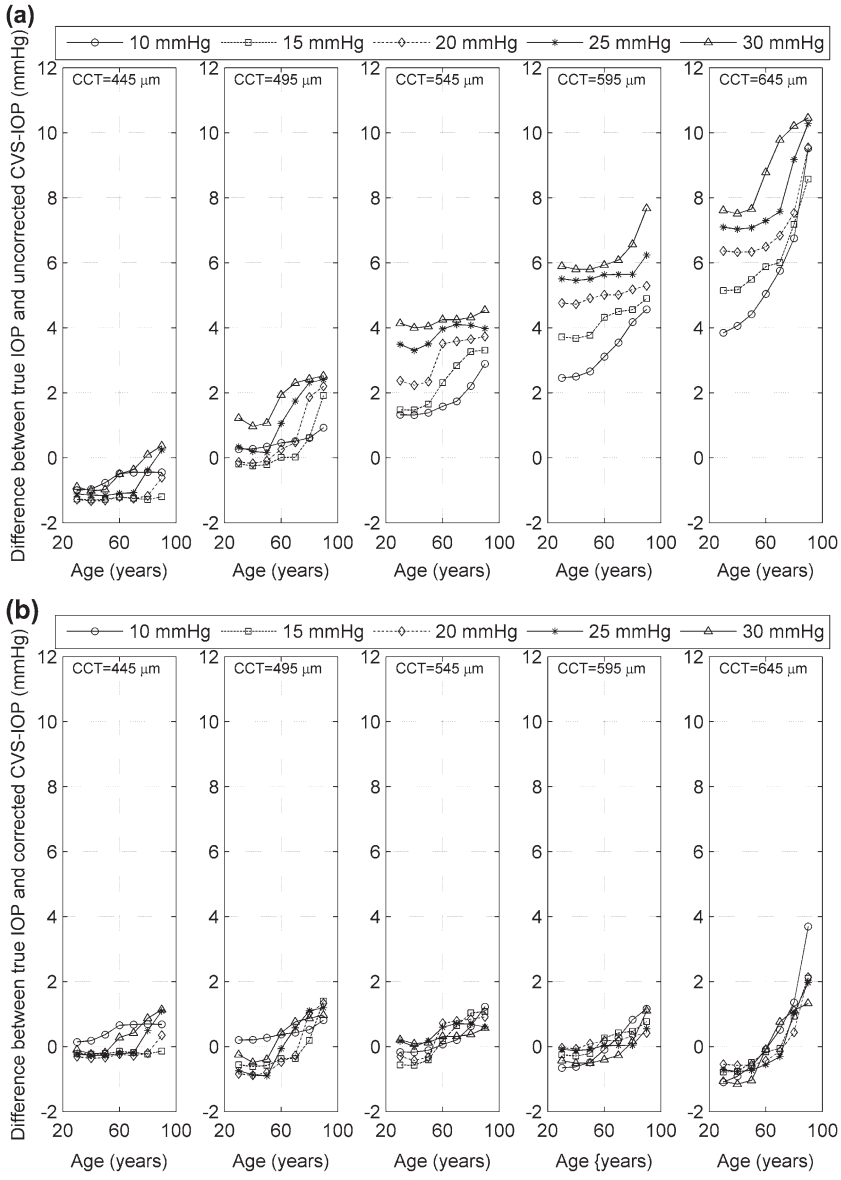

Figure 6. Difference between the (a) true IOP and CVS-IOP and (b) true IOP and IOPc for different true IOP levels, CCT values and ages.

Table 2. Mean Corvis output for four cases considered in a validation study of numerical results.

Case #	CVS-IOP (mm Hg)	CCT (μm)	Age (year)	*R* (mm)
Case 1	17.3	581	68	7.82
Case 2	15.3	529	58	7.29
Case 3	11.3	537	31	7.55
Case 4	12.3	554	46	7.28

the association identified in earlier work between stress–strain behaviour and age (Elsheikh, Geraghty et al. 2010; Elsheikh, Geraghty, Rama et al. 2010; Geraghty et al. 2012). Constant values of the shape factor, axial length and sclera diameter of 0.82, 23.7 mm and 23.0 mm, respectively, were assumed since they were not measured clinically and were found numerically to have a negligible effect on IOP estimations.

The four models were analysed and their output compared to Corvis parameters. Figure 7(a) and (b) shows a selection of the comparisons held, which concentrate on two parameters with good repeatability and direct relevance to corneal stiffness (Nemeth et al. 2013); namely the maximum apical deformation and the first applanation time (A1-time). The comparisons demonstrated a close match between the numerical predictions and the Corvis output with the differences remaining within ±8% in all cases.

Validation against trends in clinical data

In a second validation step, the clinical data-set described above was used to evaluate the effectiveness of the correction algorithm in reducing reliance of IOP on the cornea's stiffness parameters. Figure 8(a) presents uncorrected CVS-IOP vs. CCT, where strong association was

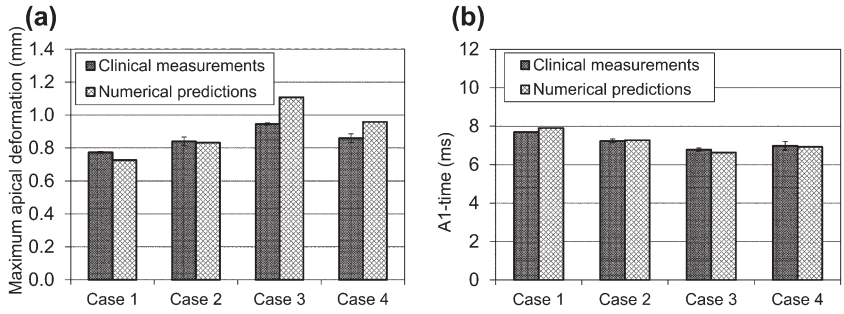

Figure 7. Comparison of numerical predictions with clinical measurements of (a) the maximum apical deformation and (b) the first applanation time (A1-time).

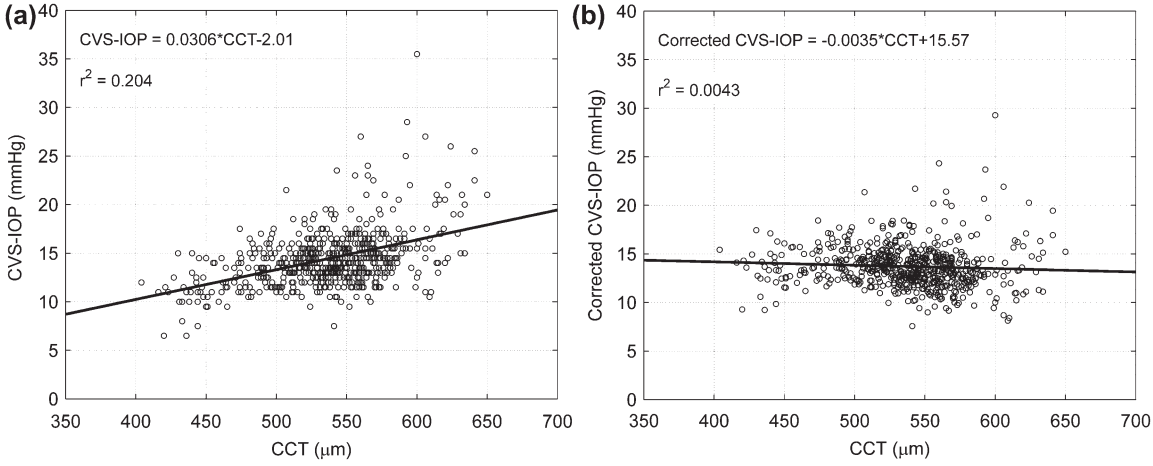

Figure 8. Association between CVS-IOP measurement and CCT, (a) before correction and (b) after correction.

evident from the regression and gradient of the trend line (r^2 = 0.204, gradient = 0.0306 mm Hg/μm). Figure 8(b) shows the results after applying equation (1), leading to a reduction in r^2 to 0.004 and the gradient to −0.0035 mm Hg/μm. Meanwhile, the mean CVS-IOP increased slightly from 14.45 ± 2.83 mm Hg before correction to 14.92 ± 2.40 mm Hg after correction. Similar to the numerical results, the clinical CVS-IOP was found to be correlated weakly with age (Figure 9(a)). However, using Equation (1), the coefficient of determination of CVS-IOP with age was reduced from 0.009 to 0.0005 and the gradient from 0.024 to 0.0043 mm Hg/year (Figure 9(b)).

The above results simultaneously considered the right and left eyes of the study participants. Repeating the analysis for left eyes, separate from right eyes, produced only slight changes in results. For left eyes, applying the IOP algorithm reduced association of CVS-IOP with CCT (from r^2 = 0.210, gradient = 0.0296 mm Hg/μm to r^2 = 0.0078, gradient = −0.0044 mm Hg/μm) and age (from r^2 = 0.006, gradient = 0.018 mm Hg/year to r^2 = 0.000, gradient = −0.0012 mm Hg/year). Similar results were obtained for right eyes with reduced association with CCT (from r^2 = 0.200, gradient = 0.0317 mm Hg/μm to r^2 = 0.0021, gradient = −0.0025 mm Hg/μm) and age (from r^2 = 0.0129, gradient = 0.031 mm Hg/year to r^2 = 0.0023, gradient = 0.010 mm Hg/year).

In addition to the univariate regression analysis presented above, the effects of CCT and age on clinical CVS-IOP were considered in a stepwise multiple regression analysis. Considering left and right eyes simultaneously and using CVS-IOP as a dependent variable and CCT and age as independent variables, only CCT was found to have a significant effect on IOP measurements ($p < 0.001$, $F = 161.892$, $r^2 = 0.204$). Thus, about 20.4% of the variance of CVS-IOP could be accounted for by CCT. Adding age to the analysis showed an insignificant effect on CVS-IOP ($t = 1.301$, $p = 0.194$). This analysis was repeated for the numerical results obtained from the FE analyses, and similar results were obtained. CCT was again the only parameter with a significant effect on CVS-IOP ($p < 0.001$, $F = 22.474$, $r^2 = 0.115$), while age had an insignificant effect ($t = 0.967$, $p = 0.338$).

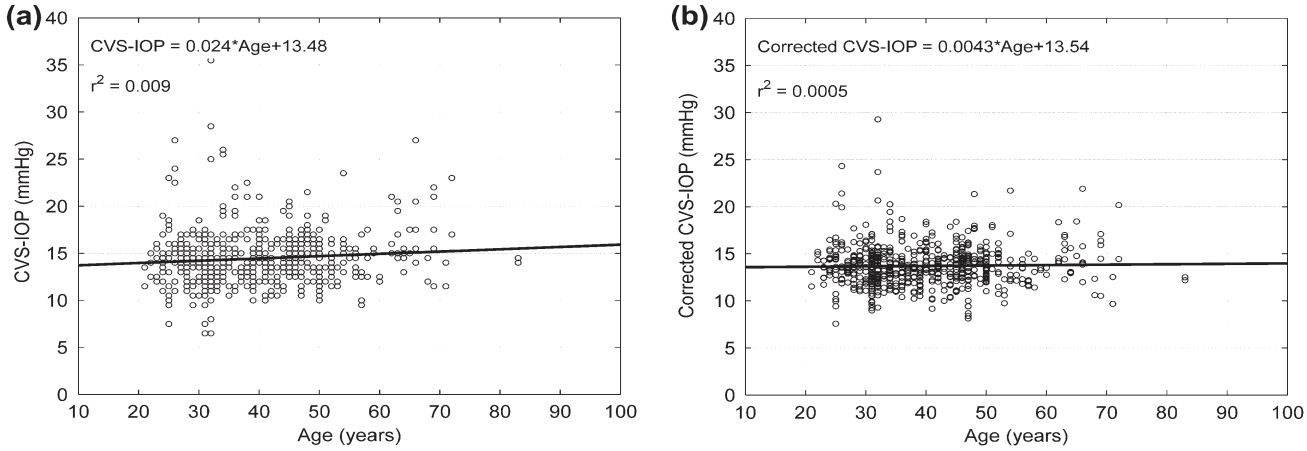

Figure 9. Association between IOP measurements and age, (a) before correction and (b) after correction.

Discussion

The study evaluated the effect of major corneal stiffness parameters on the IOP measurements by the Corvis. The Corvis has a number of unique features over other tonometers. First, it is able to measure corneal thickness directly without a need for a separate device, making it possible to directly correct for the effect of CCT on IOP. CCT measurements by the Corvis were found to have good repeatability and accuracy compared to ultrasound pachymetry (Smedowski et al. 2014; Nemeth et al. 2013; Reznicek et al. 2013). Second, the several deformation parameters the device collects may make it possible to quantify corneal material behaviour, which could then be considered in the further correction of IOP measurements.

In this paper, the effect on CVS-IOP measurements of both corneal geometric stiffness parameters (CCT, *R*, *P*) and material stiffness (while assuming correlation with age (Pallikaris et al. 2005; Elsheikh et al. 2007; Geraghty et al. 2012)) has been quantified. The results demonstrated clear effect of CCT on CVS-IOP, a relatively smaller effect of material behaviour (as it varies with age) and almost no influence of *R* or *P*. Similar results were obtained for GAT-IOP which, while being different in the nature of the force applied on the cornea, still applies a mechanical force and correlates the resulting corneal deformation to the value of IOP (Stodtmeister 1998; Eysteinsson et al. 2002; Browning et al. 2004; Kohlhaas et al. 2006).

The development of a correction algorithm for CVS-IOP relied initially on numerical simulation that is representative of the eye's geometric and material characteristics and the Corvis procedure. Numerical simulation was found to be a reliable tool in modelling the cornea's response to mechanical loads such as those applied by tonometers. Similar earlier work has led to a number of correction equations for GAT and ORA, which were later successfully validated clinically (Kwon et al. 2008; Elsheikh et al. 2009; Davey et al. 2013).

Building on earlier work, a parametric study, based on representative numerical models of the eye and the Corvis procedure, was conducted. The study considered wide ranges of variation in CCT, *R*, *P*, age and true IOP, and provided for each model an estimate of CVS-IOP; the Corvis IOP measurement. Similar to clinical data, the numerical results provided confirmation that CVS-IOP was strongly correlated with CCT, true IOP and, to a smaller extent, age. Based on these trends, an algorithm quantifying the correlation of CVS-IOP with CCT, true IOP and age was developed using the least squares method, and proposed as a means to provide estimates of IOP that were less affected by variations in corneal mechanical stiffness.

The numerical simulations of the Corvis procedure were validated in two distinctive steps against clinical data. First, they were validated against clinical results obtained *in vivo* for four randomly selected eyes with wide variations in CVS-IOP, age and CCT. The close match between the numerical and clinical results for all four eyes demonstrated the reliability of the simulations and their ability to accurately model the Corvis procedure.

Second, the correction algorithm was tested against a clinical data-set of 634 healthy eyes. Uncorrected CVS-IOP measurements were significantly correlated with CCT (r^2 = 0.204, gradient = 0.0306 mm Hg/μm) and less correlated with age (r^2 = 0.009, gradient = 0.024 mm Hg/year). Introducing the correction algorithm reduced the dependency of CVS-IOP on both CCT (r^2 = 0.004, gradient = –0.0035 mm Hg/μm) and age (r^2 = 0.0005, gradient = 0.0043 mm Hg/year) considerably.

The correction algorithm presented in this paper offers a novel, simple, yet effective, method to obtain IOP

estimates that are less affected by the main corneal stiffness parameters, removing dependency on a major error source and producing more reliable IOP estimates for glaucoma management.

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Disclosure statement

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