Influence of Pachymetry and Intraocular Pressure on Corneal Deformation Parameters Provided by Corvis ST: Normative Values and Suspect Pathology

Paolo Vinciguerra, MD[1-2]; Ahmed Elsheikh, PhD[3-4]; Emanuela Morenghi, PhD[5], Cynthia J. Roberts, PhD[6], Renato Ambrósio Jr, MD, PhD[7-8], Claudio Azzolini, MD[9], Riccardo Vinciguerra, MD[9].

Affiliation:

[1]Eye Center, Humanitas Clinical and Research Center, Via Manzoni 56, Rozzano (MI) – Italy.

[2]Vincieye Clinic, Milan, Italy.

[3]School of Engineering, University of Liverpool – Liverpool, United Kingdom

[4] NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, UK

[5]Biostatistic Unit, Humanitas Research Hospital, Rozzano (Milano), Italy

[6]Department of Ophthalmology, Department of Biomedical Engineering, The Ohio State University – Columbus, OH, USA

[7]Rio de Janeiro Corneal Tomography and Biomechanics Study Group – Rio de Janeiro, Brazil

[8]Department of Ophthalmology, Federal University of São Paulo – São Paulo, Brazil

[9]Department of Surgical Sciences, Division of Ophthalmology, University of Insubria, Varese, Italy.

Corresponding author:

Dr Paolo Vinciguerra, Humanitas Clinical and Research Center, Via Manzoni 56, 20089 Rozzano (Milan), Italy Email: paolo.vinciguerra@humanitas.it , phone +390255211388, fax +390257410355

Financial disclosures :

Financial Disclosure(s): Dr. Ambrósio, Dr. Vinciguerra, Dr. Roberts are consultants for OCULUS Optikgeräte GmbH. Dr. Elsheikh has received research funding from OCULUS Optikgeräte GmbH.

“None of the remaining authors have any financial disclosures”

Running head

Corvis: Normative values, influence of IOP and CCT

PRECIS

Normative values of Corneal Deformation Parameters measured by the Corvis ST are provided, including the influence of corrected intraocular pressure and pachymetry.

ABSTRACT:

Purpose: To evaluate the influence of pachymetry and intraocular pressure and to provide normative values for all Corneal Deformation Parameters (CDPs) provided by dynamic Scheimpflug Analysis.

Materials and Methods: A total number of 1009 eyes measured with an ultra high speed Scheimpflug camera were included in this retrospective study. The biomechanical response data were analyzed to obtain normative values with their dependence on clinically-validated corrected IOP estimates developed using the finite element method (IOP_{FEM}), central corneal thickness (CCT) and age as well as to evaluate the influence of the factors IOP_{FEM}, CCT and age.

Results:

The results showed that all CDPs were correlated with IOP_{FEM}, except HC radius and Inverse Concave Radius. The analysis of the relationship of CDPs with CCT indicated that HC radius, Inverse Concave Radius and Deformation Amplitude (DA) Ratio were correlated with CCT (rho values of 0.342, -0.427 and -0.498), which can be considered a biomechanical characteristic of the tissue. The age group sub-analysis of CDPs revealed significant differences with respect to age in most of the parameters. Finally, custom software was created to compare normative values to imported exams.

Conclusion:

HC radius, Inverse Concave Radius and DA Ratio were shown to be suitable parameters to evaluate in-vivo corneal biomechanics due to their independence from IOP and their correlation with pachymetry and age. The creation of normative value ranges for each CDP with regard to IOP and CCT values allows interpretation of an abnormal examination without the need to match every case with another CCT and IOP matched normal patient.

In 1619 Scheiner provided the first precise description of the corneal shape using glass balls of known curvatures[1]. From that first description, many other diagnostic tools have been developed from keratometry to corneal topography (front surface curvature maps),[2] then into 3-D corneal tomography systems.[3] More recently, it has been appreciated that corneal biomechanical behavior plays an important role in maintaining corneal shape, which is necessary for light refraction and clear vision,[4] and should therefore be considered in understanding the development of ectatic diseases[5, 6] and the results of surgery.[4, 7] Until recently, the evaluation of corneal biomechanical properties had been restricted to ex-vivo laboratory studies,[5, 8] and to mathematical corneal models.[9-11] However, this changed with the introduction of the first instrument to be able to evaluate corneal biomechanical response parameters in-vivo: The Ocular Response Analyzer (ORA, Reichert Inc., Depew, NY)[12]. The ORA is a modified non-contact tonometer (NCT) designed first to provide a more accurate measurement of intraocular pressure (IOP) through compensation for corneal biomechanics. It analyzes corneal behavior during a bi-directional applanation process induced by an air jet, and produces estimates of corneal hysteresis and corneal resistance factor along with a set of 36 waveform-derived parameters.[13-15] The Corvis ST (OCULUS Optikgeräte GmbH; Wetzlar, Germany) was later introduced as an NCT, which monitors the response of the cornea to an air pressure pulse using an ultra-high speed (UHS) Scheimpflug camera, and uses the captured image sequence to produce estimates of IOP and deformation response parameters.[16]

Several articles have been recently published on the possible applications of this new device, particularly evaluating possible biomechanical differences in the cornea after undergoing refractive surgery procedures,[17-22] between normal and keratoconic patients,[23-26] after cross-linking[27] and in glaucoma patients.[28-31] However it has been demonstrated that IOP and pachymetry have important influences on most corneal biomechanical metrics provided by both the Corvis ST and ORA.[32, 33] It is therefore relevant to investigate the distribution and normal limits for the in-vivo corneal biomechanical data derived from corneal deformation parameters (CDPs), and determine if these metrics have correlations with IOP measurements and corneal thickness.

The aim of this article is to evaluate the influence of pachymetry and intraocular pressure on response parameters and to provide normative values for all CDPs provided by Corvis ST in healthy patients.

MATERIALS AND METHODS

Institutional review board (IRB) ruled that approval was not required for this record review study, and it was conducted according to the ethical standards set in the 1964 Declaration of Helsinki, as revised in 2000. However, all patients provided informed consent before using their data in the study. One thousand and nine eyes of 603 healthy patients attending Vincieye Clinic in Milan, Italy were included in this retrospective study. All patients had a complete ophthalmic examination including the Corvis ST and Pentacam exams. The Corvis' output parameters from each measurement were exported to a spreadsheet and analyzed to obtain normative values, as well as test their correlations with new and clinically-validated IOP-corrected estimates developed using the finite element method (IOP_{FEM}), central corneal thickness (CCT) and age. Age was chosen as an influencing factor as older patients tend to have stiffer corneas than younger ones, even though the standard deviation might be large for all ages.[34]

The inclusion criteria of this study were the presence in the database of a Corvis ST exam, a Belin Ambrosio Enhanced Ectasia Index total deviation (BAD-D) from the Pentacam less than 1.6 standard deviations (SD) from normative values and a signed informed consent. Exclusion criteria were any previous ocular surgery or disease, myopia over 10D and any concomitant or previous glaucoma or hypotonic therapies. The BAD-D cut off of 1.6 SD was used because it is described as the best performing screening parameter with values of 1.65/1.88 associated, respectively, with a 95% and 97.5% confidence interval with an acceptable false negative rate of less than 1%.[35] Only Corvis ST exams with quality score "OK" were included in the analysis. Additionally, a second manual, frame-by-frame analysis of the exam, made by an independent masked examiner, was performed to ensure quality of each acquisition. The main criterion was good edge detection over the whole deformation response, with the exclusion of alignment errors (x-direction). Similarly, blinking errors were omitted.

In order to analyze the IOP, CCT, and age dependency of Corvis ST corneal deformation parameters obtained by the research software 1.2b1191, the dataset was split into 4 different IOP_{FEM} groups, 4 different CCT and 4 different age groups. The IOP_{FEM} groups (and similarly for the CCT groups and Age groups) were defined as follows: In the first step the lowest 5 percent percentile and the highest 5 percent percentile for IOP_{FEM} were filtered out and not considered in further analysis. This was done to guarantee that the group sizes were not too small for the groups with low IOP_{FEM} and high IOP_{FEM} (and similarly for groups with low and high CCT, and low and high age). Following this exercise, 907 eyes remained in the IOP_{FEM} groups (912 eyes in CCT groups and 907 in age groups). These eyes were split into 4 IOP_{FEM} groups such that the difference between highest and lowest IOP_{FEM} values were similar for each IOP_{FEM} group. The same procedure was used to define 4 CCT groups and 4 age groups. Subgroups characteristics are summarized in Table 1.

All measurements with the Corvis ST were taken by the same experienced technician (S.T.). The Corvis ST uses an ultrahigh-speed Scheimpflug camera that captures 4330 images per second and covers 8.0 mm of the cornea in a single horizontal meridian. The instrument's light source is an LED light of 455 nm wavelength. The air impulse produces a maximum pressure of 25 kiloPascals. A quality score (QS) is available just after the measurement is taken for assessing the reliability of the measurement. This is based on a series of parameters that are obtained so that a QS is also available for the pachymetry and IOP data.[16]

IOP measurement

Together with CDPs, Corvis ST provides standard IOP and pachymetry measurements, and a new and validated, corrected IOP estimate.[36] It was developed using numerical, finite element simulations of the Corvis ST procedure applied on human eye models with different tomographies (including thickness profiles), ages and IOP values.[8, 37-40] The analysis was used to provide IOP_{FEM}; which are IOP estimates significantly less affected by corneal parameters and given as a function of measured IOP (CVS-IOP), CCT and age. The IOP_{FEM} algorithm[36] took the form:

$IOP_{FEM} = (C_{CCT1} \times C_{CVS\text{-}IOP} + C_{CCT2}) \times C_{age}$

where,

IOP_{FEM} = an estimate of true IOP or the corrected value of measured IOP, C_{CCT1}, C_{CCT2} = parameters representing the effect of variation in CCT among patients (mm):

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

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

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

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

Corneal deformation parameters

CDPs provided by Corvis ST include: A1 Time (time from starting until first applanation), A1 Length (horizontal length of the portion of flattened cornea at the first applanation), A1 Velocity (speed of corneal apex at first applanation), A2 Time (time from starting until second applanation), A2 Length (horizontal length of the portion of flattened cornea at the second applanation), A2 Velocity (speed of corneal apex at second applanation), Peak Distance (distance between the two bending peaks created in the cornea at the maximum concavity state), Radius of highest concavity (radius of the central cornea at the maximum concavity state) and Deformation Amplitude (maximum depth of deformation at the highest concavity state).

The Deformation Amplitude refers to the largest displacement of corneal apex in the anterior-posterior direction at the moment of highest concavity.[13, 16] During the measurement, the Whole Eye globe Movement (WEM) affects this parameter. As the cornea deforms and approaches maximum displacement, the whole eye displays a slow linear motion in the anterior-posterior direction. When the cornea reaches maximum displacement, the whole eye motion becomes more pronounced and nonlinear in nature, as the air puff pressure continues to increase to a consistent maximum value. The deflection amplitude is displacement of the corneal apex in reference to the overlayed cornea in initial state. Therefore, the deformation amplitude is the sum of pure corneal deflection amplitude and whole eye movement.

Other parameters can be extrapolated from the highest concavity (HC) moment: HC Radius and Inverse Concave Radius. The first parameter describes the radius of curvature at the time of highest concavity, based on a parabolic fit. The Inverse Concave Radius (1/R) is plotted over the time of the air pulse.[13, 16] The Peak Distance describes the distance between the two highest points of the cornea's temporal-nasal cross-section at the highest concavity moment, which is not the same as the deflection length.[13]

A new parameter called central-peripheral deformation amplitude (DA Ratio) describes the ratio between the deformation amplitude at the apex and the average deformation amplitude in a nasal and temporal zone 2mm from the center. The greater the difference in these two values, the less resistant is the cornea to deformation. Therefore, one would expect higher values of DA Ratio to be associated with softer corneas.

The Delta Arclength, another new parameter, describes the change of the Arclength during the highest concavity moment from the initial state, in a defined 7mm zone. This parameter is calculated 3.5mm from the apex to both sides in the horizontal direction (Figure 1a). The temporal changes in the delta arclength are also calculated for the exact same zone and a plot is generated.

Examples of the calculation of HC parameters, Delta Arclength and Deflection Area are shown in figure 1a-b-c.

STATISTICAL ANALYSIS:

Descriptive statistics were calculated for 14 different parameters (Deformation amplitude, Maximum deformation amplitude, Deflection amplitude, Deflection area, Whole Eye Movement, Peak distance, Applanation Length 1-2, Corneal Velocity 1-2, delta Arc Length, Radius of Highest Concavity, Inverse Concave Radius and Deformation Amplitude Ratio) for each IOP_{FEM} group, each CCT group and each age group. The statistical analysis was performed with SPSS version 22 (IBM Corp. in Armonk, NY, USA).

Differences between data were evaluated with analysis of variance (ANOVA). The chosen level of significance was $p<0.05$. The association between variables was expressed with Eta values (the proportion of the total variance that is attributed to an effect) and Spearman correlation coefficient.

In addition, the influence of the same Corvis ST parameters on IOP_{FEM}, CCT and age was also analyzed by plotting the mean temporal diagrams for these Corvis ST parameters for each subgroup. The temporal diagrams represent the change of each parameter over the whole deformation response until the cornea has recovered to its initial state. This allows evaluation of the influence of IOP_{FEM}, CCT and age not only at one or two time points, but during the whole deformation response. The mean curves for each subgroup were plotted with Excel 2010 (Redmond; Washington, USA).

Normative value ranges were created with the mean values of the selected subgroup ± two standard deviations. Custom software was created to compare normative values to imported exams. It allows the user to compare the imported exam to normative values based on the IOP_{FEM} and CCT values of that exam. Additionally the software is able to provide graphs illustrating the difference of the imported exam from the normative values with regards to CCT and IOP_{FEM}. In this paper we show normative values of the 4 IOP_{FEM} and CCT groups.

RESULTS:

Mean IOP was 14.55±3.03 mmHg (Figure 2), mean IOP_{FEM} was 14.45±2.53 mmHg (Figure 3), mean central corneal thickness was 529±38µm (Figure 4), mean age was 45±15 years (Figure 5). Subgroups characteristics are summarized in Table 1.

PACHYMETRY GROUPS:

The analysis of the influencing factors for this set of subgroups showed that the 4 CCT groups did not show significant differences for IOP_{FEM} and age but were significantly different for uncorrected IOP ($p<0.001$), confirming that the IOP_{FEM} correction algorithm is able to compensate for these confounding factors.

The ANOVA analysis of corneal deformation parameters between the CCT subgroups showed a significant difference in all CDPs, with different levels of association revealed by dissimilar eta values and rho values (Table 2). Radius of HC, Inverse Concave Radius and DA Ratio were the three CDPs with the highest eta square values (respectively 0.337, 0.409 and 0.420) and rho values (0.342, -0.427 and -0.498). The level of association of Inverse Concave Radius and DA Ratio is also shown in the scatter plots in Figures 6a and 7a, whereas the mean curves for the selected CDP in the different subgroups are shown in Figures 6b and 7b.

INTRAOCULAR PRESSURE GROUPS:

The analysis of the influencing factors for this set of subgroups showed that the 4 IOP_{FEM} groups did not differ statistically for age but had a significant difference for pachymetry ($p=0.017$).

The results of CDPs' analysis between the IOP_{FEM} groups showed a significant difference in all parameters evaluated excluding HC Radius and Inverse Concave Radius ($p=0.152$ and $p=0.845$), which were more influenced by CCT (Figure 8a-b) . Similarly the eta values for these parameters showed a very low correlation with IOP_{FEM} (Table 3). WEM, while being significantly different between the groups, showed a very low association with IOP_{FEM}, with an eta value of 0.099 and rho value of -0.130.

AGE GROUPS:

The comparative results for age groups showed a significant difference in pachymetry and IOP_{FEM}, indicating slightly higher CCT and IOP_{FEM} values with increasing age, with low eta values (respectively 0.146 and 0.094).

The results of the ANOVA for all the analyzed parameters with respect to age revealed significant differences in all parameters evaluated, excluding Deformation Amplitude, Maximum deformation Amplitude and Inverse Concave Radius. Conversely WEM, DA ratio and A2 Velocity were the three parameters that were most greatly influenced by age with the following eta and rho values: 0.438 and 0.464 for Whole Eye Movement, 0.260 and 0.238 for DA ratio and 0.285 and 0.300 for A2 Velocity, respectively. Figure 9a shows the WEM scatter plot and 9b the mean curves for the different age groups.

<u>NORMATIVE VALUES:</u>

Normative values of the IOP_{FEM} subgroups and the four CCT subgroups are shown in Tables 4-5. All values are expressed as minimum and maximum values for the selected subgroups and CDP.

The custom software is able to create normative values for each mmHg of IOP_{FEM} and CCT, however, in order not to compromise the graphs' legibility all these values were not included in the manuscript. Moreover, to present the possible clinical application of the custom software we show four cases of healthy patients with different IOP values (Figures 10a-b-c-d). In all the cases the imported profile fits inside the mean ± 2SD range of the normative values displayed. The program provides three charts, to allow the comparison of the actual exam with regards to IOP_{FEM} and pachymetry values (Figure 11a-b-c).

Conversely Figure 12 shows the imported profile of a keratoconic patient. The profile clearly extends outside of the mean ± 2SD normative value range displayed.

DISCUSSION

The in-vivo measurement and interpretation of corneal biomechanics is extremely difficult due to the complexity of the viscoelastic biomechanical behavior.[13, 41] A material with simple elastic properties could be described with a single number, the elastic modulus, defined by the slope of the stress-strain curve. In an elastic material, the loading and unloading phase follow the same path. The cornea, however, is a viscoelastic material and that causes an increase in the measurement's complexity. The behavior is different during loading and unloading and its response to an applied force has a time-dependent component. The consequence is that the experimental conditions affect the resulting measurements and that a faster strain rate produces a stiffer corneal response. Additionally the stress-strain relationship is nonlinear, during both the loading and unloading phases, with a non-constant elastic modulus.[42] Another confounding factor is IOP: according to Laplace's Law, the wall tension is a function of the internal pressure. This implies that as IOP increases, the wall tension will increase and due to the nonlinear properties, and a soft cornea with higher IOP may exhibit stiffer behavior than a fundamentally stiffer cornea with a lower IOP. The same complexity affects IOP measurements as they are influenced by corneal stiffness, which is not only dependent on the thickness, as widely accepted, but also the tissue elastic modulus, which changes with age and medical history and additionally increases with greater values of IOP.

As previously mentioned, in order to evaluate the IOP, CCT, and age dependency of Corvis ST CDPs the dataset was divided into 4 different IOP_{FEM} groups, 4 different CCT and 4 different age groups.

Pachymetry groups

The comparative analysis of the pachymetry subgroups indicated that the 4 CCT groups did not show significant differences for IOP_{FEM} and age but were significantly different for uncorrected IOP. This result demonstrated that the IOP_{FEM} correction algorithm is able to compensate for these important confounding factors and confirms pre-clinical validation of the formula.[36] This outcome has a profound impact on the evaluation of in-vivo corneal biomechanics because the creation of a corrected IOP algorithm with greatly reduced influence by CCT and age, which contribute to stiffness, is the first step to evaluating corneal biomechanics. It is near impossible to correctly interpret biomechanical characteristics of a cornea unless the IOP corrected for these factors is known, due to the Laplace law. These findings were confirmed by previous reports, which indicated that IOP and pachymetry have important influences on most corneal biomechanical metrics provided by Corvis ST and ORA.[32, 33]

The conclusions of these earlier studies were that firstly IOP, and then pachymetry are important in deformation response evaluation and must be taken into consideration. Additionally, the authors concluded that comparisons of research groups based on ORA and CVS with different IOPs and CCTs may lead to possible misinterpretations if either one are not considered in the analysis.

The analysis of CDPs relationship with CCT showed that HC Radius, Inverse Concave Radius and DA Ratio were highly correlated with CCT, which is a major biomechanical characteristic of the tissue. All these CDPs showed high eta and rho values, revealing good association with CCT.

Intraocular pressure groups

The main result of this analysis indicated that HC Radius and Inverse Concave Radius were not significantly influenced by IOP but were more influenced by CCT. This finding demonstrated that Inverse Concave Radius and HC Radius are good parameters to correctly evaluate in-vivo corneal biomechanics due to its relative independence from IOP. Another important finding is the confirmation that many parameters used in earlier publications (e.g. deformation amplitude) are strongly correlated with IOP[32, 33] and that, if IOP is not matched or compensated statistically, comparison between groups would not be valid.

Age groups

Comparative analysis with respect to age groups indicated a significant difference in CCT and IOP, suggesting slightly higher CCT and IOP values with increasing age but with very weak association, as indicated by very low eta and rho values. The significant difference in IOP must be considered with caution, since the p value was 0.046 and the literature shows no independent age effect on IOP[43, 44]. Furthermore the eta values are extremely low (particularly for IOP_{FEM}).

The main finding of this sub-analysis was that many CDPs revealed significant differences with respect to age which confirms the change in corneal biomechanical characteristics in older people.[34] Conversely, Deformation Amplitude, Delta Arclength and Inverse Concave Radius did not show significant differences. This last finding appeared in contradiction with the tendency of Inverse Concave Radius to be correlated with major corneal biomechanical characteristics. However, if we consider the differences of the HC curves (from which both HC radius and Inverse Concave Radius are derived) and their dependence on age and CCT, (Figure 13) there is no difference between the age groups (as shown by the mean values and box blots of this parameter) of the maximum Inverse Radius, which appears shortly after first applanation. However, at highest concavity there is a significantly difference between the age groups (even though the influence of age is rather small). Therefore, the time point chosen during the air puff can make a difference when evaluating corneal biomechanical characteristics. Studies are in progress to further evaluate this finding.

Whole Eye Movement primarily followed by DA ratio and A2 velocity, were the three parameters that were most greatly influenced by age. The high correlation between WEM and age could be explained with the change in the retrobulbar fat composition with regards to age [45].

Normative values

The availability of an original dataset of more than one thousand healthy patient exams allowed the creation of normative value ranges for each CDP with regard to IOP and CCT values.

With this custom software, we propose that every CDP of each exam will be shown in comparison to the corresponding normative value ranges with dependence on IOP_{FEM}. This software will hopefully be able to show each patient with an abnormal examination without the need to match every case with another CCT and IOP matched normal patient. This is the first time, to our knowledge, that it is possible to have normative value ranges for Corvis ST parameters, compensated for influencing factors.

CONCLUSIONS

In conclusion, our analysis of CDPs with respect to IOP_{FEM}, CCT and Age confirms literature findings that IOP and CCT are important confounding factors for in-vivo biomechanical evaluation, and adds the influence of age. HC Radius, Inverse Concave Radius and DA ratio, were shown to be good parameters to evaluate in-vivo corneal biomechanics due to their relative independence from IOP and their correlation with CCT and age. Additionally our normative value ranges provide, for the first time, the possibility to interpret corneal biomechanics in the context of normative values and suspect pathology in clinical practice.

Acknowledgment

The authors would like to thank Silvia Trazza (Vincieye Clinic, Milan) who collected the data.

References

1. Daxecker F. Christoph Scheiner's eye studies. *Doc Ophthalmol* 1992;81:27-35.

2. Wilson SE, Ambrosio R. Computerized corneal topography and its importance to wavefront technology. *Cornea* 2001;20:441-454.

3. Ambrosio R, Jr., Belin MW. Imaging of the cornea: topography vs tomography. *J Refract Surg* 2010;26:847-849.

4. Dupps WJ, Jr., Wilson SE. Biomechanics and wound healing in the cornea. *Exp Eye Res* 2006;83:709-720.

5. Andreassen TT, Simonsen AH, Oxlund H. Biomechanical properties of keratoconus and normal corneas. *Exp Eye Res* 1980;31:435-441.

6. Roberts CJ, Dupps WJ, Jr. Biomechanics of corneal ectasia and biomechanical treatments. *J Cataract Refract Surg* 2014;40:991-998.

7. Roberts C. Biomechanical customization: the next generation of laser refractive surgery. *J Cataract Refract Surg* 2005;31:2-5.

8. Elsheikh A, Geraghty B, Rama P, Campanelli M, Meek KM. Characterization of age-related variation in corneal biomechanical properties. *J R Soc Interface* 2010;7:1475-1485.

9. Liu J, Roberts CJ. Influence of corneal biomechanical properties on intraocular pressure measurement: quantitative analysis. *J Cataract Refract Surg* 2005;31:146-155.

10. Dupps WJ, Jr. Biomechanical modeling of corneal ectasia. *J Refract Surg* 2005;21:186-190.

11. Carvalho LA, Prado M, Cunha RH, et al. Keratoconus prediction using a finite element model of the cornea with local biomechanical properties. *Arq Bras Oftalmol* 2009;72:139-145.

12. Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. *J Cataract Refract Surg* 2005;31:156-162.

13. Roberts CJ. Concepts and misconceptions in corneal biomechanics. *J Cataract Refract Surg* 2014;40:862-869.

14. Mikielewicz M, Kotliar K, Barraquer RI, Michael R. Air-pulse corneal applanation signal curve parameters for the characterisation of keratoconus. *Br J Ophthalmol* 2011;95:793-798.

15. Hallahan KM, Sinha Roy A, Ambrosio R, Jr., Salomao M, Dupps WJ, Jr. Discriminant value of custom ocular response analyzer waveform derivatives in keratoconus. *Ophthalmology* 2014;121:459-468.

16. Ambrósio Jr R, Ramos I, Luz A, et al. Dynamic ultra high speed Scheimpflug imaging for assessing corneal biomechanical properties. *Revista Brasileira de Oftalmologia* 2013;72:99-102.

17. Frings A, Linke SJ, Bauer EL, Druchkiv V, Katz T, Steinberg J. Effects of laser in situ keratomileusis (LASIK) on corneal biomechanical measurements with the Corvis ST tonometer. *Clin Ophthalmol* 2015;9:305-311.

18. Frings A, Linke SJ, Bauer EL, Druchkiv V, Katz T, Steinberg J. [Corneal biomechanics : Corvis(R) ST parameters after LASIK]. *Ophthalmologe* 2015.

19. Hassan Z, Modis L, Jr., Szalai E, Berta A, Nemeth G. Examination of ocular biomechanics with a new Scheimpflug technology after corneal refractive surgery. *Cont Lens Anterior Eye* 2014;37:337-341.

20. Pedersen IB, Bak-Nielsen S, Vestergaard AH, Ivarsen A, Hjortdal J. Corneal biomechanical properties after LASIK, ReLEx flex, and ReLEx smile by Scheimpflug-based dynamic tonometry. *Graefes Arch Clin Exp Ophthalmol* 2014;252:1329-1335.

21. Shen Y, Chen Z, Knorz MC, Li M, Zhao J, Zhou X. Comparison of corneal deformation parameters after SMILE, LASEK, and femtosecond laser-assisted LASIK. *J Refract Surg* 2014;30:310-318.

22. Shen Y, Zhao J, Yao P, et al. Changes in corneal deformation parameters after lenticule creation and extraction during small incision lenticule extraction (SMILE) procedure. *PLoS One* 2014;9:e103893.

23. Ali NQ, Patel DV, McGhee CN. Biomechanical responses of healthy and keratoconic corneas measured using a noncontact scheimpflug-based tonometer. *Invest Ophthalmol Vis Sci* 2014;55:3651-3659.

24. Tian L, Huang YF, Wang LQ, et al. Corneal biomechanical assessment using corneal visualization scheimpflug technology in keratoconic and normal eyes. *J Ophthalmol* 2014;2014:147516.

25. Tian L, Ko MW, Wang LK, et al. Assessment of ocular biomechanics using dynamic ultra high-speed Scheimpflug imaging in keratoconic and normal eyes. *J Refract Surg* 2014;30:785-791.

26. Ye C, Yu M, Lai G, Jhanji V. Variability of Corneal Deformation Response in Normal and Keratoconic Eyes. *Optom Vis Sci* 2015;92:e149-153.

27. Bak-Nielsen S, Pedersen IB, Ivarsen A, Hjortdal J. Dynamic Scheimpflug-based assessment of keratoconus and the effects of corneal cross-linking. *J Refract Surg* 2014;30:408-414.

28. Coste V, Schweitzer C, Paya C, Touboul D, Korobelnik JF. [Evaluation of corneal biomechanical properties in glaucoma and control patients by dynamic Scheimpflug corneal imaging technology]. *J Fr Ophtalmol* 2015;38:504-513.

29. Lee R, Chang RT, Wong IY, Lai JS, Lee JW, Singh K. Novel Parameter of Corneal Biomechanics That Differentiate Normals From Glaucoma. *J Glaucoma* 2015.

30. Salvetat ML, Zeppieri M, Tosoni C, Felletti M, Grasso L, Brusini P. Corneal Deformation Parameters Provided by the Corvis-ST Pachy-Tonometer in Healthy Subjects and Glaucoma Patients. *J Glaucoma* 2014.

31. Tian L, Wang D, Wu Y, et al. Corneal biomechanical characteristics measured by the CorVis Scheimpflug technology in eyes with primary open-angle glaucoma and normal eyes. *Acta Ophthalmol* 2015.

32. Bao F, Deng M, Wang Q, et al. Evaluation of the relationship of corneal biomechanical metrics with physical intraocular pressure and central corneal thickness in ex vivo rabbit eye globes. *Exp Eye Res* 2015;137:11-17.

33. Huseynova T, Waring GOt, Roberts C, Krueger RR, Tomita M. Corneal biomechanics as a function of intraocular pressure and pachymetry by dynamic infrared signal and Scheimpflug imaging analysis in normal eyes. *Am J Ophthalmol* 2014;157:885-893.

34. Elsheikh A, Wang D, Brown M, Rama P, Campanelli M, Pye D. Assessment of corneal biomechanical properties and their variation with age. *Curr Eye Res* 2007;32:11-19.

35. Villavicencio OF GF, Henriquez MA, Izquierdo L Jr, Ambrosio RR Jr, Belin MW. Independent Population Validation of the Belin/Ambrosio Enhanced Ectasia Display: Implications for Keratoconus Studies and Screening. *Int J Kerat Ect Cor Dis* 2014;3:1-8.

36. Joda AA, Shervin MMS, Kook D, Elsheikh A. Development and validation of a correction equation for Corvis tonometry. *Computer Methods in Biomechanics and Biomedical Engineering* 2015;1-11.

37. Elsheikh A, Alhasso D, Rama P. Assessment of the epithelium's contribution to corneal biomechanics. *Exp Eye Res* 2008;86:445-451.

38. Elsheikh A. Finite element modeling of corneal biomechanical behavior. *J Refract Surg* 2010;26:289-300.

39. Elsheikh A, Alhasso D, Gunvant P, Garway-Heath D. Multiparameter correction equation for Goldmann applanation tonometry. *Optom Vis Sci* 2011;88:E102-112.

40. Davey PG, Elsheikh A, Garway-Heath DF. Clinical evaluation of multiparameter correction equations for Goldmann applanation tonometry. *Eye (Lond)* 2013;27:621-629.

41. Pinero DP, Alcon N. In vivo characterization of corneal biomechanics. *J Cataract Refract Surg* 2014;40:870-887.

42. Elsheikh A, Wang D, Pye D. Determination of the modulus of elasticity of the human cornea. *J Refract Surg* 2007;23:808-818.

43. Nomura H, Ando F, Niino N, Shimokata H, Miyake Y. The relationship between age and intraocular pressure in a Japanese population: the influence of central corneal thickness. *Curr Eye Res* 2002;24:81-85.

44. Rochtchina E, Mitchell P, Wang JJ. Relationship between age and intraocular pressure: the Blue Mountains Eye Study. *Clin Experiment Ophthalmol* 2002;30:173-175.

45. Regensburg NI, Wiersinga WM, van Velthoven ME, et al. Age and gender-specific reference values of orbital fat and muscle volumes in Caucasians. *Br J Ophthalmol* 2011;95:1660-1663.

Legends:

Figure 1

Calculation of highest concavity parameters, delta Arclenght and deflection area

Figure 2

Distribution of IOP (uncorrected) in the evaluated population

Figure 3

Distribution of IOP_{FEM} in the evaluated population

Figure 4

Distribution of pachymetry in the evaluated population

Figure 5

Distribution of age in the evaluated population

Figure 6

Scatter plot and mean curves in the different subgroups of Inverse Concave Radius with regards to pachymetry

Figure 7

Scatter plot and mean curves in the different subgroups of Inverse Concave Radius

Figure 8

Scatter plots of Inverse Concave Radius and Highest Concavity Radius with regards to IOP_{FEM}

Figure 9

Scatter plot and mean curves in the different age subgroups of Whole Eye Movement

Figure 10

Showing four cases of healthy patients with different IOP values. In all the cases the imported profile fits inside the mean ± 2SD range of the normative values displayed.

Figure 11

Showing a clinical example of the use of normative values: the display is designed with three graphs. The central one (B) shows the diagram of the selected CDP (in this case Deflection

Amplitude and Inverse Concave Radius) with the normal ranges the particular IOP of the patient in the evaluated exam. The other two charts display the obtained results compared to the whole normal range in dependency of CCT (graph C) and IOP_{FEM} (graph A). The actual profile fits inside the mean ± 2SD range of the normative values displayed.

Figure 12

The imported profile of a keratoconic patient: the diagram clearly extend outside of the mean ± 2SD normative value range displayed.

Figure 13

Differences of the curves of highest concavity (from which both HC radius and Inverse Concave Radius are derived) in dependency of age and CCT. Mean values and box blots of these parameters show that there is no difference between the age groups at the point of maximum Inverse Radius which appears very shortly after first applanation. However, at highest concavity there is a significantly difference between the age groups.

Table 1 Subgroups characteristics with range of values and number of eyes in each group

	Group 1	Group 2	Group 3	Group 4
IOP_{FEM}	<12.8 mmHg (188)	12.8-14.5 mmHg (361)	14.8-16.7 mmHg (240)	>16.8 mmHg (118)
Age	<33 years (261)	34-46 years (247)	47-60 years (217)	>61 years (182)
CCT	<503 µm (215)	504-533 µm (299)	534-564 µm (293)	>565 µm (105)

Table 2 Correlation of CDPs with Pachymetry

	Eta	Rho
Maximum Deformation Amplitude	0,231	-0.232
Peak Distance	0,167	-0.175
HC Radius	0,337	-0.342
Inverse Concave Radius	**0,409**	**-0.427**
A1 Length	0,104	0.078
A1 Velocity	0,209	-0.224
A2 Length	0,197	0.193
A2 Velocity	0,293	0.304
HC Deformation Amplitude	0,231	-0.232
HC Deflection Amplitude	0,246	-0.238
Whole Eye Movement	0,098	-0.089
HC Deflection Area	0,182	-0.186
Delta Arclenght	0,101	-0.089
DA Ratio	**0,420**	**-0.498**

Table 3 Correlation of CDPs with IOP_{FEM}

	Eta	Rho
Maximum Deformation Amplitude	0,561	-0.602
Peak Distance	0,513	-0.515
HC Radius	**0,076**	**0.062**
Inverse Concave Radius	**0,030**	**0.022**
A1 Length	0,113	0.087
A1 Velocity	0,381	-0.385
A2 Length	0,167	0.121
A2 Velocity	0,484	0.500
HC Deformation Amp.	0,561	-0.602
HC Deflection Amplitude	0,504	-0.516
Whole Eye Movement	**0,099**	**-0.130**
HC Deflection Area	0,496	-0.517
Delta Arclenght	0,336	0.344
DA Ratio	0,246	-0.316

Table 4 Normative values with regards to pachymetry showing minimum and maximum normative values for the selected corneal deformation parameters and subgroups

Pachymetry group	Normative	Deformation Amplitude	HC Radius	Inverse Concave Radius	A1 Length	A1 Velocity	A2 Length	A2 Velocity	HC Deformation Amplitude	HC Deflection Amplitude	Whole Eye Movement	HC Deflection Area	DA Ratio	HC delta Arclength	Peak Distance
<503µm	Min	0,928775	5,258757	0,147455	1,625602	0,114193	0,857153	-0,63268	0,928775	0,715529	0,155315	2,248372	1,5028353	-0,178269	4,52489
	Max	1,328285	7,789783	0,218665	1,970478	0,212327	2,364727	-0,23876	1,328285	1,161911	0,448825	4,610108	1,7396933	-0,081191	5,65819
504-533µm	Min	0,913046	5,331248	0,140776	1,664096	0,114326	0,929156	-0,599142	0,913046	0,697716	0,160146	2,184049	1,4587721	-0,190173	4,458993
	Max	1,313634	8,261552	0,206244	1,955364	0,207474	2,358404	-0,229758	1,313634	1,142964	0,449714	4,585351	1,7304101	-0,082547	5,673247
534-564µm	Min	0,858674	5,49037	0,136776	1,675711	0,10289	1,116397	-0,552998	0,858674	0,659616	0,167939	2,099056	1,4337682	-0,183416	4,403309
	Max	1,290826	8,66735	0,197564	1,963249	0,20249	2,358823	-0,196682	1,290826	1,108144	0,439181	4,390644	1,6783982	-0,087124	5,608011
>565µm	Min	0,837102	5,489475	0,127137	1,664587	0,101426	1,357232	-0,517782	0,837102	0,627208	0,201776	1,979436	1,4208714	-0,189186	4,306955
	Max	1,289678	9,273405	0,192783	1,958833	0,197354	2,261548	-0,196618	1,289678	1,077952	0,448344	4,216244	1,6579814	-0,080854	5,556465

Table 5 Normative values with regards to IOP_{FEM} showing minimum and maximum normative values for the selected corneal deformation parameters and subgroups

IOP_{FEM} group	Normative	Deformation Amplitude	HC Radius	Inverse Concave Radius	A1 Length	A1 Velocity	A2 Length	A2 Velocity	HC Deformation Amplitude	HC Deflection Amplitude	Whole Eye Movement	HC Deflection Area	DA Ratio	HC delta Arclength	Peak Distance
<12.8 mmHg	Min	1,018202	4,765895	5,303227	0,138947	1,607489	0,129298	0,830581	-0,644068	1,018202	0,788882	0,179797	2,648010	-0,193878	1,470033
	Max	1,332458	5,687509	8,262986	0,207425	1,990809	0,207478	2,376610	-0,283507	1,332458	1,165863	0,449862	4,708980	-0,091250	1,743791
12.80-14.5 mmHg	Min	0,948127	4,635490	5,390839	0,133935	1,621851	0,124361	0,966614	-0,578620	0,948127	0,740144	0,162265	2,462837	-0,191341	1,448313
	Max	1,291036	5,564997	8,389050	0,210857	1,986316	0,204714	2,370704	-0,250959	1,291036	1,121252	0,446233	4,432105	-0,090205	1,733144
14.8-16.7 mmHg	Min	0,891457	4,445808	5,351459	0,134707	1,689634	0,112506	1,148371	-0,508179	0,891457	0,684689	0,156580	2,177505	-0,166614	1,445165
	Max	1,214302	5,425992	8,537600	0,208401	1,945016	0,197819	2,362850	-0,217394	1,214302	1,042902	0,432787	4,017812	-0,087161	1,700231
>16.8 mmHg	Min	0,850708	4,269833	5,118763	0,132871	1,691190	0,093035	1,181243	-0,462256	0,850708	0,625834	0,147937	1,929284	-0,164252	1,423837
	Max	1,161105	5,293845	8,776372	0,211620	1,962301	0,189863	2,312790	-0,198625	1,161105	0,995979	0,451334	3,750258	-0,076240	1,679818