Influence of Pachymetry and Intraocular Pressure on Dynamic Corneal Response Parameters in Healthy Patients

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ABSTRACT

PURPOSE: To evaluate the influence of pachymetry, age, and intraocular pressure in normal patients and to provide normative values for all dynamic corneal response parameters (DCRs) provided by dynamic Scheimpflug analysis.

METHODS: Seven hundred five healthy patients were included in this multicenter retrospective study. The biomechanical response data were analyzed to obtain normative values with their dependence on corrected and clinically validated intraocular pressure estimates developed using the finite element method (bIOP), central corneal thickness (CCT), and age, and to evaluate the influence of bIOP, CCT, and age.

RESULTS: The results showed that all DCRs were correlated with bIOP except deflection amplitude (DefA) ratio, highest concavity (HC) radius, and inverse concave radius. The analysis of the relationship of DCRs with CCT indicated that HC radius, inverse concave radius, deformation amplitude (DA) ratio, and DefA ratio were correlated with CCT (rho values of 0.343, -0.407, -0.444, and -0.406, respectively). The age group subanalysis revealed that primarily whole eye movement followed by DA ratio and inverse concave radius were the parameters that were most influenced by age. Finally, custom software was created to compare normative values to imported examinations.

CONCLUSIONS: HC radius, inverse concave radius, DA ratio, and DefA 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 values allows the interpretation of an abnormal examination without the need to match every case with another normal patient matched for CCT and IOP.

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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 to describe corneal shape, from keratometry to corneal topography (front surface curvature maps),[2] then into three-dimensional corneal tomography systems.[3] More recently, it has been shown 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 mathematical corneal models.[9-11] However, this

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changed with the introduction of the first instrument able to evaluate corneal biomechanical response parameters in vivo: the Ocular Response Analyzer (ORA) (Reichert Inc., Depew, NY).[12] The ORA is a modified noncontact tonometer designed first to provide a more accurate measurement of intraocular pressure (IOP) through compensation for corneal biomechanics. It analyzes corneal behavior during a bidirectional 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 a noncontact tonometer, which monitors the response of the cornea to an air pressure pulse using an ultra-high-speed Scheimpflug camera, and uses the captured image sequence to produce estimates of IOP and deformation response parameters.[16]

Several articles have recently been published on the possible applications of the Corvis ST, 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 patients with glaucoma.[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.[32-34] It is therefore relevant to investigate the distribution and normal limits for the in vivo corneal biomechanical data derived from dynamic corneal response parameters, and determine whether these metrics have correlations with IOP and corneal thickness.

This article evaluates the influence of pachymetry and IOP on response parameters and provides normative values for all dynamic corneal response parameters provided by the Corvis ST in healthy patients.

PATIENTS AND METHODS

Seven hundred five healthy patients were included in this multicenter retrospective study. The patients were enrolled in three clinics located on three different continents to include variability from different ethnic groups. A total of 306 patients were enrolled from Vincieye Clinic, Milan, Italy; 227 patients from the Rio de Janeiro Corneal Tomography and Biomechanics Study Group, Rio de Janeiro, Brazil; and 172 patients from Eyereum Eye Clinic, Seoul, Korea. The institutional review board ruled that approval was not required for this record review study, and it was conducted according to the tenets of the Declaration of Helsinki. However, participants provided informed consent before their data were used in the study.

All patients had a complete ophthalmic examination, including the Corvis ST and Pentacam (Oculus Optikgeräte) examinations. The Corvis ST output parameters from each measurement were exported to a spreadsheet and analyzed to obtain normative values as well as test their correlations with pachymetry, age, and clinically validated corrected IOP estimates developed using the finite element method biomechanic IOP (bIOP), central corneal thickness (CCT), and age 35 years. Age was chosen as an influencing factor because older patients tend to have stiffer corneas than younger ones, even though the standard deviation (SD) might be large for all ages.[35]

The inclusion criteria of this study were the presence in the database of a Corvis ST examination, a Belin/Ambrósio Enhanced Ectasia Index total deviation (BAD-D) from the Pentacam less than 1.6 SD from normative values, and a signed informed consent. The BAD-D cut-off was used because it is described as the best performing screening parameter for ectasia with values of 1.65 and 1.85 associated with a 95% and 97.5% confidence interval, respectively, with an acceptable false-negative rate of less than 1%.[36]

Exclusion criteria were any previous ocular surgery or disease, myopia greater than 10.00 diopters (D), and any concomitant or previous glaucoma or hypotonic therapies. All measurements with the Corvis ST were taken by the same experienced technicians and captured by automatic release to ensure the absence of user dependency. Only Corvis ST examinations with quality score "OK" were included in the analysis. Additionally, a second manual, frame-by-frame analysis of the examination, made by an independent masked examiner, was performed to ensure the 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.

Only one eye per patient was randomly included in the analysis to avoid the bias of the relationship between bilateral eyes that could influence the analysis result.

To analyze the bIOP, CCT, and age dependency of Corvis ST dynamic corneal response parameters obtained by research software, the dataset was split into four different bIOP groups, four different CCT groups, and four different age groups. The bIOP groups were defined as follows. In the first step, the lowest 5th percentile and the highest 5th percentile for bIOP 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 bIOP and high bIOP. CCT and age groups were defined similarly. Following this exercise, 636 eyes remained (634 eyes each in

TABLE 1
Subgroup Characteristics

Parameter	Group 1	Group 2	Group 3	Group 4
bIOP (mm Hg)	< 13.2 (n = 116)	13.2 to 14.9 (n = 198)	14.9 to 16.5 (n = 217)	> 16.6 (n = 105)
Age (y)	< 32 (n = 266)	32 to 45 (n = 197)	45 to 58 (n = 99)	> 58 (n = 72)
CCT (μm)	< 520 (n = 136)	520 to 546 (n = 211)	547 to 573 (n = 196)	> 573 (n = 91)

bIOP = biomechanic intraocular pressure; CCT = central corneal thickness

the CCT and age groups and 636 in the bIOP groups). These eyes were split into four groups such that the difference between highest and lowest values were similar for each group. Subgroup characteristics are summarized in **Table 1**.

The Corvis ST uses an ultra-high-speed Scheimpflug camera that captures 4,330 images per second and covers 8 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 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 quality score is also available for the pachymetry and IOP data.[16]

IOP Measurement

Together with dynamic corneal response parameters, the Corvis ST provides standard IOP and pachymetry measurements and a new and validated corrected IOP estimate (bIOP).[37] 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.[8,35,38-40] The analysis was used to provide bIOP, which are IOP estimates significantly less affected by corneal parameters and given as a function of measured IOP, CCT, and age. The bIOP formula used was a modified algorithm of the published formula[37]:

$$IOP_{cor} = C_{CCT1} * C_{AP1} * C_{age1} + C_{CCT2} * C_{age2} + C_{DCR} + a19$$

where a1 to a19 are all constants, bIOP is an estimate of true IOP or the corrected value of measured IOP, C_{age1} and C_{age2} are the effect of variation in age (years), C_{DCR} is the correction based on biomechanical response (highest concavity radius), and C_{CCT1} and C_{CCT2} are parameters representing the effect of variation in CCT among patients (mm):

- $C_{CCT1} = (a1 * CCT3 + a2 * CCT2 + a3 * CCT + a4)$
- $C_{AP1} = (a5 * AP1 + a6)$
- $C_{age1} = (a7 * [Ln(Beta)]2 + a8 * [Ln(Beta)] + a9)$
- $C_{CCT2} = (a10 * CCT3 + a11 * CCT2 + a12 * CCT + a13)$
- $C_{age2} = (a14 * [Ln(Beta)]2 + a15 * [Ln(Beta)] + a16)$
- $Beta = 0.5852 * EXP(0.0111 * Age[year])$
- $C_{DCR} = a17 *$ highest concavity radius $+ a18$

Dynamic Corneal Response Parameters

All corneal response parameters provided by the Corvis ST are derived from the various phases of the deformation of the cornea.

The instrument produces an air puff that forces the cornea inward (ingoing phase) through first applanation (inward applanation) into a concavity phase until it achieves the highest concavity. Then, the cornea undertakes a second applanation (outward applanation) before returning to its natural shape.

The applanation of the cornea is defined by the transition from a convex to a concave shape in a zone 0.5 mm in diameter around the corneal apex. Other measured parameters are: the speed of corneal apex at first and second applanation (A1 and A2 velocity); the distance between the two bending peaks created in the cornea at the maximum concavity state (peak distance); the radius of the central cornea at the maximum concavity state, based on a parabolic fit (highest concavity radius); and the maximum depth of deformation at the highest concavity state (deformation amplitude).

The deformation amplitude refers to the movement of the corneal apex in the anterior-posterior direction and is determined as the highest displacement of the apex at the highest concavity moment.[13,16] During the measurement, there is a slight but significant movement of the whole eye globe. 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. The deformation amplitude is indeed the sum of actual corneal deflection amplitude and the whole eye movement. The nasal and temporal edge points that are 4 mm away from the corneal apex are used to track the whole eye movement, which can be seen in

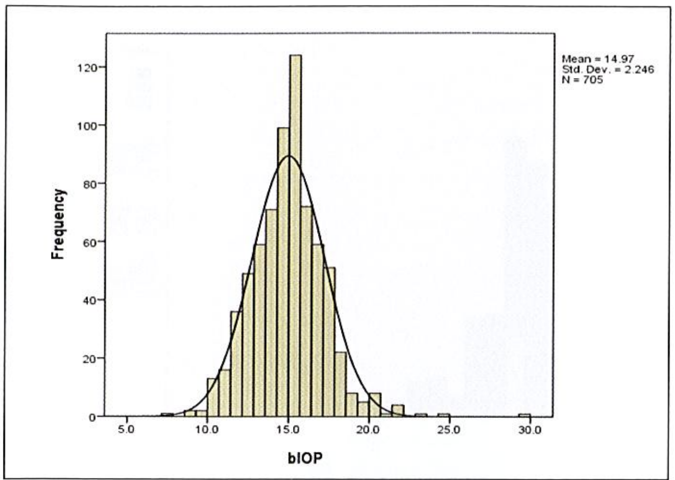


Figure 1. Distribution of biomechanic intraocular pressure (bIOP) in the evaluated population.

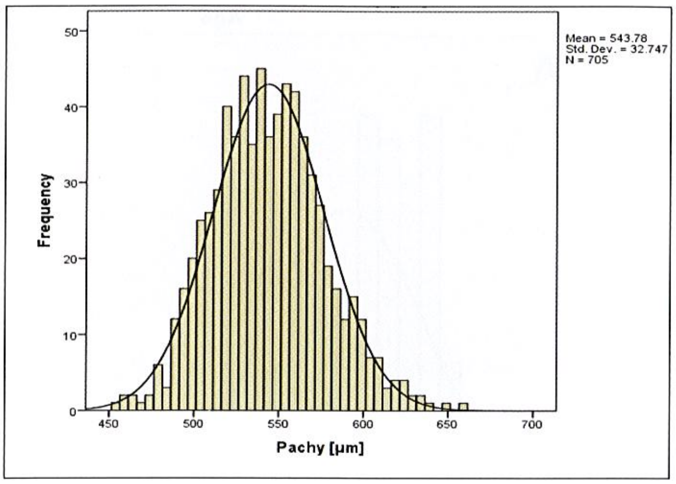


Figure 2. Distribution of pachymetry in the evaluated population.

the video of corneal deformation, especially near the end of the air puff where the corneal deflection has already recovered. The deflection amplitude is displacement of the corneal apex in reference to the overlayed cornea in its initial state. Therefore, the deformation amplitude is the sum of pure corneal deflection amplitude and whole eye movement. The deflection area describes the "displaced" area of the cornea in the analyzed horizontal sectional plane due to the deformation of the cornea.

Other parameters can be extrapolated from the highest concavity moment: inverse concave radius and peak distance. The inverse concave radius (1/R) is plotted over the time of the air pulse and the integrated sum is calculated between the first and second applanation events.[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]

Two new parameters called central-peripheral deformation amplitude ratio and deflection amplitude ratio describe the ratio between the deformation/deflection amplitude at the apex and the average deformation/deflection amplitude in a nasal and temporal zone 1 mm (2 mm for deflection amplitude ratio) from the center. The greater the difference between the center and defined paracentral regions, the less resistant is the cornea to deformation. Therefore, one would expect higher values of deformation amplitude ratio and deflection amplitude ratio to be associated with softer corneas. In particular, this difference is pronounced in ectatic corneas.

The delta arc length, another new parameter, describes the change of the arc length during the highest concavity moment from the initial state in a defined 7-mm zone. This parameter is calculated 3.5 mm from the apex to both sides in the horizontal direction (**Figure A**, available in the online version of this article). The temporal changes in the delta arc length are also calculated for the exact same zone and a plot is generated.

Examples of the calculation of highest concavity parameters, delta arc length, and deflection amplitude are shown in **Figure A**.

All of these new parameters were included in the analysis because we expected a weak correlation with IOP and strong correlation with bending stiffness.

Statistical Analysis

Descriptive statistics were calculated for 12 different parameters (deformation amplitude, deflection amplitude, deflection area, whole eye movement, peak distance, corneal velocity 1, corneal velocity 2, delta arc length, highest concavity radius, inverse concave radius, deflection amplitude ratio, and deformation amplitude ratio) for each bIOP group, each CCT group, and each age group. Additionally, descriptive statistics were calculated to evaluate the possible differences between the three centers and the ethnic groups.

The statistical analysis was performed with SPSS for Windows software (version 22; SPSS, Inc., Chicago, IL) and R Statistical Software (Foundation for Statistical Computing, Vienna, Austria).

Differences between data were evaluated with analysis of variance (ANOVA). A P value less than .05 was considered significant. The association between variables was expressed with Spearman correlation coefficient.

In addition, the influence of the same Corvis ST parameters on bIOP, CCT, and age was analyzed by plotting the mean temporal diagrams for these Corvis ST parameters for each subgroup. The temporal diagrams

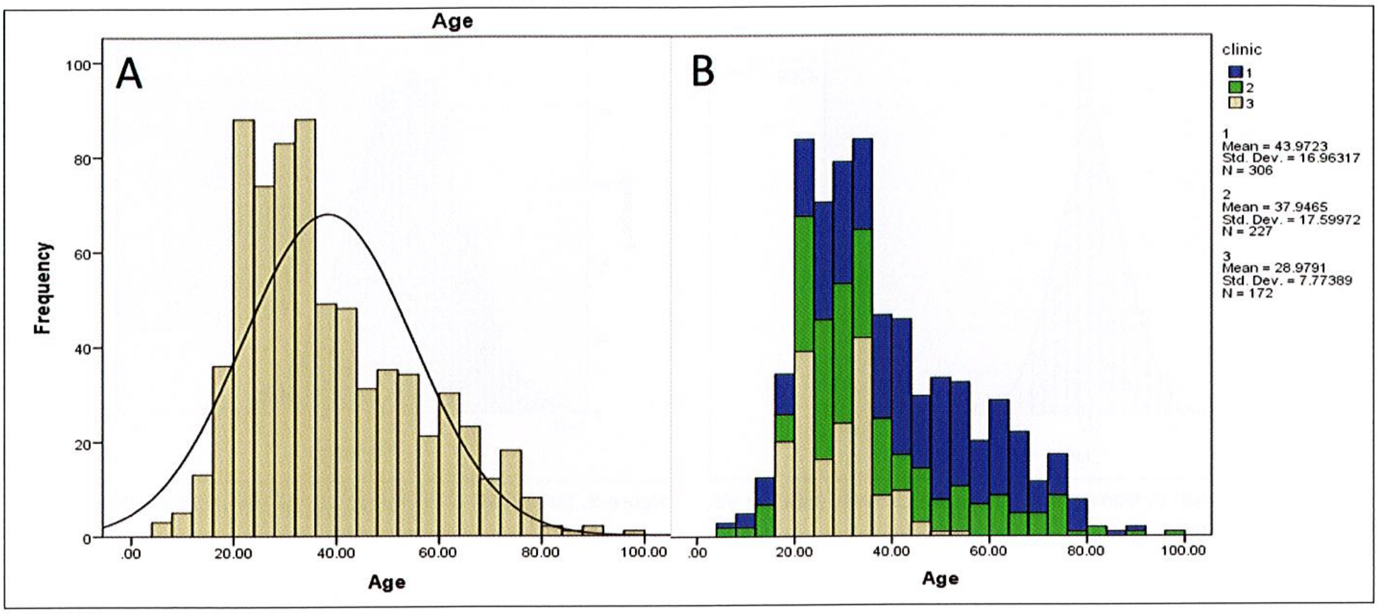


Figure 3. Distribution of age in the evaluated population in (A) the global population and (B) divided by clinic of enrollment (1 = Europe, 2 = South America, and 3 = Asia).

TABLE 2

Spearman Correlation Coefficients and Significance of Dynamic Corneal Response Parameters With Regard to Pachymetry

Parameter	Rho	*P*
Peak distance * Pachygroup	-0.263	< .001
HC radius * Pachygroup	0.343	< .001
Inverse concave radius * Pachygroup	-0.407	< .001
A1 velocity * Pachygroup	-0.253	< .001
A2 velocity * Pachygroup	0.326	< .001
DA * Pachygroup	-0.277	< .001
HC DefA * Pachygroup	-0.307	< .001
Whole eye movement * Pachygroup	-0.064	.146
HC deflection area * Pachygroup	-0.242	< .001
HC dArc length * Pachygroup	-0.120	.021
DA ratio * Pachygroup	-0.444	< .001
DefA ratio * Pachygroup	-0.406	< .001

HC = highest concavity; A1 = applanation time 1; A2 = applanation time 2; DA = deformation amplitude; DefA = deflection amplitude; dArc = delta arc

represent the change of each parameter over the whole deformation response time until the cornea has recovered to its initial state. This allows evaluation of the influence of bIOP, 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 (Microsoft Corporation, Redmond, WA).

Normative value ranges were created with the mean values of the selected subgroup ± 1.96 SD. Custom software was created to compare normative values to imported examinations. It allows the user to compare the imported examination to normative values based on the bIOP and CCT values of that examination. Additionally, the software is able to provide graphs illustrating the difference of the imported examination from the normative values with regard to CCT and bIOP.

RESULTS

Global Population

Mean bIOP was 14.97 ± 2.24 mm Hg (**Figure 1**), mean CCT was 543 ± 33 µm (**Figure 2**), and mean age was 38 ± 16 years (**Figure 3A**). There were 320 (45.4%) left eyes and 385 (54.6%) right eyes. Subgroup characteristics with regard to bIOP, pachymetry, and age are summarized in **Table 1**.

Clinic Populations

The comparative analysis of the characteristics of the enrolled patients in Europe (Clinic 1), South America (Clinic 2), and Asia (Clinic 3) gave the following results.

The ANOVA analysis showed a nonsignificant difference between the pachymetry values of the enrolled patients between the clinics ($P > .05$); conversely, the mean values of bIOP were significantly different ($P < .001$) between the clinics with a mean of 14.1 ± 2.35 mm Hg for Europe, 15.26 ± 2.13 mm Hg for South America, and 15.0 ± 2.24 mm Hg for Asia. However, given the stratification of the normative values for bIOP values,

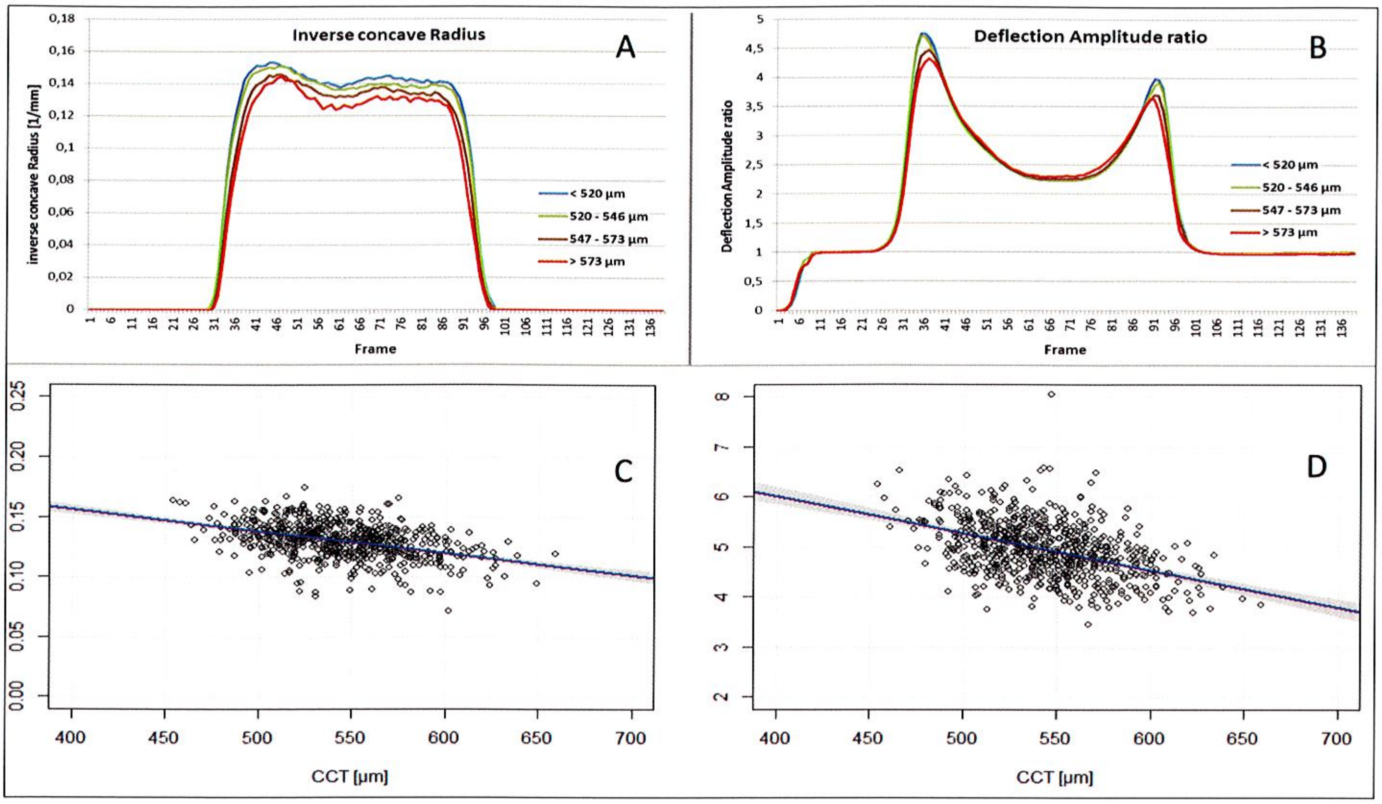


Figure 4. Mean curves and scatter plot for the different subgroups of (A and C) inverse concave radius and (B and D) deflection amplitude ratio with regard to pachymetry. CCT = central corneal thickness

this difference, probably due to ethnic and age disparity, did not affect the subsequent analysis.

As shown in **Figure 3B**, the enrolled patient demographics were different between the clinics. Whereas Europe and South America enrolled patients from all age groups, Asia enrolled mainly patients between 20 and 50 years old; this difference was statistically significant ($P < .001$). As a consequence, the presented normative data of patients older than 50 years do not include the Asian population.

PACHYMETRY GROUPS

The analysis of the influencing factors for this set of subgroups showed that the four CCT groups did not show significant differences for bIOP and age but were significantly different for uncorrected IOP ($P < .001$), confirming that the bIOP correction algorithm is able to compensate for these confounding factors.

The ANOVA analysis of dynamic corneal response parameters between the CCT subgroups showed a significant difference in most dynamic corneal response parameters, with different levels of association revealed by dissimilar rho values (**Table 2**). Highest concavity radius, inverse concave radius, deformation amplitude ratio, and deflection amplitude ratio were the dynamic corneal response parameters with the highest rho values (0.343, -0.407, -0.444, and -0.406, respectively). The level of association of inverse concave radius and deflection amplitude ratio is also shown in the scatter plots in **Figures 4C-4D**, whereas the mean curves for the selected dynamic corneal response parameters in the different subgroups are shown in **Figures 4A-4B**.

IOP GROUPS

The analysis of the influencing factors for this set of subgroups showed that the four bIOP groups did not differ statistically for pachymetry ($P = .077$) but were significantly different for age ($P < .01$).

The results of dynamic corneal response parameter analysis between the bIOP groups showed a significant difference in all parameters evaluated, excluding deflection amplitude ratio, highest concavity radius, and inverse concave radius ($P = .784$, .098, and .803, respectively), which were more influenced by CCT, as shown previously (**Figures 5A-5B**). Similarly, the rho values for these parameters showed a low correlation with bIOP (**Table 3**).

AGE GROUPS

The comparative results for age groups showed a significant difference in bIOP, indicating slightly low-

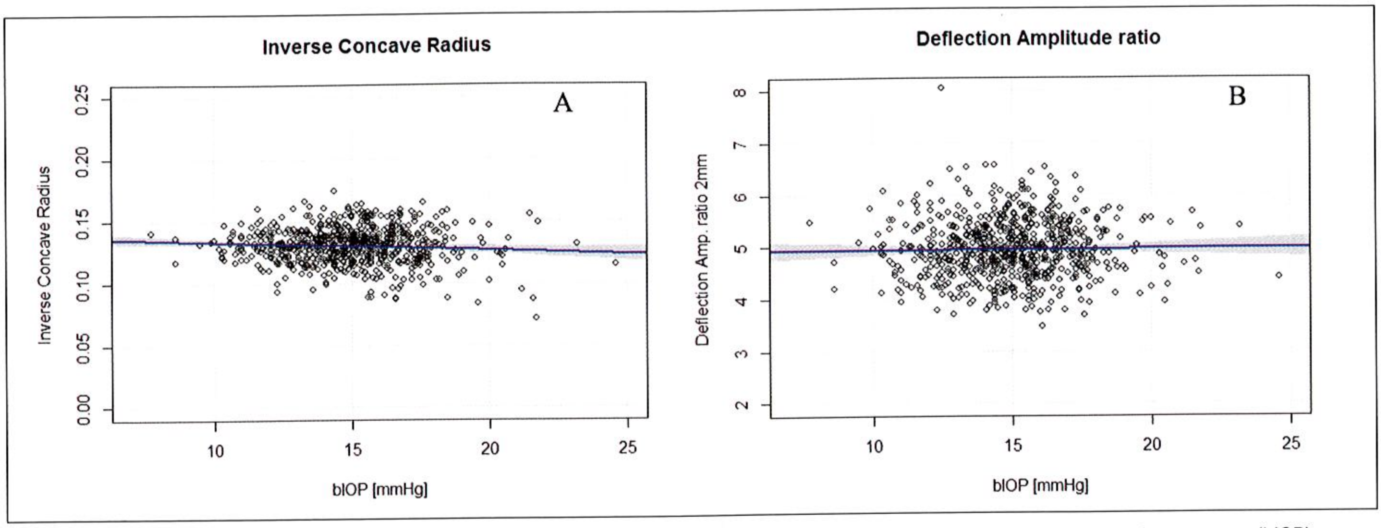


Figure 5. Scatter plots of (A) inverse concave radius and (B) deflection amplitude ratio with regard to biomechanic intraocular pressure (bIOP).

TABLE 3

Spearman Correlation Coefficients and Significance of Dynamic Corneal Response Parameters With Regard to bIOP

Parameter	Rho	*P*
Peak distance * bIOP	-0.528	< .001
HC radius * bIOP	0.128	.098
Inverse concave radius * bIOP	-0.052	.803
A1 velocity * bIOP	-0.277	< .001
A2 velocity * bIOP	-0.399	< .001
DA * bIOP	-0.640	< .001
HC DefA * bIOP	-0.523	< .001
Whole eye movement * bIOP	-0.328	< .001
HC DefA * bIOP	-0.517	< .001
HC dArc length * bIOP	0.326	< .001
DA ratio * bIOP	-0.165	.011
DefA ratio * bIOP	0.045	.784

bIOP = biomechanic intraocular pressure; HC = highest concavity; A1 = applanation time 1; A2 = applanation time 2; DA = deformation amplitude; DefA = deflection amplitude; dArc = delta arc

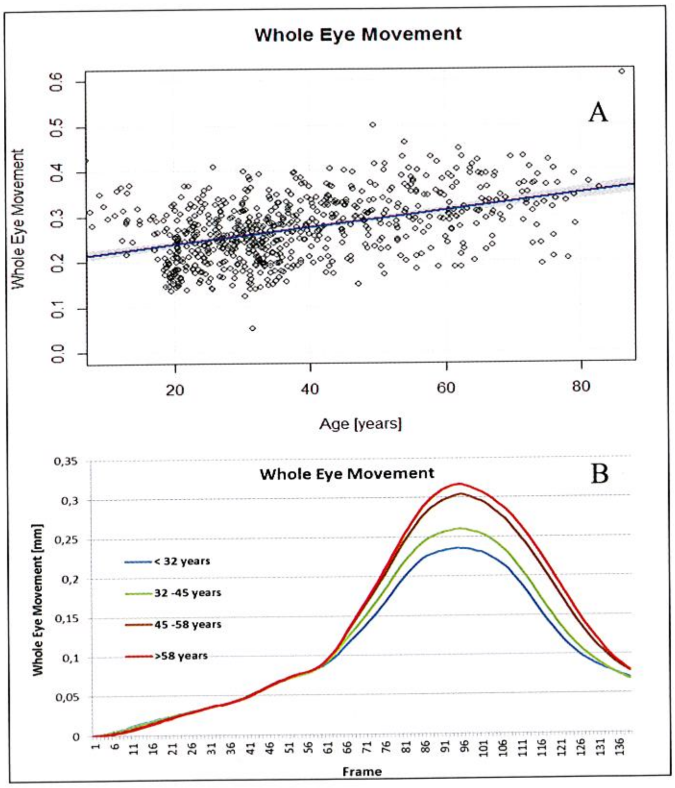


Figure 6. (A) Scatter plot and (B) mean curves in the different age subgroups for whole eye movement.

er bIOP values with increasing age (15.5 ± 1.95 mm Hg in age group 1, 14.9 ± 2.0 mm Hg in age group 2, 14.1 ± 2.3 mm Hg in age group 3, and 14.93 ± 2.12 mm Hg in age group 4).

The results of the ANOVA for all analyzed parameters with respect to age revealed significant differences in all parameters evaluated, excluding peak distance, deflection amplitude, highest concavity deflection area, and highest concavity delta arc length. Conversely, whole eye movement, deformation amplitude ratio, and inverse concave radius were the three parameters that were most greatly influenced by age with the following rho values: 0.428 for whole eye movement, -0.237 for deformation amplitude ratio, and -0.171 for inverse concave radius. **Figure 6A** shows the whole eye movement scatter plot and **Figure 6B** shows the mean curves for the different age groups.

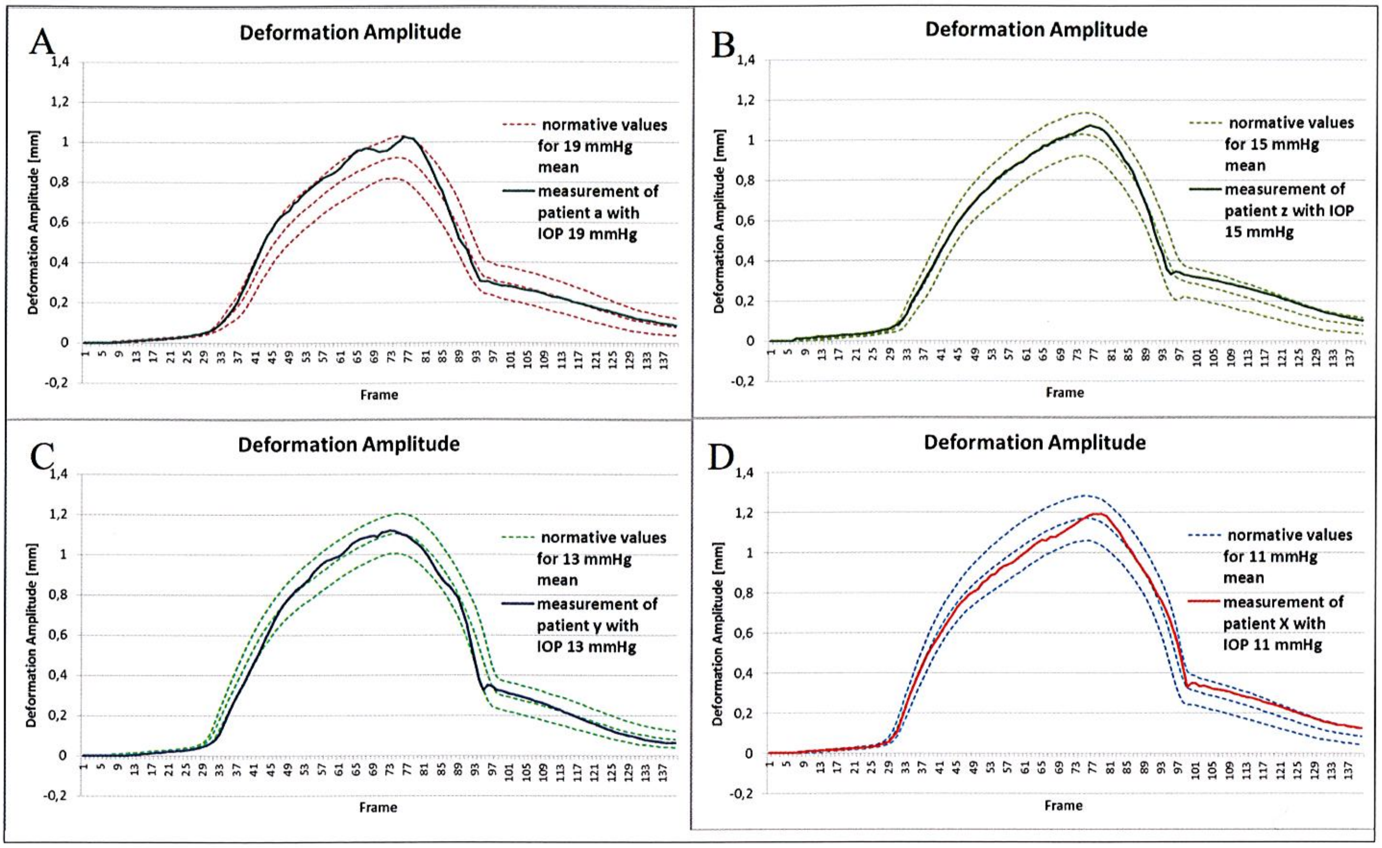


Figure 7. Showing four cases of healthy patients with different biomechanic intraocular pressure (bIOP) values. (A) 19 mm Hg, (B) 15 mm Hg, (C) 13 mm Hg, and (D) 11 mm Hg. In all cases the imported profile fits inside the mean ± 2 standard deviation range of the normative values displayed.

NORMATIVE VALUES

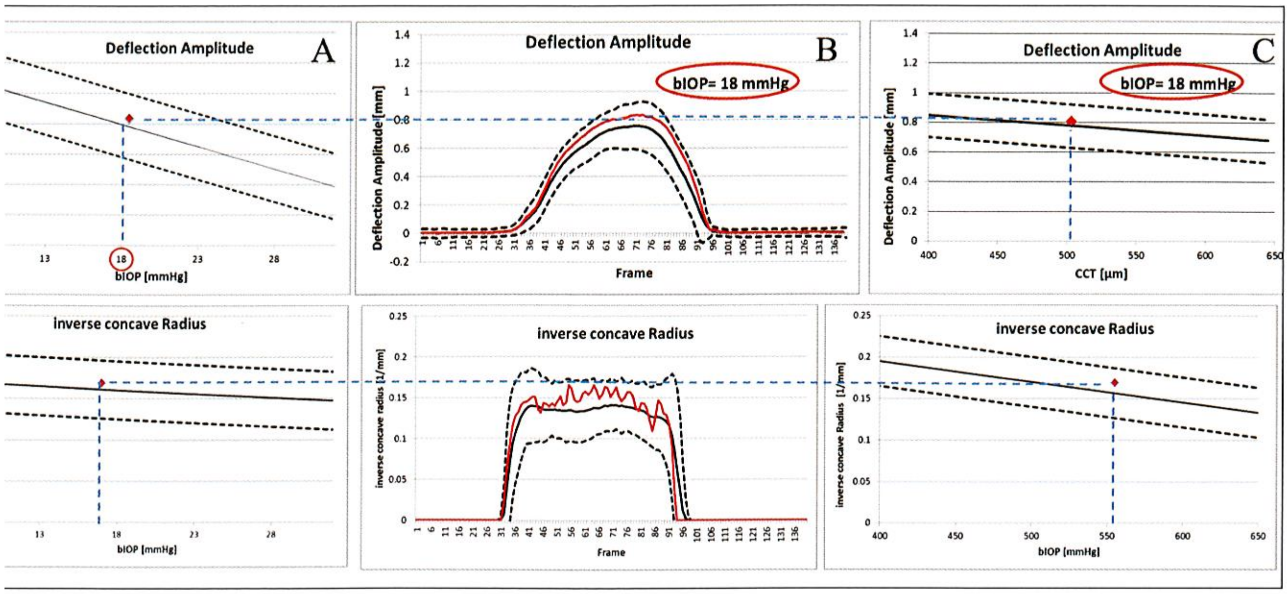
Normative values of the bIOP, CCT, and age subgroups are shown in **Table A, Table B,** and **Table C** (available in the online version of this article). All values are expressed as minimum and maximum values for the selected subgroups and dynamic corneal response parameters.

The custom software is able to create normative values for any amount of bIOP and CCT, but all of these values were not included in the manuscript to avoid compromising the graphs' legibility.

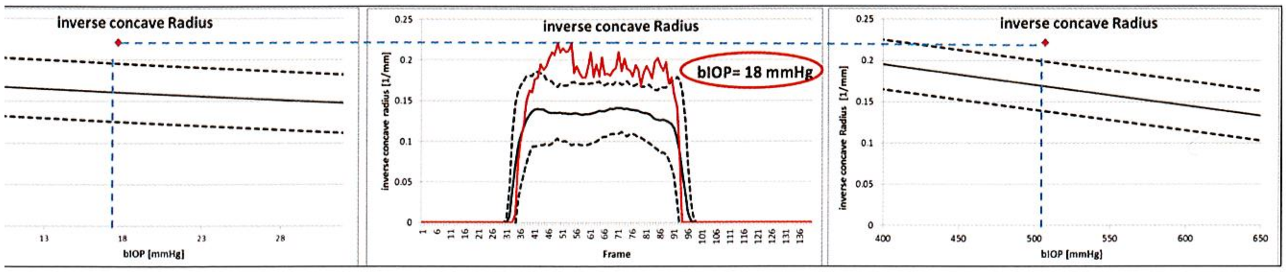
To present the possible clinical application of the custom software, we show four cases of healthy patients with different IOP values (**Figure 7**). In all cases the imported profile fits inside the mean ± 1.96 SD range of the normative values displayed. The program provides three charts to allow the comparison of the actual examination with regard to bIOP and pachymetry values (**Figure 8**). Conversely, **Figure 9** shows the imported profile of a patient with keratoconus. The profile clearly extends outside of the mean ± 2 SD 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. However, the cornea 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, without a 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 the wall tension will increase as IOP increases and, due to the nonlinear properties, a soft cornea with a higher IOP may exhibit stiffer behavior than a fundamentally stiffer cornea with a lower IOP. The same complexity affects IOP measurements because they are influenced by corneal stiffness, which is not only dependent on



Showing a clinical example of the use of normative values: the display is designed with three graphs. The central one (B) shows the dia- ıe selected dynamic corneal response parameters (in this case deflection amplitude and inverse concave radius) with the normal ranges of ılar biomechanic intraocular pressure (bIOP) of the patient in the evaluated examination. The other two charts display the obtained results to the whole normal range in dependency of (C) central corneal thickness and (A) bIOP. The actual profile fits inside the mean ± 2 standard ʼange of the normative values displayed.



The imported profile of a keratoconic patient: the diagrams clearly extend outside of the mean ± 2 standard deviation normative value range bIOP = biomechanic intraocular pressure

:kness, as widely accepted, but also the tissue nodulus, which changes with age and medical and also increases with higher values of IOP. :eviously mentioned, to evaluate the IOP, CCT, dependency of Corvis ST dynamic corneal re- parameters, the dataset was divided into four .t bIOP groups, four different CCT groups, and ferent age groups.

Groups

availability of three biomechanical databases ree different continents allowed, for the first our knowledge, the evaluation to include vari- rom more than one ethnic group. Our compara- ılysis of the characteristics of the populations trated a significant difference in terms of bIOP ı the three clinics. It is not the first time that a ce in IOP has been found in populations with lar ethnicity,[43,44] but in this case, this particular finding did not cause bias in the analysis because it was stratified by IOP.

Pachymetry Groups

The comparative analysis of the pachymetry subgroups indicated that the four CCT groups did not show significant differences for bIOP and age but were significantly different for uncorrected IOP. This result demonstrated that the bIOP correction algorithm, and particularly the modified version used, is able to compensate for these important confounding factors and confirms preclinical validation of the formula.[37] 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 almost impossible to correctly interpret biomechanical characteristics of a cornea unless the IOP corrected for ıctors is known, due to the Laplace law. These s were confirmed by previous reports, which ed that IOP and pachymetry have important ins on most corneal biomechanical metrics proıy the Corvis ST and ORA.[32-34]

conclusions of these earlier studies were that .d pachymetry are important in deformation ;e evaluation and must be taken into consider-\dditionally, the authors concluded that com-.s of research groups based on the ORA and ST with different IOPs and CCTs may lead to e misinterpretations if either is not considered .nalysis.

analysis of the relationship between the dy-corneal response parameters and CCT showed ;hest concavity radius, inverse concave radius, ation amplitude ratio, and deflection amplitude ere highly correlated with CCT. All of these dy-corneal response parameters showed high rho revealing good association with CCT.

OUPS

main result of this analysis indicated that de-. amplitude ratio, highest concavity radius, and concave radius were not significantly influ-ıy IOP, but were more influenced by CCT. This demonstrated that deflection amplitude ratio, concavity radius, and inverse concave radius d parameters to correctly evaluate in vivo cor-ımechanics due to their relative independence)P. Another important finding is the confirma-ıt many parameters used in earlier publications formation amplitude) are strongly correlated)P[32,33] and that, if IOP is not matched or com-ıd statistically, comparison between groups ıot be valid.

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comparative results for age groups showed a ant difference in bIOP, indicating slightly low-values with increasing age. The significant dif-in terms of IOP must be considered with cau-ven the small change in terms of bIOP, and the re shows no independent age effect on IOP.[45,46] more, all of the published results refer mainly .mann applanation tonometry,[46,47] which does 'e an integrated correction of age and CCT to te IOP, as is included in bIOP. However, this will need further studies.

le eye movement, deformation amplitude ratio, 'erse concave radius were the three parameters re most greatly influenced by age. The high cor-. between whole eye movement and age and not with CCT could be explained by the change in the retrobulbar fat composition with regard to age,[48] which may induce modifications in the displacement of the eye under the air puff.

Conversely, the correlation of deformation amplitude ratio and inverse concave radius with age, together with their correlation with pachymetry, probably indicates their capability of quantifying corneal biomechanics. It is well known that the elastic modulus increases with age.[49]

NORMATIVE VALUES

The availability of a multicenter dataset of more than 700 healthy patients allowed the creation of normative value ranges for each dynamic corneal response parameter with regard to IOP, CCT, and age values.

With this custom software, we propose that every dynamic corneal response parameter of each examination be shown in comparison to the corresponding normative value ranges with dependence on bIOP, age, and pachymetry. This software will hopefully be able to show each patient with an abnormal examination without the need to match every case with another normal patient matched for CCT and IOP. 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 and including variability from different continents. More studies are in progress (which will include more patients from each continent) to include an ethnic group normative database.

CONCLUSIONS

Our analysis of dynamic corneal response parameters with respect to bIOP, 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. Highest concavity radius, inverse concave radius, deformation amplitude ratio, and deflection amplitude 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 of interpreting corneal biomechanics in the context of normative values and suspect pathology in clinical practice.

AUTHOR CONTRIBUTIONS

Study concept and design (RV, CJR, RA, PV); data collection (RV, RA, DSYK, BTL); analysis and interpretation of data (RV, AE, CJR, RA, EM, CA, PV); writing the manuscript (RV); critical revision of the manuscript (AE, CJR, RA, DSYK, BTL, EM, CA, PV); statistical expertise (RA, EM); supervision (PV)

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