Detection of Keratoconus with the new Corvis ST Biomechanical Index.

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Running head

Corvis Biomechanical Index for the diagnosis of keratoconus

PRECIS

A new multivariate biomechanical index for the diagnosis of keratoconus, based on thickness profile and corneal deformation parameters, is introduced and validated on external database.

ABSTRACT:

Purpose: To evaluate ability of the new Biomechanical Index (BI), based on thickness profile and corneal deformation parameters, to separate normal from keratoconus patients.

Materials and Methods: Six hundred and sixty-two patients were included in this multicenter retrospective study. Patients were enrolled in two clinics located in different continents to test the capability of the BI to separate healthy and keratoconic eyes in more than one ethnic group. Database 1 comprised 255 healthy and 79 keratoconus whether database 2 included 227 healthy and 101 keratoconus. The biomechanical response data were analyzed and logistic regression was employed to combine the best individual parameters in database 2. Optimal cutoff points of the BI was obtained, subsequently, the formula was externally validated in Database 1.

Results:

The final formula included Deformation Amplitude ratio at 1 and 2 mm, Applanation 1 velocity, Highest Concavity Radius and Arth (Horizontal thickness profie).

The ROC curve analysis of database 2 showed an Area Under the Curve (AUC) of 0.978 with a cut-off value of 0.5. This cut off correctly classified 97.3% of the cases with 99.6% specificity and 92.1% sensitivity. In the validation dataset (database 1) the same cut-off point classified correctly 100% of the cases with 100% specificity and 100% sensitivity.

Conclusion:

In conclusion BI showed to be highly sensitive and specific alone to separate healthy from ectatic eyes. The presence of an external validation dataset confirms this finding and suggest the possible use of BI in everyday clinical practice to aid the diagnosis of ectasia.

INTRODUCTION

The early diagnosis of corneal ectasia is of foremost importance both in the screening for refractive surgery and for the early treatment of keratoconus.

If we consider the refractive point of view, the occurrence of ectasia after a refractive procedure is very rare and feared occurrence because of the problems related to a vision threat or reduction in a patient that previously had a very high quality corrected visual acuity. However, many cases of ectasia have been reported after LASIK despite patients' low risk scores on standard screening tests.[1, 2] On the other hand, some patients with recognized ectatic risk factors remain stable many years after LASIK.

Conversely, considering the diagnosis of the ectatic disease in the general population, keratoconus is normally diagnosed in adolescence or childhood[3-5] and the time of diagnosis is a negative prognostic factor for increased risk of corneal transplant.[6] The early diagnosis and, as a consequence, its early treatment with corneal collagen cross-linking at the first sign of progression can halt keratoconus at a stage where visual acuity is still high.

Current clinical instruments, such as topography and tomography, can detect alteration in the shape of the cornea but cannot measure the mechanical stability which is thought to be the initiating event of the disease. For this reason, there has been increasing interest in developing instruments to measure the in-vivo biomechanical properties of the cornea. The first one to be developed was the Ocular Response Analyzer (ORA, Reichert Inc., Depew, NY)[7]. The ORA is a adapted non-contact tonometer (NCT) designed first to provide a more accurate measurement of intraocular pressure (IOP) through compensation for corneal biomechanics. It examines 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.[8-10] The most recent version of the device enables the measurement of 2 new keratoconus-specific parameters: the keratoconus match index (KMI) and the keratoconus match probability (KMP). The capability of ORA to diagnose keratoconus was tested in several articles[10-12] but never reached the gold standard.

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.[13] At the present time, Corvis do not provide an automatic analysis of corneal biomechanics such as the KMI or the KMP.

The aim of this article is to develop a combined parameter (Biomechanical Index-BI) based on different Corneal Deformation Parameters (CDP) provided by the Corvis ST to separate keratoconus from normal subjects.

MATERIALS AND METHODS

Six hundred and sixty-two patients were included in this multicenter retrospective study. The patients were enrolled in two clinics located in 2 different continents to include variability from different continents and to test the capability of the Biomechanical Index (BI) to separate healthy and keratoconic eyes in more than one ethnic group. A total of three hundred and thirty-four patients (255 healthy and 79 keratoconus) were enrolled from Vincieye Clinic in Milan, Italy (Database 1) and three hundred and twenty-eight patients (227 healthy and 101 keratoconus) from the Rio de Janeiro Corneal Tomography and Biomechanics Study Group – Rio de Janeiro, Brazil (Database 2). 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, subjects provided informed consent before using their data in the study.

All patients had a complete ophthalmic examination, including the Corvis ST and Pentacam (OCULUS Optikgeräte GmbH; Wetzlar, Germany) exams.

The inclusion criteria of this study for the keratoconic population was the presence of a bilateral clear keratoconus without any previous ocular surgeries, such as corneal collagen cross linking or intracorneal rings implant. Conversely, the inclusion criteria the healthy subjects 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 in both eyes 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%.[14] 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. Moreover, all exams re-evaluated of Vincieye Clinic were blindly by an expert of Anterior Segment (Dr R. Ambrosio) to confirm the diagnosis. Similarly, all the exams of Rio de Janeiro clinic were blindly re-evaluated by Dr P. Vinciguerra. All measurements with the Corvis ST were taken by the same experienced technicians. 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.[13]

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.

The Corvis ST output parameters by the research software 1.2b1191 from each measurement were exported to a spreadsheet and analyzed to

Corneal deformation parameters (CDPs)

CDPs provided by Corvis ST include: A1 Velocity (speed of corneal apex at first 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), Highest concavity radius (radius of the central cornea at the maximum concavity state, based on a parabolic fit) and Deformation Amplitude (maximum depth of deformation at the highest concavity state).

The Deformation Amplitude (DA) refers to the largest displacement of corneal apex in the anterior-posterior direction at the moment of highest concavity.[8, 13] During the measurement, the Whole Eye globe Movement (WEM), another measured parameter, affects DA. 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 (DefA) 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. 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 (HC) moment: ad 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.[8, 13] 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.[8]

Two new parameters called central-peripheral deformation amplitude ratio (DA Ratio) and deflection amplitude ratio (DefA 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 or 2 mm (2 mm for DefA 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 DA Ratio and DefA Ratio to be associated with softer corneas.

The Delta Arclength (HCdArclength), 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. The temporal changes in the delta arclength are also calculated for the exact same zone and a plot is generated.

Corvis ST is able to generate, additionally to the simple central corneal thickness, a new index, called Arth, fully based on the thickness profile of the horizontal Scheimpflug camera as follow:

1. Corneal thickness is calculated from the thinnest point to the periphery in 0.2 mm steps and the percentage thickness increase (PTI) is calculated. At each position PTI values describe how many percent the cornea is thicker than at the thinnest point.
2. The ratio between the percentage values (PTIs) and the corresponding normative value for each position is calculated along the complete thickness profile.
3. The average ratio for all positions provides the Pachymetric Progression Index: A value higher than one indicates a faster thickness increase than usually, a lower value indicates a slower thickness increase towards the periphery than usually.
4. The ratio between corneal thickness at the thinnest point and the Progression index provides ARTh (ARTh = CT thinnest / Pachym etric Progression). A smaller value indicated a thinner cornea and / or a faster thickness increase towards the periphery.

STATISTICAL ANALYSIS:

Receiver operating characteristic (ROC) curves were applied to determine the overall predictive accuracy of corneal deformation parameters and the combination of them, as described by the area under the curve (AUC). These curves are obtained by plotting sensitivity versus 1-specificity, which is calculated for each value observed. An area of 100% implies that the test perfectly discriminates between groups.

Logistic regression with forward stepwise inclusion was employed to combine the best individual indices for the creation of the Corvis Biomechanical Index (BI) using database 2. The parameters included in the analysis were IOP, Pachymetry (CCT), Deformation Amplitude, Applanation 1 Velocity, Peak Distance, HCdArclength, HC Deflection Area, DAratio 2mm, DAratio 1mm, DefA ratio, Inverse Concave Radius, Radius HC and ARTh.

Only for the creation of the formula, outliers were excluded. Outliers were defined as > 3rd quartile plus 1.5 IQD (interquartile distance: distance between 1. and 3rd quartile) or < 1st quartile minus 1.5 IQD. Outliers were removed for CCT, IOP, IOP_{FEM}, HC Def. Amp, DA ratio 2mm, DAratio 1mm, A1 velocity, ARTh, Radius HC, Integrated Inverse Radius and Mean Inverse Radius. These parameters were chosen to exclude outliers because were known to have a good ROC curves. In the case of A1 velocity it was included because known from previous studies, to be either correlated with IOP[15] or known to be able to increase the sensitivity and specificity in multivariate analysis (data from unpublished data from other datasets). After the creation of the formula, outliers were re-included to test the capability of BI to separate normal from keratoconus in the complete dataset 2. Optimal cutoff points of the BI was obtained from the ROC curves as those closest to the perfect classification point. Subsequently, to exclude over fitting, the formula was externally validated in Database 1.

The statistical analysis was performed with SPSS version 23 (IBM Corp. in Armonk, NY, USA).

RESULTS:

Two hundred and eighty-nine left eyes and three hundred and seventy-three right eyes were included.

Database 1 comprised 136 left and 198 right eye whether database 2 included 153 left and 175 right eyes. The mean age ± standard deviation of normal eyes was 43±17 years in database 1 and 37±17 years in database 2, conversely the mean age of keratoconic patients was 37±12 in database 1 and 32 ±12 in database 2.

Considering only the keratoconic population in database 1 the mean Kmax was 54.11±6.17 and mean BAD-D value was 8.26±0.44, in database 2 mean Kmax was 55.53±9.24 and mean BAD-D was 9.98±17.23, all these difference were not statistically significant ($p>0.05$).

In Table 1 and 2 are summarized the Topographic Keratoconus Classification (TKC) provided by Pentacam for both database.

The stepwise logistic regression, based on database 2 produced the following formula:

BI = EXP (Beta) / (1+ EXP(Beta))

where

Beta = B1 * DAratio 1mm + B2 * DAratio2mm + B3 * ARTh + B4 * HC Radius + B5 * A1 Velocity + B6

With: B1= -36.17, B2 = 7.98; B3= -0.027, B4 = -1.41, B5 = -65,95, B6 = 50.04

Beta values of all parameters used in the equation were highly significant ($p<0.01$).

The ROC curve analysis of database 2 showed an Area Under the Curve (AUC) of 0.978 with a cut-off value of 0.5 (Figure 1). This cut off correctly classified 97.3 % of the cases with 99.6 % specificity and 92.1 % sensitivity.

In the validation dataset (database 1) the same cut-off point classified correctly 100% of the cases with 100 % specificity and 100 % sensitivity (Figure 2).

The ROC curve analysis of the combined dataset showed an Area Under the Curve (AUC) of 0.986 and a very good predictive accuracy of BI (Figure 3).

Table 3 shows the gain in sensitivity and specificity with each step of the logistic regression, whereas Figure 4 shows the increase of the AUC.

DISCUSSION:

It is well known that keratoconic corneas are significantly "weaker" or had lower elastic modulus than normal corneas.[16, 17] These results were proven with stress-strain measurement using strip extensiometry experiments. However, in the last years a new theory for biomechanical pathogenesis of keratoconus was proposed basing on the existing biomechanical models and clinical topographic and tomographic data.[18] This theory, later supported by the studies of Scarcelli et al[19], proposed that the initiating event in keratoconus could be a focal reduction in biomechanical properties, resulting in thinning as the weaker area strains more than the surrounding stronger areas. The cause may be an underlying pathology, or perhaps a genetic predisposition with an external insult as a trigger, such as eye rubbing in a focal region.

The consequence is that the focal reduction in elastic modulus generates greater deformation for the same load. This is followed by bulging with increased curvature, which redistributes the stress and the cycle continues. Thus, it is the disparity in corneal properties which drives the continued progression.

A direct consequence of this theory is that it might be possible to diagnose an ectasia before this biomechanical cycle of decompensation leads to increase of curvature and thickness reduction.

For this reason the in-vivo evaluation of corneal biomechanics for the diagnosis of keratoconus has always been of foremost interest.

This multicenter study included more than 600 cases from two different continents. The exclusion of one eye per patient eliminated the risk of a bias due to the relationship between bilateral eyes. Considering the population of the two dataset, database 2, had a slightly higher amount of early keratoconus cases, in particular 6 cases were classified as normal by the TKC but abnormal with the

BAD-D and the double experts revision (P.V. and R.A.). For this reason database 2 was used to create the formula because thought to be more challenging.

The main result of our study is the diagnostic capability of BI alone to distinguish between normal and keratoconus. Indeed, the multivariate diagnostic model created showed to be highly sensitive and specific with an overall AUC of 0.986. In both database BI correctly classified more than 95% of the cases. In the validation dataset 100% of the eyes were correctly classified.

It is the first time in literature, to our knowledge, that a combination of Corvis parameter is able to provide these results. All the published studies, indeed, produced a AUC lower than 0.900[20-22], even though some of these studied refer to subclinical cases.[23]

However, this dynamic Scheimpflug device is relatively new and many similar studies were performed with the Ocular Response Analyzer. The majority of the manuscripts, however, even those where the Waveform Derivatives are evaluated produced a lower AUC[11, 12, 24-26]. Hallahan et al and Ventura et al showed comparable AUC, nevertheless those studies included a significant lower number of cases and controls and did not have an external validation.[10, 27]

The presence of an external validation is of foremost importance when considering a multivariate analysis, first of all to exclude over fitting, secondly because the cut-off value in one database may not produce the same results in a second independent one.

The inclusion of this validation in our study, which produced even better results than in database 2, confirms the diagnostic performance of BI. It is the first time in literature, to our knowledge, that a high number validation dataset is used to confirm the diagnostic ability of an ectasia detection formula.

A possible criticism of our study could be the decision to use Arth and A1 velocity, the first one because it is a pure thickness profile, already with a very good AUC and the second one because its AUC is not as good as the others parameters included. However, as showed in table 2, sensitivity and specificity increased meaningfully with the addition of the other 4 CDPs, that confirms the importance of the biomechanics in evaluating ectasia. Furthermore, Arth can be considered either a thickness parameter inside the multivariate analysis to separate normal from keratoconus as well as a correction parameter for the possible difference in thickness between the patients to correctly evaluate biomechanics. As matter of fact it is known that many CDPs are correlated with thickness.[28, 29] Regarding the inclusion of A1 velocity, even though its poor single capability of separating healthy from keratoconus, its presence increased the sensitivity by 2 percentage point (see table 1). We hypothesize that, given its correlation with IOP (known from previous unpublished or under review studies) it compensates for the difference in the IOP in the single cases. Instead of A1 velocity one could also use IOP but A1 velocity worked better in the combination. Furthermore its beta value was highly significant.

A deliberate limitation of our study was the exclusion from the databases of form fruste keratoconus (FFKC) and subclinical cases. Another study is in process, with very promising results, to test the capability of BI alone and in combination with Pentacam indexes to separate healthy from FFKC.

In conclusion, our study introduces BI for keratoconus diagnosis that showed to be highly sensitive and specific alone to separate healthy from ectatic eyes. The presence of an external validation dataset from another continent confirms this finding and suggest the possible use of BI in everyday clinical practice to aid the diagnosis of ectasia. More studies are in progress to show the capability of BI alone and in combination with tomographic indexes to separate healthy from subclinical cases.

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