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Introduction to Clinical Assessment of Corneal Biomechanics

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Why are corneal biomechanics important to the clinician? They characterize the stiffness of the cornea in response to the load provided by intraocular pressure (IOP). The stiffer the cornea, the less it stretches with IOP. Therefore visual outcomes of corneal treatments or procedures may be altered by the fundamental corneal properties which influence the ultimate shape of the first refractive surface. Clinical uses range from screening for diseases such as keratoconus and glaucoma, to overcoming the well-known errors in measurement of IOP using the common applanation tonometer, to predicting responses to corneal procedures such corneal collagen crosslinking (CXL) and laser vision correction (LVC). In addition, many new applications are under active study.

The clinical assessment of corneal biomechanics has evolved rapidly since the first instrument to provide detailed information on biomechanical deformation parameters in vivo was introduced, including the depth and shape of corneal displacement from ultra-high speed Scheimpflug imaging during air puff loading.[1] Many of the dynamic corneal response parameters (DCR's) are heavily influenced by IOP, including deformation amplitude (DA) and other depth parameters. This makes intuitive sense since IOP opposes the deformation induced by the air puff.

However, multiple DCR's are less sensitive to IOP, and actually quite sensitive to corneal stiffness. These include the shape parameters: radius of curvature at highest concavity, inverse concave radius (which is equivalent to concave curvature), and DA Ratio, which is the ratio between the displacement in the center to the displacement in the periphery.[2] Stiffness can be thought of as resistance to deformation, so that the lower the shape DCRs (flatter curvature, lower DA Ratio), the more resistant to deformation, and the stiffer is the cornea. On the other hand, the two stiffness parameters (SP) at first applanation (A1) and highest concavity (HC) are defined as load (air pressure minus IOP) divided by displacement, so that the greater resistance to deformation leads to lower displacement in the denominator and greater values of SP-A1 and SP-HC with a stiffer response.[3]

The initial clinical problem to be addressed was keratoconus detection, since it was hypothesized that the first identifiable corneal modification would be biomechanical in nature, and subsequent changes in thickness profile and curvature would be secondary responses to primary biomechanical weakening.[4] A new Corvis Biomechanical Index (CBI) was developed and implemented on the device with over 98% correct classification of healthy vs keratoconic eyes.[5]

Subsequently, a tomographic biomechanical index (TBI) was developed based on artificial intelligence that combined biomechanical and tomographic features into a more robust tool for the detection of ectatic corneas.[6] In addition, a biomechanically corrected IOP (bIOP) value was simultaneously developed, in order to account for the influence of both central corneal thickness and corneal stiffness on IOP measurement. [7] It has been reported that bIOP does not change after refractive surgery, unlike applanation tonometry.[8]

Multiple shape DCRs along with the stiffness parameters, have been shown to be sensitive to changes produced by CXL for keratoconus at 6 months (accelerated CXL),[9] 2 years (accelerated CXL),[10] and 4 years (Dresden CXL protocol)[11] after CXL. The shape parameters reported to produce significant differences include inverse concave radius, integrated inverse radius, radius at highest concavity, DA Ratio, SP-A1, and SP-HC, depending on the protocol and follow-up time point. Also, the accelerated CXL used for "extra" procedures with refractive surgery has been shown to produce less change in corneal biomechanics after surface ablation than a matched group without the extra procedure.[12] All previously mentioned shape DCRs showed significant differences in both surface ablation groups, but only inverse radius and DA Ratio were sensitive enough to differentiate the group with an extra procedure from the group without CXL.[12]

As development continues, new algorithms are introduced which will be described in the subsequent articles, including an improvement of TBI for keratoconus detection with optimization on big data, a new post Laser Vision Correction analysis, as well as a new stress-strain index (SSI) which can differentiate material stiffness with SSI from bulk structural stiffness with the SP parameters.[13]

Material stiffness applies to the individual components of the cornea, independent of thickness, and SSI has also been shown to be less dependent on IOP. Structural stiffness is at the corneal tissue level, and includes thickness. For example, one chopstick could be snapped in half with only hand strength. However a large bunch of chopsticks held together cannot be snapped in half so easily. The properties of the chopsticks don't change at the material level, but the overall stiffness changes at the bulk "tissue" level. As these new algorithms are made available, improved tools can be directly applied to patient care and exciting new research avenues will be enabled.

Enhanced Artificial Intelligence for the Detecting Corneal Ectasia Based on the Integration of Scheimpflug Corneal Tomography and Biomechanics

Author: Renato Ambrósio Jr, MD, PhD (Rio de Janeiro, Brazil)

The last three decade witnessed a genuine revolution on corneal diagnostic technologies towards multimodal imaging, which has transformed our ability to detect mild or sub-clinical forms of corneal ectasia.[14] In fact, screening for candidates at risk for "iatrogenic" progressive ectasia (keratectasia) after corneal laser vision correction (LVC) procedures has gone beyond (not over) identifying very mild keratoconus, towards characterizing the inherent ectasia susceptibility of the cornea.[15-17]

Placido-disk based corneal topography is sensitive to detect abnormalities in patients with normal visual acuity and unremarkable biomicroscopy.8 However, different studies involving eyes with regular topography from patients with clinical ectasia in the fellow eye (Very Asymmetric Ectasia, VAE-NT) have established the need and the opportunity to augment accuracy further using different technologies.[19-25]

Going beyond shape: Biomechanical characterization

Further detail of the corneal architecture is conceivable through 3-D Scheimpflug tomography (front and back elevation and thickness map),[26] and segmental tomography (epithelial and Bowman's mapping) using spectral domain OCT and very-high-frequency ultrasound.[27,28] Nevertheless, clinical biomechanical assessments emerged as fundamental for characterizing the inherent ectasia progression susceptibility of the cornea.[29-31] The OCULUS Corvis ST has an ultra-high-speed Scheimpflug camera to monitor corneal deformation during non-contact tonometry.[32] In 2016, the Corvis Biomechanical Index (CBI) and the Tomographic Biomechanical Index (TBI) for ectasia detection were introduced for this device using machine learning algortihm.

Artificial Intelligence for ectasia risk assessment

Machine learning for generating artificial intelligence (AI) has been widely recognized in order to give clinicians aid for improving care to the patients.[23,33-38] The BAD-D, available at the Belin/Ambrósio Enhanced Ectasia Display from the Pentacam,[20,39] and the Corneal Biomechanical Index (CBI),[40,41] available in the Vinciguerra Screening Report from the Corvis ST, were developed using logistic regression analysis (LRA) for optimizing the detection of corneal ectasia. However, more advanced AI have been used for the Pentacam Random Forest Index (PRFI) [42] and in the Tomographic Biomechanical Index (TBI) [23,43]

The concept of integrating corneal tomography and biomechanical data for enhancing ectasia detection was established on anecdotal cases.[22,44] The TBI developed by Ambrósio, Roberts & Vinciguerra is available on the integrated Pentacam and Corvis ST software (ARV-Display).[23] Figure 1 shows the ARV-Display of a topographical normal eye whereas the fellow eye has clinical ectasia. Both CBI and TBI are clearly abnormal (0.73 and 1.00, respectively) whereas the topography and tomography show no signs of ectasia. Cases like that reflect the need of combining biomechanical data with tomographic data. Such cases with normal topography from patients with very asymmetric ectasia represent the most important model for developing and testing novel strategies for enhancing ectasia detection.

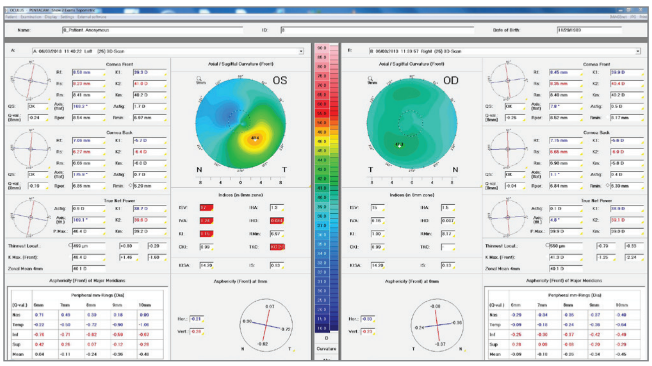

Figure 1a. Topography of the left and right eye of a case of Very Assymmetric Ectasia with normal topography OD and kc stage 2 OS.

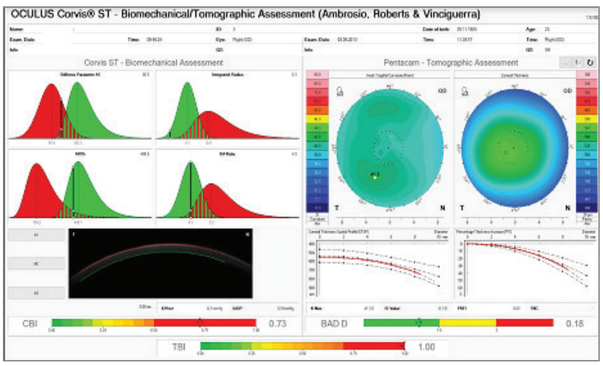

Figure 1b. Tomographic Biomechanical Assessment OD with abnormal TBI and CBI.

The original TBI study involved one eye randomly selected from 480 normal eyes and 204 keratoconic corneas, along with ninety-four VAE-NT eyes and the respective seventy-two unoperated ectatic (VAE-E) from these patients. The area under the receiver operating characteristic curves (AUROCs) was 1.0 for detecting clinical ectasia and 0.985 for distinguishing normal and VAE-NT cases (90.4% sensitivity with 96% specificity). The TBI was externally validated in different studies.[43,45–49] In all these studies the TBI had superior accuracy compared to the other tested topographic or tomographic parameters but the sensitivity was found lower in some studies involving VAE-NT.[48,49] While some of these cases may truly represent unilateral ectasia,[50,51] the opportunity to further improve accuracy with boosted machine learning AI algorithms in this larger multicentric dataset was perceived.

Multicenter Study for improving accuracy of the TBI

This study includes one eye randomly selected from 1,737 normal and from 1,237 keratoconus corneas, along with 537 VAE-NT cases with their 473 respective unoperated ectatic fellow eyes. The large amount of data from altogether 3984 eyes allows training with advanced AI methods and reduces the risk of overfitting.

In this dataset, the first version of the TBI had 98.5% sensitivity and 98.9% specificity to detect clinical ectasia and still was more accurate than any other parameter available. However, the sensitivity for the VAE-NT cases was 79%. The further enhanced AI improved the sensitivity for VAE-NT cases to 88%, keeping the specificity higher than 90% and with no change on the accuracy for the clinical ectasia cases (KC+VAE-E cases).

Conclusion

In conclusion, combing biomechanical data with tomographic data is fundamental for detecting cases with high ectasia susceptibility of the cornea. Machine learning on big datasets using advanced AI methods can help to further increase the accuracy of the TBI.

Post-operative Biomechanical Evaluation After Laser Vision Correction

Authors: Paolo Vinciguerra, MD; Riccardo Vinciguerra, MD (Milan, Italy)

Laser vision correction (LVC) is widely accepted procedure to correct refractive errors such as myopia, hyperopia and astigmatism. It is known to have an excellent safety profile, however, in a small amount of cases, iatrogenic ectasia can develop, either in PRK, LASIK or SMILE.

The early detection of post-LVC ectasia is of foremost importance as it can be treated with corneal collagen cross-linking and avoid progression that can even lead to an indication for corneal transplants.

Up today, the gold standard for early post LVC ectasia detection (when diagnosis is not clear) is to perform 2 different tomographic scans that shows progression such as steepening and thinning in a localized area. Unfortunately, this approach has the drawback to accept progression to be able a clear diagnosis.

In-vivo corneal biomechanics with Corvis ST (OCULUS, Germany) has previously proved to significantly improve the diagnosis of early and subclinical keratoconus (kc), particularly when combined with tomography.[5,6] Yet, CBI and TBI are always abnormal in patients after LVC because they are designed to separate normal patient from kc.

In this article we present a new version of the CBI, named CBI-LVC, that aims to separate stable post LVC patients with post LVC ectasia.

This new index was created using a very large database of normal, keratoconus, stable post LVC patients (PRK, LASIK and SMILE) and diagnosed post LVC ectasia. In details we included a total of 4,422 eyes of which 1,507 normal, 1,240 keratoconus, 449 post-LVC stable patients and 21 post-LVC ectasia.

To be able to provide a semi-automatic separation also an index to separate keratoconus patients from LVC was created. As a matter of fact, both of these patients would appear abnormal with CBI.

Logistic regression was employed to determine the optimal combination of best predictors from the individual indices for the creation of a Corvis Biomechanical Index (CBI-LVC) for the accurate separation between post LVC and keratoconus and between stable post LVC and LVC induced ectasia. To avoid overfitting 80% of the database was used as training dataset and 20% was used as validation.

With a cut-off value of more than 0.353 a mild modification of the published CBI has a Sensitivity of 87.8% and a Specificity of 95.8% to separate normal from Kc/post LVC. The second index, which was aimed to separate keratoconus from post LVC, with a cut-off of 0.7266 had a sensitivity of 94.0% and a specificity of 93.2%.

At last the CBI-LVC was able to accurately separate stable post LVC from ectasia after LVC with a sensitivity of 94.1% and a specificity of 95.5 %. Figure 2 shows the step by step approach with sensitivity and specificity.

It is the first time, to our knowledge, that an index based on biomechanics is able to produce such an efficient separation between stable post LVC and LVC induced ectasia and is tested and validated in such a big database.

This index will soon be implemented in the native Corvis software. When a patient is acquired with Corvis ST, three different steps are executed automatically:

1. Step 1: The CBI will automatically detect whether the cornea is normal or kc/post LVC. This is tested with the CBI logistic regression equation. If the patient is normal the biomechanical assessment is already finished after step 1.

2. Step 2: If the CBI is indicating an "abnormal" biomechanical behaviour a second logistic regression is applied that tests whether the patient has rather keratoconus or whether the soft biomechanical response is caused by laser vision correction. If the patient has more likely a keratoconus once more the biomechanical evaluation is finished after this step and the CBI provides the risk for the disease.

3. Step 3: In case the soft corneal behaviour is more likely caused by LVC the doctor will be asked to confirm whether the patient had indeed previous refractive surgery. If post LVC will be selected the software will automatically switch from CBI to the new LVC-CBI that is able to separate stable LVC from ectasia with a sensitivity of 94.1% and specificity of 95.5%.

OUTLOOK: BIOMECHANICAL ANALYSIS POST LVC

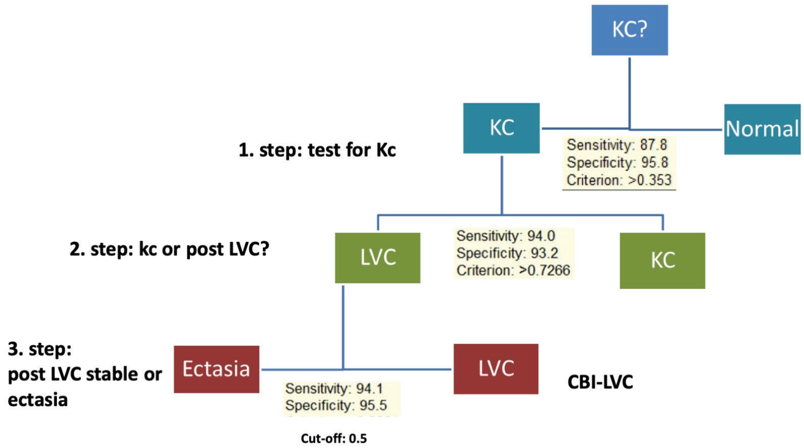

Figure 2. Three steps for automatically evaluation of biomechanical stability post-op.

Despite of this automatic approach the clinician will always have the possibility to choose the button "post LVC". In this case the software will automatically present the newly developed CBI-LVC independent on the results of steps 1 and 2.In conclusion, our study introduces LVC-CBI which was shown to be highly sensitive and specific alone to separate stable from ectatic LVC eyes. We suggest the use of LVC-CBI in everyday clinical practice, together with topography and tomography, to assess the biomechanical stability after LVC and to aid the diagnosis of post LVC ectasia.

A New Biomechanical Comparison Display for the Corvis ST

Authors: Riccardo Vinciguerra, MD; Paolo Vinciguerra, MD (Milan, Italy)

The evaluation of changes in corneal biomechanics is of foremost importance for the follow up of corneal diseases in which the tissue gets softer such as keratoconus, ectasia after Laser Vision Correction and Pellucid marginal degeneration and to evaluate the outcomes of procedures that make the cornea softer (Laser vision correction for example) or stiffer (Cross-Linking).

In particular, the assessment of the effect of corneal collagen cross-linking (CXL) in the first follow-ups after the surgery is of primary importance, however, the well-known decrease of corneal thickness, the decline of visual acuity and increase of curvature in the first postoperative months make this task very challenging. The best way of judging the outcome of CXL would be to directly assess the its stiffening effect.

In previous studies we were able to show significant rise in corneal stiffness as demonstrated by a significant increase of Dynamic Corneal Response parameters (DCRs) such as Stiffness Parameter A1 (SP-A1) and Highest Concavity (SP-HC) and a significant decrease of Inverse Concave Radius (1/R), and Deformation Amplitude Ratio (DAratio) ($p<0.05$).[9]

The study proved that new DCRs by the Corvis ST are able to detect early changes in biomechanics following CXL and those are measurable before corneal shape modifications take place.

At last, we recently introduce the stress-strain index, that proved to be able to successfully measure corneal material stiffness, while being less dependent on bIOP and CCT, and correlated with age in healthy population.[13] However, until now, the comparison was still very rudimental done with the manual transcription of the parameters and subsequent evaluation.

The first step to be able to compare two exams is the knowledge of the repeatability of the instrument in normal and keratoconic patients that was done in two previous studies (keratoconus repeatability is in press in Journal of Cataract and Refractive Surgery 2019).[52] Based on these studies it was possible to calculate the two sided confidence intervals to know whether the change in DCRs between one exam and the other is significant.

In this article we introduce a new Biomechanical Comparison display for the Corvis ST aimed to help the comparison of two different exams. (Figure 3)
The display aims to automatically provide the comparison of two exams done with the Corvis ST and indicate whether the difference between the two exams is significant (either towards the softer or stiffer side).

Below an example of the display in a patient pre and post corneal collagen cross-linking.

The biomechanical comparison display shows respectively:

- On the top the values of CCT, and pressure (bIOP and non-corrected) for both exams.
- In the middle of the display the two videos of corneal deformation pre (blue) and red (post) and the overlap of the two. In this case, as the cornea gets stiffer, we observe less deformation of the red cornea (post CXL).
- In the middle on the right the display shows the difference of SSI with the relative stress strain curves, as expected SSI gets significantly stiffer (more 95% confidence interval).
- In the bottom of the display, similarly to SSI; the values of deformation amplitude ratio, inverse concave radius, Ambrosio Thickness profile and Stiffness Parameter A1 are shown for measurements A and B. For both examinations the multiple of the standard deviation each value deviates from a healthy population is also given as “SD” value. The differences of “SD” values between measurement A and B are also shown.
- In the lowest line of the boxes it is provided whether these changes are significant or not by comparing them with the two-sided confidence interval for keratoconus eyes. It is automatically highlighted whether the changes indicate a softening, a stiffening or whether the changes are not significant.
- As expected, these parameters, except of the thickness profile show significant stiffening after CXL in the shown case. (Figure 3)

Obviously, this display could also show significant softening in cases of progressive keratoconus or ectasia.

In conclusion, we introduce a new comparison display for the evaluation of two exams of the Corvis ST of the same patients which aims to help in the evaluation of changes in corneal biomechanics.

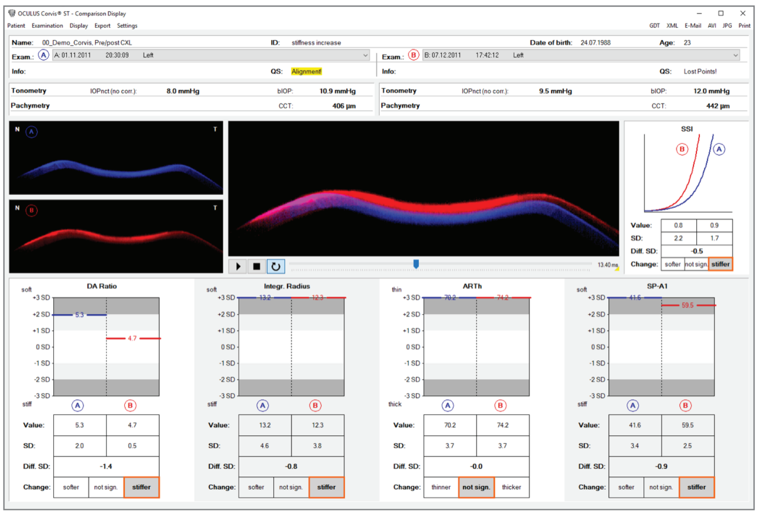

Figure 3a. Biomechanical Comparison Display with a case before and after corneal crosslinking.

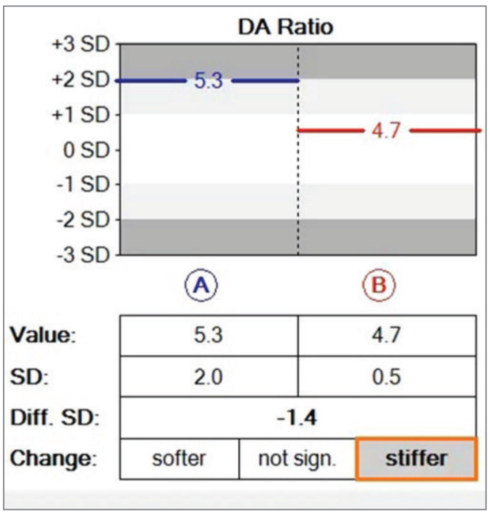

Figure 3b. Quantification of biomechanical changes before and after CXL.

Development and Validation of a Material Stiffness Parameter Based on the Corvis ST

Authors: Bernardo Lopes, MD, PhD; Prof. Ahmed Elsheikh, PhD (Liverpool, UK)

Measuring corneal material stiffness in vivo is of great clinical importance and it's also a great challenge. Corneal deformation behaviour under the air puff of instruments such as the Corvis ST is highly dependent on the intraocular pressure (IOP), the shape of the eye, especially the corneal thickness (CT), and the corneal material stiffness. This makes the task of separating the effects of these three components on corneal behaviour quite difficult. While we can accurately measure the CT with Scheimpflug imaging, measuring the IOP and material stiffness is not straightforward. Furthermore, as the mechanical behaviour of the cornea is nonlinear, the tangent modulus (Et) of the tissue – a measure of material stiffness – is not constant and increases with IOP and both stress and strain.

A method to accurately measure the IOP with less dependence on the material stiffness was developed based on precise numerical simulations of the corneal deformation responses to the Corvis ST exam and extensively validated experimentally and in various clinical scenarios. [12,53-54] The biomechanically-corrected IOP (bIOP) has been shown to have no significant correlation with CCT and age, and to be unaffected by corneal stiffness changes after refractive surgery and collagen UVA crosslinking (CXL). The success in determining IOP was an important step in efforts to measure the cornea's biomechanical behaviour, and in particular the whole stress-strain behaviour that can determine the corneal Et under any IOP.

The stress-strain index (SSI) was developed based on the results of a large numerical simulation of corneal biomechanical behaviour under the Corvis ST air pressure in eyes with a wide range of IOP, corneal shape and material stiffness. (Figure 4) [13] The expectation that SSI would be correlated with age while being independent of IOP and corneal thickness was first tested in two clinical sets from Italy and Brazil (480 healthy participants) and subsequently confirmed in a larger multicentric study involving 1664 healthy subjects and 1686 keratoconic patients. (Figure 5) In this study, it was observed that the SSI was independent of both IOP and CCT while being correlated with age in healthy (but not keratoconic) eyes. In eyes with keratoconus, the SSI further showed significant gradual deterioration in material stiffness with disease progression. (Figure 6) The SSI was then used to evaluate the short-term effect of corneal crosslinking (3 month post-CXL). A group of 41 patients submitted to the standard Dresden's protocol was tested, and a significant increase in SSI was observed between the pre-CXL (0.78±0.19) and the post-CXL stage (0.87±0.21, p= 0.03). (Figure 7)

These studies desmonstrated the success of the SSI, measured in vivo, in representing the corneal material stiffness, being less dependent on bIOP and CCT, and correlated with age in healthy population. The SSI further showed deterioration with keratoconus progression and increases following corneal crosslinking. Further studies are being conducted to assess the new index as an optimisation tool for the crosslinking procedure, to assess the postoperative state of refractive surgery and the preoperative surgical screening. With this index, the Corvis ST can provide clinicians with meaningful and comprehensive corneal biomechanical evaluation in real-time.

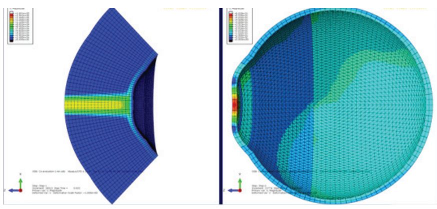

Figure 4. Numerical simulation of an eye under the Corvis ST exam.

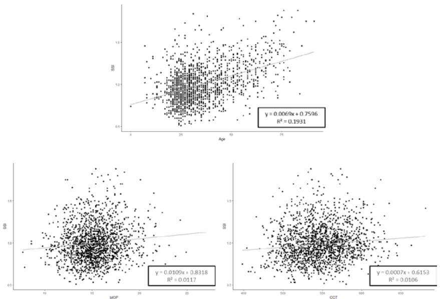

Figure 5. Correlation of the SSI with age, bIOP and CCT in a healthy multicentric population (n=1664). There is a significant correlation with age (R2 = 0.19) and weak correlation with bIOP and CCT (R2 = 0.01).

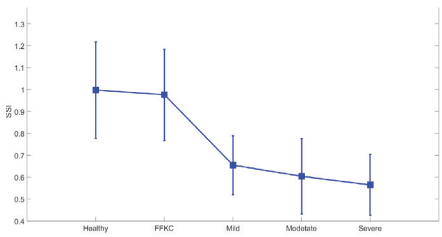

Figure 6. SSI distribution among healthy and keratoconic patients in different stages of the disease.

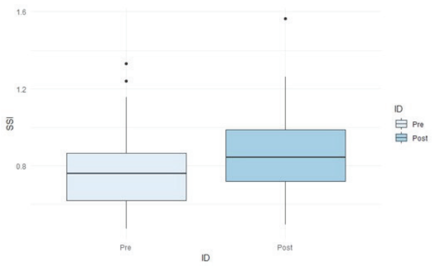

Figure 7. SSI increase after crosslinking procedure.

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