Enhanced Screening for Ectasia Susceptibility Among Refractive Candidates: The Role of Corneal Tomography and Biomechanics

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Abstract Progressive “iatrogenic” ectasia or keratectasia is a very severe complication of laser vision correction procedures. This is more common after LASIK, in which the lamellar cut promotes a larger biomechanical impact than the excimer laser ablation. However, ectasia has been also reported after surface ablation. Considering the severity of such complication, prevention is the best approach. Preoperative abnormal topography has been classically considered as the most important risk factor for ectasia development. Other risk factors are young age, high myopic corrections, low residual stromal bed and thin cornea. Multiple laser retreatments and thick flaps are additional risk factors, as are postoperative trauma or intense eye rubbing. However, there are mysteries related to the cases that develop ectasia with no identifiable risk factors, and also to the cases of successful LASIK that remain stable despite of multiple risk factors

(including abnormal topography). Corneal ectasia may occur due to two distinct mechanisms: 1. preoperative abnormal (weak) corneal stroma; and 2. severe biomechanical impact (weakening) from the procedure. While these mechanisms are distinct, there is an association and overlapping between the level of susceptibility of any cornea and the biomechanical impact of the procedure. Corneal tomography and biomechanical assessment provide an advanced understanding of the cornea that augments the sensitivity to identify a very mild (forme fruste keratoconus) form of ectasia, that may still present with relatively normal front surface topography. Such an enhanced screening approach not only augments the sensitivity to detect susceptible cases, but also provides higher specificity for a cornea with irregular topography, considered as a keratoconus suspect, that may be suitable for laser vision correction.

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Introduction

Progressive “iatrogenic” ectasia or keratectasia has emerged as a rare but very severe complication of laser vision correction procedures [1, 2]. In post-laser in situ keratomileusis (LASIK) ectasia, the lamellar cut and excimer laser ablation lead to a state of biomechanical failure with an inability to support the continuous stresses caused by intraocular (IOP) pressure, extra-ocular muscles action, blinking, eye rubbing and other forces [3]. While, ectasia is by far more common after LASIK, it has been also reported after surface ablation procedures [4], which have lower biomechanical impact than LASIK on the cornea. Interestingly, a case of unilateral

keratectasia after LASIK was described, while the fellow eye remained stable after photorefractive keratectomy (PRK) [5]. Also, a case of bilateral progressive ectasia was reported in a patient that had LASIK only in one eye [6]. Considering the severity of such complication [7], prevention is the best approach. The identification of corneas at higher risk or susceptibility represents a major challenge for refractive surgeons. Clinical decisions should be done based on scientific evidence and on individual practice experience [8].

Classic methodology for screening refractive patients includes corneal topography and central corneal thickness (CCT) [9•]. Randleman and coworkers designed the ectasia risk scoring system (ERSS), [10•] based on a retrospective case–control study, which included Placido disc-based corneal topography, CCT, level of correction, residual stromal bed (RSB) and patient's age. Abnormal pre-operative topography and age were the most significant predictive variables for ectasia development. The ERSS was validated by a second study [10, 11•], but the relatively lack of proper sensitivity, with 8 % of false negatives, had been the major limitation of such a well-designed approach [12]. Another retrospective study from an independent center reported 36 cases with post-LASIK ectasia, from which 9 (25 %) eyes were classified as low-risk and 7 (19 %) eyes as moderate-risk [13]. The relatively high incidence of false negatives on the ERSS is in agreement with other reported cases of ectasia after LASIK in the absence of identifiable risk factors [14, 15, 16•, 17]. In addition, a relatively high incidence of false positives may be registered, mainly if a younger population of LASIK candidates with normal topographies is evaluated [18, 19]. Therefore, there is an indisputable recognition for the need for improving both the sensitivity and specificity of the diagnostic tools for screening ectasia risk.

The Concept of Enhanced Screening for Detecting Ectasia Susceptibility

The presence of an 'overlooked' ectatic disorder preoperatively is unquestionably the best predictor for the development of progressive ectasia after laser vision correction [2, 13, 20, 21]. In these cases, the corneal procedure is an aggravating factor for the acceleration of the ectatic process. However, if there is significant weakening caused by the refractive surgery (i.e., LASIK thick flap creation, excessive tissue removal due to high corrections, retreatments), ectasia may also occur in an otherwise healthy cornea [3, 22–24]. In this situation, the biomechanical failure results from the scant RSB for maintaining corneal strength after the procedure.

A lower-limit RSB of 250 μm has been considered acceptable, but some authors considered it to be more

appropriate to consider 300 μm as the limit of event to calculate half of corneal central thickness as the limit for each case [22, 25, 26]. Despite attempts to establish a threshold for a stable RSB, there are cases with RSB higher than 250 μm that developed post-LASIK ectasia [16•, 27, 28], while there are cases with RSB even lower than 200 μm that remained stable [29]. The biomechanical impact of the ablation on the anterior stroma is much less pronounced in surface ablation procedures [30, 31]. However, keratectasia cases were also reported after these procedures [25, 32].

Thus, the main goal of screening methods for refractive candidates should be the characterization of the level of susceptibility or predisposition for developing ectasia for each cornea. This purpose is illustrated in Figs. 1 and 2, with concepts that will be described later in the text.

The main goal of the enhanced screening of ectasia risk among refractive candidates should be the identification of very mild abnormalities, since the referred ectasia susceptibility condition would be likely present in the preoperative state of cases with unexplained ectasia after LASIK [16•]. For assessing the individual susceptibility for developing ectasia, we have since 2004 routinely performed three-dimensional corneal tomography and biomechanical analysis using the Pentacam Corneal Tomographer (Oculus GmbH, Wetzlar, Germany) and the Ocular Response Analyzer (ORA, Reichert Ophthalmic Instruments, Buffalo, NY), respectively. (Ambrósio Jr R et al. Clinical Evidence of the Enhanced Sensitivity and Specificity of Corneal Tomography and Biomechanics for Screening Ectasia in Refractive Candidates ePoster ASCRS 2009).

Topography vs Tomography

"Corneal topography" has been classically used for the reconstruction of the front (anterior) corneal surface, which is commonly achieved by Placido disc-based systems. Corneal topography represented a true revolution in the diagnosis and management of corneal disease [33], and has a recognized role in the development of refractive surgery [9•, 34, 35].

"Corneal tomography" represents a three-dimensional reconstruction of the cornea. It should be used for the characterization of the elevation of the front and back surfaces of the cornea, along with pachymetric mapping. Different technologies, such as horizontal slit scanning, rotational Scheimpflug, arc scanning with very high frequency ultrasound, and optical coherence tomography are available in many commercial instruments [36, 37].

It is also important to recognize and accept the differences between corneal topography and tomography, but

Fig. 1 Enhanced sensitivity on a post-LASIK ectasia with no identifiable pre-operative risk factor. BAD-D Pre op was 2.43 and ART-Max was 292

Fig. 2 Enhanced specificity on a stable LASIK (FU > 4 years) with preoperative KCS pattern on front surface curvature. BAD-D Pre op was 1.24 and ART-Max was 437

both technologies are complementary [38•]. For example, while tomography allows for the evaluation of the back surface elevation and pachymetric mapping, which enhances the sensitivity to detect more subtle ectatic abnormalities prior to front curvature changes [16•, 39], Placido's reflection topography enables the evaluation of the tear film, which is also relevant for screening risk for dry eye after LASIK [40–43].

In previous studies, corneal topography was revealed to be very sensitive for detecting sub-clinical ectatic changes on the anterior corneal surface, even before the loss of best spectacle-corrected visual acuity and development of typical slit lamp biomicroscopy findings [44, 45]. Very importantly, it was due to the occurrence of such sub-clinical cases of keratoconus that the unquestionable argument for corneal topography as a critical tool for refractive surgery screening was raised. However, there are cases with topographic similarities of ectasia on the curvature map that may not represent true ectatic disease. These false positive cases may be related to abnormal ocular surfaces, such as anterior basement membrane dystrophy, contact-lens warpage [46], or simply a rare variation of normality [47]. Other cases with mild irregularities which do not meet the criteria for keratoconus are defined as keratoconus suspects (KCS).

Compared to topography, corneal tomography has proven to be more effective for enhancing specificity among such patients. More importantly, there are cases with subtle disease, in which corneal topography still appears to be normal, since the ectatic change is not yet present on the front surface [37]. We refer to these patients as being with high susceptibility or with a predisposition to develop ectasia, but they may be also referred to as forme fruste keratoconus (FFKC)—a term introduced by Amsler in 1961 [48–50, 51•, 52]. Clinical examples of such patients include the contralateral eyes with normal topographies from patients with very asymmetric (not truly unilateral) keratoconus, [39, 53, 54•, 55, 56] and cases with natural progression of keratoconus which have been documented to earlier have normal anterior curvature exams. These sub-clinical cases with normal topography represent an opportunity to test the sensitivity of novel exams to detect milder forms ectasia.

Why FFKC is not the Same as KCS?

It is essential to recognize that keratoconus suspect (KCS) is a topographic classification (based on front surface curvature) of an abnormal pattern that resembles keratoconus with no definitive characteristics [57]. This presentation may not always imply a true form of ectasia. On the contrary, forme fruste keratoconus (FFKC) represents a sub-clinical form of ectatic condition. Such a condition is related to a very high risk or a susceptibility to progress to

clinical keratoconus. [53] FFKC may be present despite a normal topography and CCT [39, 58, 59].

Therefore, differentiation between KCS and FFKC is of fundamental consideration when screening ectasia risk among refractive candidates. However, for such an approach, proper understanding and interpretation of tomography is critical, along with biomechanical assessments (Video clip 1).

Guidelines for the Evaluation of Corneal Shape

For a correct interpretation of color-coded topographic and tomographic maps, there are important considerations that should be taken. The first critical point is that any map should be considered valid only if the raw data upon which it is based is confirmed as reliable. In Placido disc-based exams, it is important to evaluate the centration and the mires' quality of the videokeratoscope image. In some instruments, such as the Pentacam, a quality score is available [60•].

The clinician should also recognize the type of map analyzed, along with the color-coded scale in use. Normalized or variable scales adjust to each examined eye would increase the sensitivity for detecting irregularities. Absolute fixed scales give the advantage of standardizing color recognition for particular values [61, 62•]. An absolute scale, “Ambrósio 2” (available on the Pentacam), has been developed for curvature and pachymetric maps. We advise to use this scale with 61 colors and absolute values, since the data obtained will be in accordance with studies comprising 226 normal corneas, 34 corneas with Fuchs' endothelial dystrophy, and 88 keratoconic corneas (Ambrósio, Caiado & Bonfadini, unpublished data 2009). For sagittal curvature maps, in a normal population, the average central K was $43.1 \pm 1.43\text{D}$ (SD) and the average for highest K (KMax) was $44.6 \pm 3.4\text{D}$ (SD). These values were included on the range of green to green-blue on the color-coded scale. Interestingly, the best cut off value for KMax in the ROC curve was 47.9D (sensitivity of 97.7 % and specificity of 96.9 %), so that 48D was set for the orange to red transition. Considering thickness maps, mean thinnest point (TP) value in the normal population was approximately 550 μm and standard deviation (SD) of 30 μm . Therefore, the green color was centered on the 550 and the shades of darker and lighter green were calculated to be within 1SD. The best cut-off value in the receiver operating characteristic [63] curve for keratoconus and normals was around 500 μm (sensitivity of 87 % and specificity of 90 %), which was set for the yellow threshold. On the thicker side, mean TP value for Fuchs' corneas and the best cut off value in the ROC curve was 625 μm (sensitivity of 82 % and specificity of 91 %), which was set for the threshold of green to blue [60•].

Curvature Maps

It is also critical to understand the fundamentals for the reconstruction of the maps. Basically, there are two types of maps that are commonly used in curvature maps that are relevant for ectasia screening: sagittal (or axial) maps and tangential (or instantaneous) maps. In sagittal maps, corneal curvature is determined at each measured points at a normal (90°) angle to its surface referenced to the mid-line or measurement axis. Tangential maps are more sensitive to irregularities and evaluate the local radius of curvature at each measured point. Classic screening systems such as the Rabinowitz-McDonnell were developed based on axial maps, concerning the steepness of the cornea (suspicious when higher than 47.2D) and the superior-inferior asymmetry (suspicious when higher than 1.4D) [64]. These topographic indices were developed to facilitate clinical interpretation, but we should understand their basics and limitations and be able to differentiate the normal curvature patterns from the ones described in ectatic diseases.

Elevation Maps

These maps represent the difference from the examined corneal surface (anterior or posterior) compared to a chosen reference body [65•]. Typically, the reference is calculated to have more coincident points (best-fit) with the examined surface. In order to improve the number of coincident points of the selected reference and the examined surface, float and shift optimization functions should be used. Different best-fit references can be produced, considering different areas in the calculation of the examined corneal surface. For example, in a normal prolate cornea (steeper in the center and flatter in the periphery), if a larger area is considered for calculating the best-fit sphere, a flatter reference would be chosen, which would exaggerates elevation values. For ectasia screening purposes, our preference is to fix to the 8 mm zone for calculating the best-fit sphere, since this zone is available for the majority of examined eyes. We also advise to analyze in conjunction the shape and the values on elevation maps [65•]. The elevation values at the apex, at the thinnest point [66] and the maximum value above the best-fit sphere within the central area [67] can be used.

Concerning the elevation maps, different geometric bodies can be used as reference, such as spheres, ellipsoids and toric ellipsoids. The clinician should understand the impact of selecting different geometric bodies, along with the zone diameter to calculate the best-fit. For example, the BFS allows for the identification of astigmatism, while the best-fit toric ellipsoid (BFTE) facilitates the evaluation of irregular astigmatism. Interestingly, one study reported similar performances for the elevation values at the thinnest

point of the posterior surface using BFS and BFTE (8 mm zone) [37].

The Belin Intuitive Scale with 61 colors and $2.5\ \mu\text{m}$ step has been found to be the most reliable for elevation maps. For example, in normal eyes, average elevation value at the thinnest point using a floated BFS for 8.0 mm is $3.6 \pm 4.7\ \mu\text{m}$ [66, 68], so that the yellow value of +15 at the thinnest point indicates this is suspicious and would occur in less than 3 % of normal corneas.

The “enhanced reference surface” concept, introduced by Michael W. Belin, MD, was designed to highlight the ectasia on the elevation map by excluding an area centered on the thinnest portion of the cornea from the BFS calculation. If the excluded area is more protruded, the resultant BFS would be flatter and the cone or ectatic area would be more pronounced. The most reliable “enhanced reference” is the BFS for the 8.0 mm zone after excluding all the data from a 3.5 mm zone centered on the thinnest point of the cornea. The subtraction map of the standard BFS elevation from the “enhanced elevation” detects and highlights the protrusion area and has been shown to be a key differentiator between normal and ectatic corneas. On the Belin-Ambrósio enhanced ectasia display on the Pentacam software. This approach is available on the Belin-Ambrósio enhanced ectasia display (Pentacam software) for either anterior and posterior elevations. Based on normal population studies, “green-yellow-red” color thresholds were created for this display.

Thickness Maps

Corneal tomography enables detailed pachymetric data, providing the true TP value and its location in relation to the center of the cornea, along with the thickness distribution throughout the entire cornea [60•, 69].

Previously, we have introduced and described the graphical concept of a corneal thickness spatial profile (CTSP) and percentage thickness increase (PTI) [8, 70•, 71, 72]. Starting from the TP outwards, the CTSP describes the rate of increase of corneal thickness using the average of pachymetric values within annular rings concentric to the TP separated by 0.1 mm steps. The PTI involves a similar measuring process centered on the TP, but it takes the percentage of thickness increase from the TP for the average along each ring. The Pentacam software reports CTSP and PTI of the examined cornea in graphs, along with the data of the mean and two standard deviations of a normal population. From this data, pachymetric progression indexes (PPI) are calculated for all hemi-meridian over the entire 360° of the cornea, starting from the TP. The average of all meridian is noted as the pachymetric progression average (PPI Ave) and the meridians with maximal (PPI Max) and minimal (PPI Min) pachymetric

increase are noted along with their axes. In a normal population, the averages and SD of PPI of the minimal, maximal meridians and average of all meridians are 0.58 ± 0.3 , 0.85 ± 0.18 and 0.13 ± 0.33 , respectively. The pachymetric index will be higher if the cornea gets thicker in a more abrupt pattern from the thinnest point out to the periphery (PTI and CTSP graphs falling down) [60••].

Recently, we also introduced the “relational” thickness concept, which is the thinnest pachymetric value divided by the pachymetric progression. The ART (“Ambrósio Relational Thickness”) may be calculated for the minimal (ART-Min), average (ART-Ave) and maximal (ART-Max). This tomographic concepts allow the differentiation of a normal thin cornea of a keratoconus with relatively normal CCT. The ART-Ave and ART-Max have AUROC of 0.98 and 0.99, with cut-offs of 426 and 339 μm , respectively, for diagnosing keratoconus ($n = 88$) from normals ($n = 226$) (Ambrósio, Guerra, Caiado and Belin, unpublished data 2010).

The Belin–Ambrósio Enhance Ectasia Display (BAD)

The BAD is comprehensive display, which enables a global view of the tomographic structure of the cornea, through combination of elevation and pachymetric data. Deviation of normality values were implemented for the front (df) and back (db) enhanced elevations, thinnest value, pachymetric distribution (dp) and vertical displacement of the thinnest in relation to the apex(dy). The “d” values are calculated so that a value of zero represents the average of the normal population and 1 represents the value is one standard deviation towards the disease (ectasia) value. A final “D” is calculated based on a regression analysis that weights differently each parameter. Each parameter is indicated in yellow (suspicious) when it is ≥ 1.6 SD from the mean and turns red (abnormal) at ≥ 2.6 SD from the mean. Values below 1.6 SD are reported in white and are viewed as within the normal range. However, based on studies involving eyes with very asymmetric keratoconus, a BAD-D value of more than 1.45 represents the most accurate risk factor parameter for detecting mild cases of ectasia or susceptibility [73].

Corneal Biomechanics

Development of ectasia in cases with normal preoperative exams highlights the need for an advanced understanding of corneal biomechanical properties. This approach goes beyond ectasia prevention, since it contributes for outcomes improvement, but also should be taken into account for properly assessing the intraocular pressure, which is

severely affected by corneal surgery [74–76]. The concept of *biomechanical customization* in refractive surgery was introduced by Dr. Cynthia Roberts, PhD, in the January 2005 (Volume 31, Issue 1) special issue of the Journal of Cataract & Refractive Surgery [77].

In the 2005 ESCRS meeting (Lisbon, Portugal), the Ocular Response Analyzer—ORA [74] (Reichert Inc., Depew, NY) was introduced as the first available device to evaluate in vivo corneal biomechanics [60••, 78, 79]. This tool is a non-contact tonometry (NCT), which was designed to provide a more accurate measurement of IOP through the understanding of corneal properties. The ORA has a precisely metered collimated air pulse and a quantitative electro-optical system that monitors the deformation of the cornea through the corneal reflex of an infrared light. The measurement takes approximately 20 ms. After auto-alignment to corneal apex, the air puff starts. The air pump is controlled accordingly to the first applanation signal, when there is an internal command on the instrument for the air pump to shut off, so that the decrease phase is symmetric to the increase phase. The air pressure forces the cornea to deform inward, passing first applanation, when the pressure (P1) is registered. The cornea goes into a slight concavity until the air pump shuts off, making the cornea will gradually recover to its normal configuration and noting a second applanation (P2) state. Both applanation events are registered by a peak on the corneal reflex signal (red curve), consisting in two independent pressure values. These pressure measurements (P1 and P2) are the basis for the variables reported by the original ORA software. The difference between the two pressures is called corneal hysteresis (CH) [80], a term derived from the Greek word that means “lagging behind” [60••].

CH and corneal resistance factor (CRF) have a positive statistically significant relation with central corneal thickness (CH, $r = 0.4655$; CRF, $r = 0.5760$) [74, 81]. CH and CRF are also statistically lower in keratoconus [8, 54•, 82] and also decreased after LASIK and surface ablation procedures [83, 84•, 85, 86]. No associations were found between CRF nor CH and simulated keratometry, anterior chamber depth or spherical equivalent refraction [81]. Paradoxically, there is a negative correlation between these variables and age, while there is an expected considerable increase in the values of the modulus of elasticity and age accordingly to human corneal inflation studies [60••, 87].

Previous reports described relatively low corneal hysteresis (CH) and corneal resistance factor (CRF) values in ectatic corneas compared to normal reference values [51•, 52]. In a study comprising 226 normals and 88 keratoconic eyes, the ROC curves for CH and CRF presented cut-offs of 9.4 mmHg and 8.1 mmHg, respectively. However, there is a significant overlap for the distribution of these metrics in normal and keratoconus cases. For CH, the sensitivity

and specificity were 0.816 and 0.721, respectively, while for CRF the sensitivity and specificity were 0.79 and 0.854, respectively (Ambrósio, Fontes, Bonfadim and Canedo, unpublished data 2009) [60••]. Interestingly, IOPg but not IOPcc was found statistically different among keratoconus and normals. Since 2007, our screening guideline is the following: if CH or CRF is inferior to 8.8 mmHg, the patient should be considered at potentially higher risk for corneal ectasia after LASIK and a better candidate for advanced surface ablation [52, 60••].

A new set of 36 waveform-derived parameters were introduced in the software. These variables are basically related to specific waveform characteristics, such as the width, peak, area and height of the peaks (signal during applanation moments) and general morphology of the waveforms (Luce, unpublished data 2008) [60••]. These new parameters can be very useful in cases with the same CH and highly different waveform signals and clinical characteristics [60••]. Kerautret and coworkers reported a case of unilateral corneal ectasia after bilateral LASIK, in which CH and CRF were almost equal in both eyes while waveform-derived analysis showed a lower amplitude of the applanation peaks in the ectatic eye [88•].

It is critical to provide objective metrics from these new parameters. It was found that a combination of the most relevant waveform-derived parameters would provide a better performance on the ROC curve. The new ORA display includes a table with all indices that are displayed as the deviation from normality and the keratoconus percentage similarity score. This approach has the potential to increase specificity of identifying a normal biomechanical signal in a case with a topographic keratoconus suspect finding, as well as confirming abnormal biomechanics in a mild keratoconus. Another approach is combining corneal tomography (Pentacam) and biomechanical parameters for identification of very subtle forms of ectasia. In a study, including 119 eyes with normal corneas and 15 eyes with form fruste keratoconus, a combined tomographic and biomechanical parameter was created. This variable presented an AUROC of 0.932, with sensitivity and specificity of 93.33 and 92.44 %, respectively (Ramos Lopes, Luz, Faria-Correia, Lyra, Machado, Ambrósio, unpublished data 2012).

A new NCT system integrated with an ultra-high speed (UHS) Scheimpflug camera was introduced by Oculus in 2010. The CorVis ST (Scheimpflug Technology) takes 4,330 frames per second covering 8 mm horizontally to monitor corneal response to a metered collimated air pulse with symmetrical configuration and fixed maximal internal pump pressure of 25 kPa [89]. The addition of an UHS Scheimpflug camera allows dynamic inspection of the actual deformation process, providing further detailing for biomechanical characterization of the cornea and correct IOP readings [89, 90]. As previously mentioned, integration

of biomechanical data provided by the CorVis with corneal tomography assessments (Pentacam) can enhance the identification of very mild forms of ectasia (Video Clip 1). In a study, evolving 119 eyes with normal corneas and 19 eyes with form fruste keratoconus, a new combined parameter derived from tomographic and biomechanical assessments was designed. This variable presented an AUROC of 0.999, with sensitivity and specificity of 100 and 99.2 %, respectively (Faria-Correia, Ramos, Lopes, Salomão, Luz, Oliveira. Ambrósio, unpublished data 2012).

Conclusions

The main goals of refractive surgery screening are not only to identify cases with mild ectasia, but to characterize each cornea in terms of its susceptibility to undergo biomechanical failure and ectasia. The standard screening criteria, based on corneal topography and CCT, has important limitations regarding sensitivity and specificity [12]. New technologies have already demonstrated the potential for improving the sensitivity [59] and specificity [91] for detecting ectasia risk. The combination of corneal tomography and biomechanical parameters increase the ability to detect mild forms of ectasia. However, there is still a need for retrospective case-control studies and, most importantly, prospective controlled studies which are being conducted.

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