Refra ctive and Topographic Errors in Topography-guided Ablation Produced by Epithelial Compensation Predicted by 3D Artemis VHF Digital Ultrasound Stromal and Epithelial Thickness Mapping

Dan Z. Reinstein, MD, MA(Cantab), FRCS(C), DABO, FRCOphth, FEO; Timothy J. Archer, MA(Oxon), DipCompSci(Cantab); Marine Gobbe, MST(Optom), PhD

ABSTRACT

PURPOSE: To describe and quantify the errors inherent to topography-guided ablation of irregular corneas due to natural epithelial thickness compensatory remodeling.

METHODS: Artemis very high-frequency (VHF) digital ultrasound scanning (ArcScan Inc) was performed on a cornea that had undergone radial keratotomy with inferior and superior trapezoidal keratotomies, resulting 27 years later in high irregular astigmatism (+6.50 – 8.00 × 101) and severe loss of corrected distance visual acuity (CDVA) to 20/50. The epithelial thickness profile was highly irregular, masking a significant proportion of the true stromal irregularity from front corneal surface topography, which would have resulted in significant inaccuracies had a topography-guided ablation been performed. The stromal ablation pattern of a transepithelial phototherapeutic keratotomy (PTK) ablation was modeled, which appeared logically to reduce the areas of abnormal stromal surface elevation and resembled a hyperopic astigmatic ablation of approximately 3.50 diopters of cylinder. Artemis-assisted transepithelial PTK was performed to target the stromal irregularity masked by epithelium.

RESULTS: Artemis-assisted transepithelial PTK induced a refractive change similar to that predicted (+2.24 – 3.97 × 120), demonstrating the refractive shift produced by the epithelium. The epithelial thickness profile became relatively regular and CDVA returned to 20/20. Two topography wavefront-guided ablations were performed to correct the remaining topographic irregularity and refractive error, resulting in a near plano refraction, significantly lower higher order aberrations, and CDVA of 20/20.

CONCLUSIONS: A knowledge of stromal surface shape and power shift produced by epithelial thickness profile alterations after corneal surgery has the potential of improving the efficacy and safety of custom corneal ablation. [J Refract Surg. 2012;28(9):657-663.] doi:10.3928/1081597X-20120815-02

As described by Alfred Vogt in 1921,1 it is known that the corneal epithelium has the ability to alter its thickness profile to try and reestablish a smooth, symmetrical optical surface and either partially or totally mask the presence of an irregular stromal surface.2 Such compensatory epithelial thickness changes have since been described after myopic3-5 and hyperopic6 excimer laser ablation, radial keratotomy,7 and in cases of irregular astigmatism.2,8 This is summarized by the Law of Epithelial Compensation for corneal irregular astigmatism, which we first coined in 1994:9 According to this Law of Epithelial Compensation, “if a patient presents with stable refraction and (corneal) irregular astigmatism, by definition the epithelium has reached its maximum compensatory function” with the corollary that corneal “irregular astigmatism has irregular epithelium.”

Surface topography has been the mainstay of diagnostic testing in complicated LASIK. The introduction of both topographic and whole eye aberrometry has enhanced our diagnostic capabilities in being able to understand, in a quantitative way, how irregular astigmatism and other shape irregularities produce subjective visual complaints. However, neither the understanding of the optical defect nor the front (and back) surface shape of the cornea will necessarily provide a diagnosis for the exact anatomy of the pathology that needs correcting.2,8 This is due to the fact that internal corneal refractive interfaces (such as the epithelial–stromal interface) to date are

From London Vision Clinic, London, United Kingdom (Reinstein, Archer, Gobbe); the Department of Ophthalmology, Columbia University Medical Center, New York, New York (Reinstein); and Centre Hospitalier National d’Ophtalmologie, Paris, France (Reinstein).

Dr Reinstein is a consultant for Carl Zeiss Meditec (Jena, Germany) and has a proprietary interest in the Artemis technology (ArcScan Inc, Morrison, Colorado) and is an author of patents related to VHF digital ultrasound administered by the Cornell Center for Technology Enterprise and Commercialization (CCTEC), Ithaca, New York. The remaining authors have no proprietary or financial interest in the materials presented herein.

Preparation in part fulfills the requirements for the doctoral thesis, University of Cambridge, for Dr Reinstein.

Correspondence: Dan Z. Reinstein, MD, MA(Cantab), FRCS(C), DABO, FRCOphth, FEO, London Vision Clinic, 138 Harley St, London W1G 7LA, United Kingdom. Tel: 44 207 224 1005; Fax: 44 207 224 1055; E-mail: dzr@londonvisionclinic.com

Received: March 29, 2012; Accepted: June 26, 2012
not being measured and incorporated independently into the diagnostic assessment. Refractive shifts (regression) due to epithelial remodeling after corneal refractive surgery have been known for some time.3,5 We have published many instances demonstrating how the root cause of a corneal surface abnormality is essential for an accurate diagnosis, and therefore how topography or wavefront-guided treatments may lead to a suboptimal treatment due to epithelial compensation mechanisms inherent to the cornea.2,8,10

Below we describe a case example where measurement of the epithelial thickness profile was used to make a more reliable diagnosis than that based on topography and/or whole-eye wavefront alone. Both the anatomical smoothing effect on the stroma and the optical shift produced by the epithelium are demonstrated to be of significant magnitude as to make topography- or wavefront-guided (78% optically biased to the front surface shape) custom ablation less effective for fully correcting the problem and controlling for the epithelial refractive shift.

CLINICAL EXAMPLE

A 50-year-old man from Atlanta, Georgia, was referred to our clinic (London Vision Clinic, London, United Kingdom) by an expert US-based refractive surgeon in February 2009, because of the lack of US Food and Drug Administration approval for therapeutic topography-guided repair tools despite these being available worldwide since 1998.11 The patient complained of poor vision in his left eye following several refractive incisional procedures. Original manifest refraction was approximately −6.00 diopters (D). He underwent radial keratotomy in June 1982, followed by another keratotomy procedure 2 months later consisting of crossing trapezoidal incisions12 over the inferior and superior cornea. It is unclear from the history why the trapezoidal incisions were made. Six months after the second procedure, the surgeon recommended a lamellar graft, which the patient refused. The right eye remained untreated. Since that time, the patient had sought advice from several surgeons to improve his quality of vision in the left eye.

On presentation to London Vision Clinic, the patient’s manifest refraction was +6.50 –8.00 × 110, achieving corrected distance visual acuity (CDVA) of 20/50, 27 years after the radial and trapezoid keratotomy procedures. A full ophthalmic examination was performed to assess the patient according to our standard complex case evaluation protocol as described previously,13 which included a three-dimensional Artemis very high-frequency (VHF) digital ultrasound scan (ArcScan Inc, Morrison, Colorado) to provide pachymetric maps of the individual corneal layers.

Atlas corneal front surface topography (Carl Zeiss Meditec, Jena, Germany) was irregular, showing an against-the-rule asymmetric bowtie pattern decenttered superiorly (Fig 1). WASCA Hartmann-Shack aberrometry (Carl Zeiss Meditec, Jena, Germany) showed elevated higher order aberrations with 0.91 μm of spherical
aberration and 1.06 μm total higher order root-mean-square (RMS). The Artemis epithelial thickness profile showed a high degree of irregularity with up to 35-μm thickness variation between locations within the central 4-mm zone (Fig 2). The epithelial thickness map demonstrated two localized regions of thin epithelium (40 μm), approximately 1 mm in diameter each, at a 2-mm radius inferiorly and superiorly from the corneal vertex; these regions of thin epithelium were overlying and coincident with the trapezoidal incision zones. The epithelium was thicker (up to 75 μm) along the horizontal meridian centrally, extending nasally, and at the 3-mm radius inferonasally.

To model the masking effect of the irregular epithelial thickness profile, we calculated the stromal surface topography as follows: the epithelial thickness profile was subtracted from the exported Orbscan II (Bausch & Lomb, Rochester, New York) corneal front surface elevation data to obtain the stromal surface elevation, which was then imported into VolPro CT (version 7.4; Sarver & Associates, Carbondale, Illinois) to generate the corneal front surface topography. Figure 3 shows the corneal front surface topography and stromal surface topography plotted in VolPro CT. The inferior-superior (I-S) asymmetry index calculated at the 2-mm radius (in the location of the regions of thinnest epithelium) was 3.20 D higher on the stromal surface (9.00 D) than on the corneal outer surface (5.80 D). Thus, the epithelial thickness profile was producing significant corneal surface regularization, while masking a significant proportion of the true stromal irregularity. The proportion of stromal irregularity that was being masked by the epithelium would not be taken into account by a topography-guided ablation algorithm (given that a topography-guided ablation is calculated from the corneal front surface topography with the aim of producing a regular corneal front surface). We therefore decided that the optimal first step in the treatment plan would be to perform an Artemis-assisted transepithelial phototherapeutic keratectomy (PTK) procedure targeting the component of the stromal irregularity compensated for by the epithelium using the epithelium as a natural masking agent, and avoiding excess stromal tissue removal.

To attempt an estimate of the refractive effect of the epithelial compensation, the preoperative Artemis epithelial thickness profile was mathematically manipulated to simulate transepithelial lamellar keratectomy. This was achieved by plotting the breakthrough pattern and remaining epithelium at regular lamellar depths of
PTK ablation by setting areas with no epithelium to be displayed in white (by increasing the minimum of the scale) in a technique that we called Digital Subtraction Pachymetry (DSP) in 1994\(^2\)\(^-\)\(^1\(^4\) (Fig 4). Based on the epithelial thickness map, we determined that we would perform a 65-μm Artemis-assisted transepithelial PTK ablation to maximize stromal smoothing and minimize stromal tissue wastage as we described previously.\(^2\) The epithelial thickness data were then used to calculate and map the stromal ablation that would occur for a chosen depth of 65 μm. Given the observed epithelial masking, the stromal ablation in this case would be concentrated superiorly and inferiorly in the vertical meridian where the epithelium was thinnest (a map of the predicted stromal ablation is shown in Figure 1). During the procedure, the transepithelial PTK ablation was performed in two steps, with a planned 45-μm ablation as the first step. After the first ablation, the cornea was examined (as shown in the intraoperative photograph) and the areas of exposed stroma were compared to the Artemis simulated maps, which confirmed that the first ablation was close to 45 μm. The second transepithelial PTK ablation could then be planned with an intended endpoint of 65 μm. The second intraoperative photograph shows the pattern of remaining epithelium was similar to the predicted pattern with a small patch of epithelium remaining.

The Artemis-assisted transepithelial PTK procedure was performed using the MEL 80 excimer laser. The PTK ablation was performed over an 8.0-mm diameter zone. The laser data entry ablation depth for the first PTK ablation was calculated using a conversion factor of 1.38 times the intended depth based on our previous Artemis-assisted transepithelial PTK procedures with the MEL 80.\(^2\) The laser data entry ablation depth of the first PTK ablation was 62 μm for an intended depth of 45 μm. This initial ablation had broken through the epithelium in two small areas 2 mm superior and inferior of the corneal vertex, which closely matched the simulated remaining epithelial pattern (see Fig 4). After the second PTK ablation, only a small patch of epithelium remained centrally. No further ablation was performed as the intended endpoint had been reached.

One drop each of oxybuprocaine (Benoxinate, Bausch & Lomb), dexamethasone–tobramycin (TobraDex; Alcon Laboratories Inc, Ft Worth, Texas), ofloxacin (Exocin; Allergan Ltd, Marlow, United Kingdom), and ketorolac tromethamine (Acular, Allergan Ltd) were applied immediately following the treatment. (Specifically, no mitomycin C was used.) A +3.00-D contact lens (Acuvue Oasys [Johnson & Johnson Vi-
sion Care, Wokingham, United Kingdom] BC 8.8, diameter 14.0) was applied as a bandage lens. TobraDex and Exocin were continued for 5 days until full epithelial wound closure was achieved; following this, fluorometholone (FML) and lubricants were used for 2 months.

Nine months after Artemis-assisted transepithelial PTK, uncorrected distance visual acuity (UDVA) was 20/100, manifest refraction was +4.25 − 4.50 × 101, and CDVA had improved to 20/20. A refractive change of +2.24 − 3.97 × 120 occurred compared to the preoperative refraction calculated using power vector analysis.15 This refractive change was similar to that predicted by both the difference between the corneal and stromal surface topographies (3.20 D) and the stromal ablation predicted for a transepithelial PTK by analysis of the epithelial thickness (3.50 D). The Artemis epithelial thickness profile (see Fig 2) showed that the epithelium was much more regular in thickness. The epithelial thickness difference map (see Fig 2) demonstrated that the epithelium had redistributed, becoming thicker in the superior and inferior regions where the maximum stromal ablation took place and becoming thinner centrally where the epithelium was thickest before the procedure. The change could also be seen on Atlas corneal front surface topography where the difference map showed a significant on-axis astigmatic change as predicted (see Fig 1). The presence of a smoother epithelial thickness profile proved that the Artemis-assisted transepithelial PTK procedure had succeeded in significantly reducing stromal irregularity and hence the disparity between the stromal surface and anterior corneal (topographic) surface. This reduced disparity with the stromal and epithelial surfaces now representing a similar shape meant that a topography-guided procedure would be more effective. Following Artemis-assisted transepithelial PTK, the higher order aberrations were effectively unchanged with 0.95 μm spherical aberration and 1.19 μm total higher order RMS. However, this was to be expected as the preoperative higher order aberrations comprised of mainly (86%) spherical aberration; spherical aberration would not have been affected much by the breakthrough pattern of the Artemis-assisted transepithelial PTK as it was mostly a superior/inferior ablation into the stromal tissue. In addition, the irregularities addressed by Artemis-assisted transepithelial PTK would have been of a much higher order than the 4th order analysis performed by our wavefront sensor.

A LASIK procedure was performed with the MEL 80 using a topography wavefront-guided ablation profile (see Fig 1) in a 6.50-mm zone calculated using the CRS-Master software (Carl Zeiss Meditec) based on an Atlas corneal front surface topography and the manifest refraction with an intended refractive target of plano. The VisuMax femtosecond laser (Carl Zeiss Meditec) was used to create a flap with an intended thickness of 100 μm and flap diameter of 8 mm. The maximum epithelial thickness was 65 μm, therefore, using a 100-μm flap thickness eliminated the risk of a cryptic buttonhole; given the 7.9-μm flap thickness reproducibility with the VisuMax,16 the flap would be unlikely to be thinner than 84 μm (two standard deviations). The flap resulted in two of the radial keratotomy incisions splitting open during the flap lift and a small area inferiorly that was not adequately cut by the femtosecond laser and required manual cutting using microcorneal scissors. The flap was replaced anatomically and a bandage contact lens was applied. When reviewed at postoperative day 1, the flap and incisions were perfectly apposed and the surface healing occurred without complications or epithelial ingrowth.

Eleven months later, UDVA was 20/80 and manifest refraction was +4.00 − 3.50 × 66 with CDVA 20/20. The Atlas corneal front surface topography had been further regularized with a pattern of regular astigmatism (see Fig 1), a significant change from the preoperative topography. The higher order aberrations had significantly improved with spherical aberration reduced by 71% from 0.95 to 0.27 μm and higher order RMS reduced by 51% from 1.19 to 0.58 μm.

As the epithelial thickness profile was still relatively regular, a second MEL 80 topography wavefront-guided procedure was performed to correct the remaining refractive error along with the remaining topographic irregularities. It was chosen to perform this procedure as a photorefractive keratectomy (PRK) (with epithelial removal by applying 20% ethanol for 40 seconds using a corneal well instrument), to avoid distortion that may have been produced by traction on the flap in and around the areas of the previous scarred keratotomy incisions crossing the flap. (Again, no mitomycin C was applied intraoperatively.)

Nine months later, UDVA was 20/20 and manifest refraction was plano (CDVA was 20/20). The Atlas corneal front surface had been further regularized (see Fig 1).

**DISCUSSION**

This case demonstrates how the epithelium effectively acts as a low pass filter for both local and global changes in stromal surface curvature so that the epithelium becomes thinner over relative peaks in the stroma and becomes thicker over relative troughs in the stroma. As a result, epithelial compensation has a significant impact on the refraction—compared to what it would be if the epithelium were of even thick-
ness and represented the stromal surface shape. In this case, a refractive change of $+2.24 - 3.97 \times 120$ was achieved by transepithelial PTK ablation, which was fairly accurately predicted preoperatively by analysis of the epithelial pattern and resulting predicted stromal tissue removal by DSP. Knowledge of the epithelial thickness profile prior to transepithelial PTK may be used to predict the refractive change that will be induced, improving the refractive accuracy of transepithelial PTK, which has been previously reported to be unpredictable in cases of irregular astigmatism.$^{2,17}$

We previously reported the step-wise Artemis-assisted transepithelial PTK procedure,$^2$ which affords a number of advantages. Knowledge of the epithelial thickness profile is helpful in diagnosing the anatomical basis for a patient’s subjective symptoms and aids in optimizing a treatment plan. Corneas with refractive surgical complications often present with significantly reduced stromal tissue reserves, making stromal tissue preservation a priority during the repair process. During the procedure, the DSP simulation maps can be used to monitor the progress of the transepithelial ablation intraoperatively, allowing for the epithelial ablation rate to be verified for a particular eye. After the initial ablation, this provides an opportunity to recalibrate the epithelial ablation rate to use for the remainder of the procedure and ensure that the intended endpoint is reached, again, preserving stromal tissue that is at a premium in these cases.

An irregular epithelial thickness profile may often have a detrimental effect on the effectiveness of wavefront- or topography-guided custom ablation because the true stromal irregularity is partially masked by the epithelium. Compensatory epithelial remodeling and other, currently unpredictable, biomechanical responses are the likely explanation for the less than 50% effectiveness of wavefront$^{18}$ or topography-guided$^{19}$ custom ablation profiles. This was demonstrated in the example case as, following Artemis-assisted transepithelial PTK, two additional topography wavefront-guided procedures were required to fully regularize the corneal topography.

Similarly, transepithelial PTK can only correct a proportion of the stromal irregularity—the proportion that has been compensated for by epithelial remodeling. This clinical example demonstrates how in cases of irregularly irregular astigmatism, it may be beneficial to first perform a transepithelial PTK to target the irregularities masked by the epithelium and reduce the discrepancy between the stromal surface shape and epithelial surface shape (topography). The amount of epithelial compensation depends on the rate of change of curvature with more epithelial thickness changes occurring where the irregularities are more localized. This can be appreciated by the fact that there is almost twice as much epithelial thickening after a hyperopic ablation$^4$ compared with a myopic ablation,$^5$ and the total epithelial compensation for small, very localized stromal loss such as after a corneal ulcer.$^6$ Therefore, when large and/or localized differences in epithelial thickness represent irregularly irregular astigmatism (ie, a high rate of change in curvature), an initial transepithelial PTK procedure will be more effective than a wavefront- or topography-guided procedure. Once the epithelium is more regular, a topography- or wavefront-guided ablation may be used to correct the remaining, more global and regularly irregular astigmatism (ie, a more gradual rate of change in curvature).

In theory, a transepithelial PTK ablation would correct the irregularity being masked by the epithelium and a topography-guided ablation would correct the irregularity that was not masked by the epithelium, meaning that the combination of the two would correct the whole of the stromal irregularity. This technique of performing both steps in a single procedure has been used by Chen et al$^20$ with encouraging results. However, the ability to perform this sort of procedure may be limited by the high ablation depth required for this technique, and the fact that complicated corneas are often already thinned by previous surgery. Given that repair cases are often already thin, a further variable will be the biomechanical response to the therapeutic ablation, which could render the refractive outcome less predictable and hence may require further tissue to be ablated. In many repair cases, particularly those involving previous keratotomy incisions, the biomechanical situation is more complex than in normal untreated eyes due to the presence of incisions, interfaces, and/or corneal thinning from tissue removal from prior procedures. If the transepithelial PTK and topography-guided components are performed separately, the biomechanical response to the first procedure can be corrected for by the second procedure, which would conserve tissue. Finally, the power of the epithelium to remodel and partially compensate for a stromal surface irregularity can be advantageous in that a satisfactory result can be achieved without having to correct the whole irregularity, which is another way of maximizing the remaining tissue.

It seems that the ideal solution in therapeutic refractive surgery will be the ability to create a custom ablation profile based on stromal surface topography. This could be achieved by subtracting the epithelial thickness profile from the corneal front surface topography. By incorporating the epithelial thickness data into the ablation planning software, a transepithelial PTK ablation would not be required and the custom ablation
could be performed under a flap (except for cases where the PTK ablation is required to remove scarring).

In summary, knowledge of the epithelial thickness profile can provide significant benefits to therapeutic corneal refractive surgical planning and outcomes. This article highlights how both the ocular wavefront (and refraction) or surface topography can be affected by epithelial thickness remodeling that is compensating for a stromal surface irregularity. The ideal therapeutic profile will be one that is based on the shape of the stromal surface itself.

**AUTHOR CONTRIBUTIONS**

Study concept and design (D.Z.R., T.J.A.); data collection (D.Z.R., T.J.A., M.G.); analysis and interpretation of data (D.Z.R., T.J.A., M.G.); drafting of the manuscript (D.Z.R., T.J.A.); critical revision of the manuscript (D.Z.R., T.J.A.); analysis and interpretation of data (D.Z.R., T.J.A., M.G.); drafting of the manuscript (D.Z.R., T.J.A.); critical revision of the manuscript (D.Z.R., M.G.)

**REFERENCES**