Future Challenges to Aberration-free Ablative Procedures

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One of the exciting new research areas in laser refractive surgery is the development of sophisticated devices to measure the wavefront of the optical system of the entire eye, the various implementations of which are described in this proceedings. The ability to objectively measure performance of the eye, as opposed to simple corneal shape, is critical to "customizing" ablation algorithms and generating an overall improvement of visual outcomes after refractive surgery. Anterior corneal surface topography cannot take into account contributions of optically important structures inside the eye, such as the posterior corneal surface and the crystalline lens. If a laser were programmed strictly with anterior topography data, the correction would be at best incomplete, and at worst simply wrong. Therefore, wavefront analysis is clearly important, particularly if the ultimate goal is to correct higher order aberrations along with the sphere and cylinder. However, the question must be asked whether wavefront analysis alone is sufficient to fully predict visual outcomes. Will it replace corneal topography in the quest for the perfect "aberration-free" guided procedure? Or, on the other hand, is there a piece of the puzzle still missing? If so, can corneal topography complement the wavefront measurements to help complete the picture of corneal response?

To answer these questions, the underlying theory of laser refractive surgery can be examined. Munnerlyn and colleagues[1] described what is referred to here as a "shape-subtraction" model of refractive surgery, based on geometric equations for altering the surface curvature with the cornea modeled as sphere. In a "shape-subtraction" model of a myopic procedure, the desired sphere of lesser curvature is superimposed on the original sphere of greater curvature, with the apex displaced by an amount determined by the chosen ablation diameter. If the intervening tissue is removed or "subtracted" from the original sphere by a laser, the desired sphere of lesser curvature is the result. In other words, the cornea is analogous to a piece of plastic that can be sculpted to a new shape, without taking into account how the cornea might respond to a change in its structure imposed by an ablative procedure.

The Munnerlyn formulas have been empirically modified since they were first implemented, based on statistical analyses of large numbers of treated patients. Therefore, current ablation algorithms are optimized to the mean population response. This approach has produced a majority of satistified patients over the years. However, customization requires prediction of *individual* rather than mean corneal response, and an understanding of the source of variability that still exists in the clinical results is critical to the ultimate success of future "aberration free" procedures. In addition, outcomes are currently analyzed in terms of sphere and cylinder, which is a measure of *central* corneal performance. Higher order aberrations, on the other hand, are produced by a larger region of the cornea. Therefore, aberration-reducing ablation algorithms must target a very specific corneal shape over that broader region. To acheive a specific corneal shape over the entire ablation zone, a much deeper understanding of corneal response than currently exists is also critical.

There are three underlying assumptions that define the commonly accepted shape-subtraction model, which are also shared by the concept of a purely wavefront-guided ablative procedure. They are:

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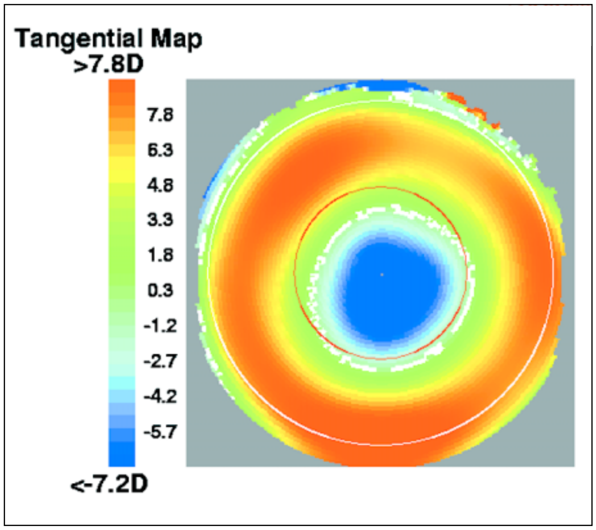

Figure 1. Tangential curvature difference map (postoperative minus preoperative) after a -12.5 D LASIK procedure with a 5.5 mm diameter ablation zone. White pixels indicate "zero" difference, defined as ±0.25 D difference. Central red circle is at 4 mm diameter and outer white circle is at 8 mm diameter. Note the increased curvature outside the ablation zone.

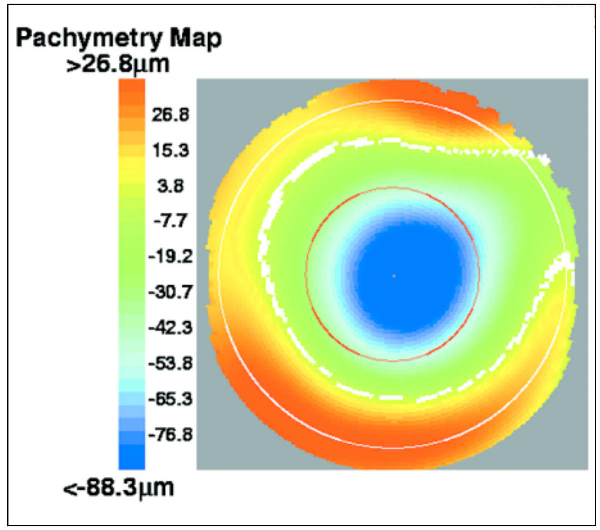

Figure 2. Pachymetry difference map (postoperative minus preoperative) after a -12.5 D myopic LASIK procedure with a 5.5 mm diameter ablation zone. White pixels indicate zero difference. Central red circle is at 4 mm diameter and outer white circle is at 8 mm diameter. Note the increased pachymetry outside the ablation zone.

1) The only part of the cornea affected by the surgery is within the ablation zone.
2) "What you cut is what you get."
3) Even if there are changes outside the ablation zone, they don't affect central shape or central vision.

Each of these assumptions will be examined in turn and found to be invalid, first with examples, followed by preliminary study data. Figure 1 is a tangential curvature difference map (postoperative minus preoperative) after a -12.5 diopter (D) laser in situ keratomileusis (LASIK) procedure using a Technolas 217 excimer laser (Munich, Germany) with a 5.5-mm diameter ablation zone. The corneal topography was acquired using an ORBSCAN I (Salt Lake City, UT). The data were exported using the recorder function, and subsequently imported into custom software, entitled "The Ohio State University Corneal Topography Tool[2]," for analysis. Centrally, there is a decrease in curvature, as expected, indicated by the negative values and blue colors. The surrounding thin white area represents zero difference between the preoperative and postoperative state. In the area outside the ablation zone, there is an unexpected increase in curvature which extends into the periphery, indicated by the

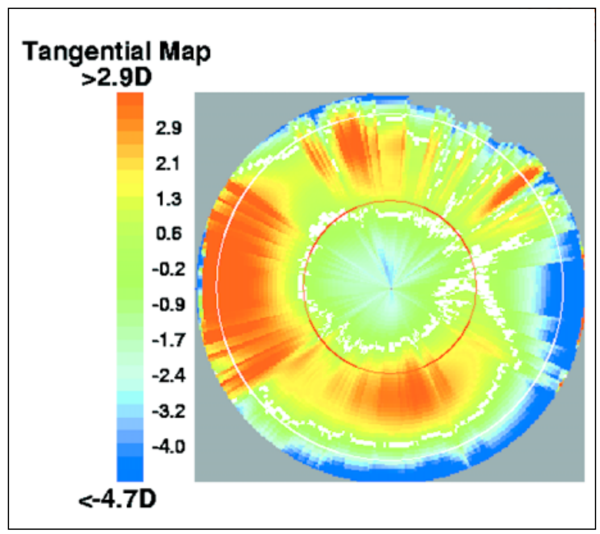

Figure 3. Tangential error difference map after a -6.5 D myopic LASIK procedure. The ablation profile was calculated based on Munnerlyn's formulas and subtracted from the preoperative topography to generate a "predicted" postoperative map. The predicted topography was then subtracted from the actual measured postoperative topography to generate this "error" map. Note greater than predicted curvature outside the ablation zone, and less than predicted curvature inside the ablation zone.

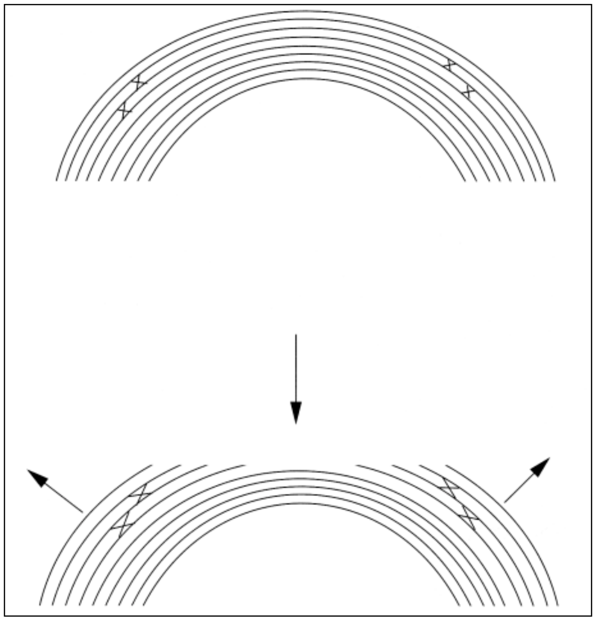

Figure 4. Biomechanical model of corneal response to laser refractive surgery. Preoperatively (TOP), the cornea is a layered structure consisting of many lamellae that stretch limbus to limbus, and is loaded via the intraocular pressure. The interlamellar spacing is defined by the tension carried in the individual lamellae. Postoperatively (BOTTOM), a defined series of lamellae are circumferentially and permanently severed. This reduces the tension in the remaining peripheral lamellar segments, allowing expansion of the peripheral layers. This expansion generates a radial force outwards (shown by arrows), which is transmitted to the lower layers via corneal crosslinking. The peripheral radial pull causes the central cornea to flatten (shown by downward arrow), independent of the ablation profile cut on the cornea.

positive values and red colors. Changes in corneal curvature clearly occur well beyond the ablation zone, challenging assumption #1. Figure 2 is a pachymetry difference map from the same patient. Inside the ablation zone, the thickness has decreased, as expected. However, outside the ablation zone, the thickness has unexpectedly increased. Although this seems paradoxical, an explanation relating to a possible biomechanical mechanism will be offered in the next section.

To examine assumption #2, a myopic ablation profile was subtracted from the preoperative topography to generate predicted postoperative topography for a sample patient. The predicted topography was subtracted from the actual measured postoperative topography to generate an error map, given in Figure 3. The assumed -6.50 D ablation profile was calculated based on Munnerlyn's formulas[1], using the actual 6.50 D targeted refractive change for the patient. The topography was acquired with an Orbscan I, and the ablation was performed using a Technolas 217 excimer laser. The tangential curvature error map indicates greater than predicted curvature change outside the ablation zone, and less than predicted curvature change in the central region. Although the true ablation profile is proprietary, and therefore an estimate had to be generated based on Munnerlyn's formulas, a linear error function would have been expected. The error function is nonlinear, which challenges assumption #2. This same procedure was followed using the actual proprietary ablation algorithms for a Summit Apex Plus laser for two LASIK patients.[3] The "error" maps generated showed the same trend for greater than predicted curvature outside the ablation zone.[3]

These anecdotal data demonstrated a consistent pattern over a group of patients, which provided the motivation for several studies, both in vitro using cadaver globes, as well as in a refractive surgery patient population. The in vitro studies demonstrated a biomechanical link between the central and peripheral cornea after a phototherapuetic keratectomy (PTK) procedure.[4-8] The depth of ablation strongly correlated with central flattening, as well as peripheral stromal thickening. These results led to the development of a biomechanical model of the corneal response to laser refractive surgery[5-9], which will be explained in more detail in the next section. The biomechanical response of the cornea is the concept which challenges assumption #3. It is known from the era of radial keratotomy that structural changes in the mid-peripheral and peripheral portion of the cornea biomechanically generate shape changes in the central cornea.[10] Laser refractive surgery also produces a structural change in the cornea to which a biomechanical response is generated over the entire cornea. Shape changes outside of the ablation zone will affect the central corneal shape, and thus have an impact on the visual outcome.

BIOMECHANICAL MODEL OF LASER REFRACTIVE SURGERY

At Ohio State, we have been developing a model for the biomechanical consequences of laser refractive surgery[3-9], which is reproduced here. Prior to surgery, the cornea is a layered structure consisting of many lamellae that stretch limbus to limbus, and is loaded via the intraocular pressure. The interlamellar spacing is defined by the tension carried in the individual lamellae. After surgery, a defined series of lamellae are circumferentially and permanently severed. This reduces the tension in the

Table 1
Anterior Tangential Average Regional Postoperative minus Preoperative Differences

	Central	Transition	Outside
		(D, mean ± SD)	
Normals	0.02±0.06	-0.07±0.31	0.00±0.31
Surgical, 1 day	-3.91±0.36*	5.11±1.13*	6.17±0.61*
Surgical, 1 wk	-2.97±0.16*	4.20±0.67*	5.72±0.36*
Surgical, 1 mo	-2.99±0.26*	4.74±0.87*	4.78±0.38*

**P* < .05 for comparison between normal differences and postoperative minus preoperative differences.*

Table 2
Anterior Elevation Average Regional Postoperative minus Preoperative Differences

	Central	Transition	Outside
		(μ, mean ± SD)	
Normals	0.5±0.06	0.00±0.00	0.00±0.8
Surgical, 1 day	-46.1±4.7*	0.3±0.2	14.9±5.9*
Surgical, 1 wk	-34.6±2.4*	0.0±0.0	10.9±4.6*
Surgical, 1 mo	-37.6±2.7*	0.0±0.0	10.6±2.7*

**P* < .05 for comparison between normal differences and postoperative minus preoperative differences.*

Table 3
Pachymetry Average Regional Postoperative minus Preoperative Differences

	Central	Transition	Outside
		(μ, mean ± SD)	
Normals	-2.6±1.6	-2.5±2.2	-1.3±1.8
Surgical, 1 day	-63.0±2.6*	1.9±3.5	11.5±5.3*
Surgical, 1 wk	-71.8±5.4*	-24.9±5.0*	-20.4±9.1*
Surgical, 1 mo	-47.0±3.6*	3.1±5.1	9.2±6.0*

**P* < .05 for comparison between normal differences and postoperative minus preoperative differences.*

remaining peripheral lamellar segments, allowing expansion of the peripheral layers. This expansion generates a radial force outwards, which is transmitted to the lower layers via corneal crosslinking. The peripheral radial pull causes the central cornea to flatten, independent of the ablation profile cut on the cornea. This is illustrated in Figure 4 for a myopic procedure. In other words, the biomechanical response will cause additional corneal flattening on top of a myopic procedure, as well as additional corneal flattening on top of a hyperopic procedure. Therefore, the biomechanics will enhance a myopic procedure and work against a hyperopic procedure. Evidence of this effect is further demonstrated by the first eight patients treated with Autonomous' CustomCornea (McDonald, pages S617-S618 in this issue). Using a purely wavefront-guided procedure, all five myopic patients were overcorrected and all three hyperopic patients were undercorrected. This is completely consistent with the biomechanical model just presented which predicts biomechanical central flattening, independent of ablation profile. Both algorithms were adjusted based on the preliminary data, and the second series of patients had better results. However, as more patients are enrolled, the differences in individual biomechanical properties may become apparent. A linear correction factor may not be sufficient to account for the biomechanical effects. Additional clinical evidence for the biomechanical response will be described in detail in a future publication.[11]

In an effort to scientifically characterize the biomechanical response to laser refractive surgery, we have begun a study to investigate changes in corneal shape, and to separate those changes due to the ablation profile, the biomechanical response and wound healing. This is in cooperation with Summit Autonomous, Inc. (Waltham, MA), who has agreed to provide their proprietary ablation algorithms for the Summit Apex Plus. Thus far, we have preliminary data on 8 eyes of four patients, with average refractive error of -6.875 ± 2.03 D sphere +0.8125 ± 0.51 D cylinder. Patients were examined at 1 day preoperative and 1 day, 1 week, and 1 month postoperatively following a LASIK procedure with a Summit Apex Plus using a Krumeich-Barraquer microkeratome. Only the Orbscan II corneal topography data will be presented here. The control group of 20 eyes of 10 subjects had repeated Orbscan I topography acquired at intervals of from 1 to 2 days. The anterior tangential, anterior elevation and pachymetry data were exported to The OSU Topography Tool for analysis. The corneal topography was divided into three regions for analysis: central 2.75 mm radius, transition zone from a radius of 2.75 to 3.25 mm, and outside the ablation zone from a radius of 3.25 to 4.5 mm. The preoperative topography was subtracted from the postoperative topography for the surgical patients, and the repeated measurements were subtracted for the normal subjects. For the elevation maps, the two surfaces were fit within the 0.5 mm transition zone. For all maps, average regional differences were calculated over the normal and surgical populations, and statistical analysis was performed using the ANOVA

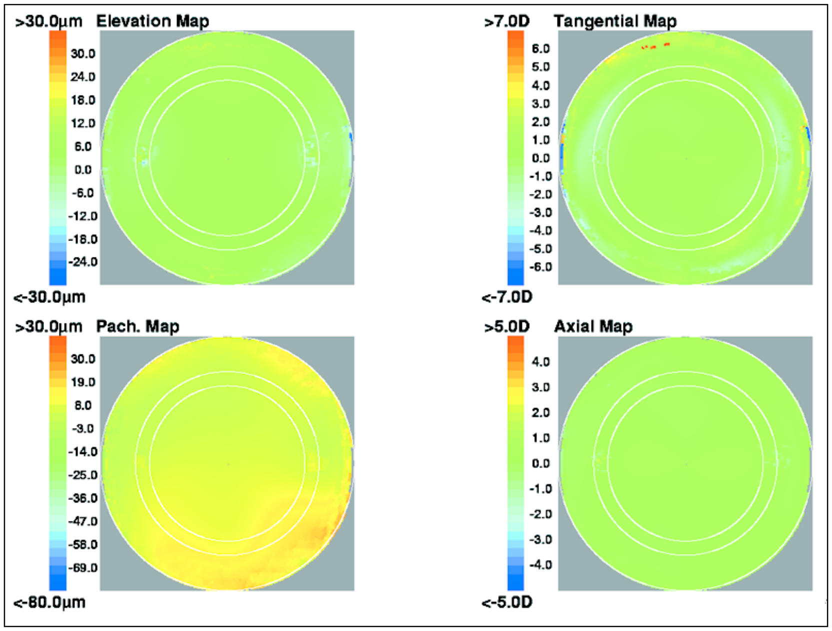

Figure 5. Average difference maps between repeated measures of 20 eyes of 10 normal subjects. The white circles define three corneal regions. The central region has radius 2.75 mm, the middle region has radius 2.75 to 3.25 mm and the outer region has radius 3.25 to 4.5 mm. Elevation (upper left) differences were calculated by fitting the two surfaces in the middle region. Average tangential differences (upper right), average pachymetry differences (lower left) and average axial differences (lower right) are also given.

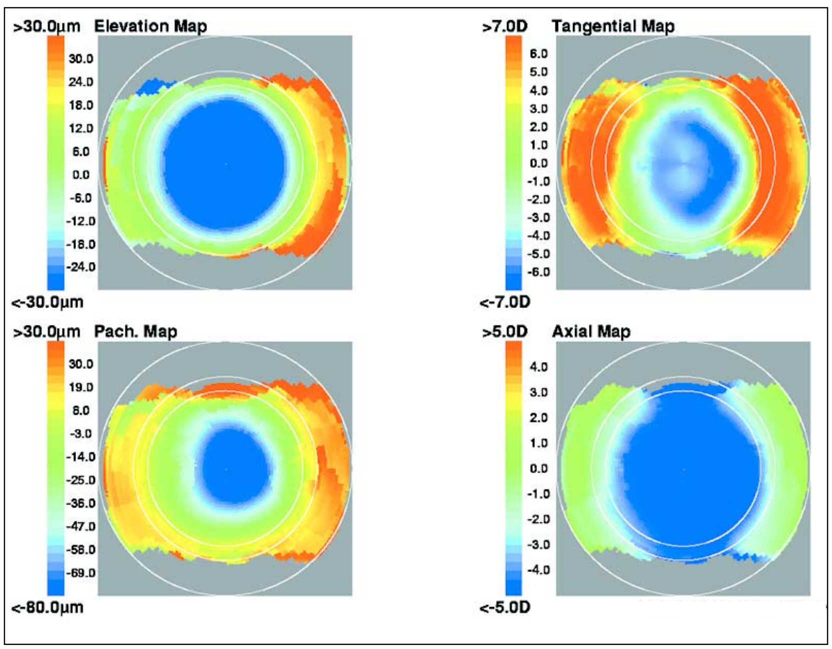

Figure 6. Average difference maps between 1 day postoperative LASIK and preoperative state for 8 eyes of 4 patients. The white circles define three corneal regions. The central ablated region has radius 2.75 mm, the middle transitional region has radius 2.75 to 3.25 mm and the outer non-ablated region has radius 3.25 to 4.5 mm. Elevation (upper left) differences were calculated by fitting the two surfaces in the transitional region, and demonstrate increased elevation in the outer zone. Average tangential differences (upper right) show increased curvature in the outer region. Average pachymetry differences (lower left) show increased pachymetry in the outer region. Average axial differences (lower right) are also given.

procedure in the software package, SAS.

Tables 1 to 3 summarize the numeric results, and Figures 5 to 8 show the average composite difference maps for all the normals (Fig 5), 1 day postoperative (Fig 6), 1 week postoperative (Fig 7), and 1 month postoperative (Fig 8). These data indicate a significant decrease in tangential curvature centrally, as expected, and a statistically significant increase in tangential curvature outside the ablation zone at all three postoperative time points. Similarly, a significant decrease in elevation was found centrally, as expected, but was accompanied by a statistically significant increase in elevation outside the ablation zone at at all three postoperative time points. Interestingly, these significant differences were found despite the low n. The pachymetry difference patterns were a little more complicated. Centrally, there was a significant decrease in

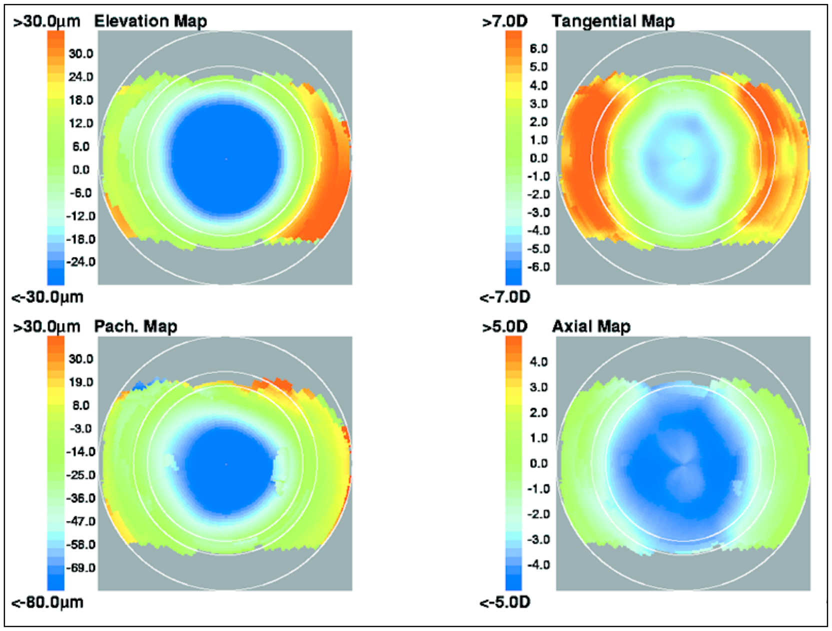

Figure 7. Average difference maps between 1 week postoperative LASIK and preoperative state for 8 eyes of 4 patients. The white circles define three corneal regions. The central ablated region has radius 2.75 mm, the middle transitional region has radius 2.75 to 3.25 mm and the outer non-ablated region has radius 3.25 to 4.5 mm. Elevation (upper left) differences were calculated by fitting the two surfaces in the transitional region, and demonstrate increased elevation in the outer zone. Average tangential differences (upper right) show increased curvature in the outer region. Average pachymetry differences (lower left) show overall dehydration. Average axial differences (lower right) are also given.

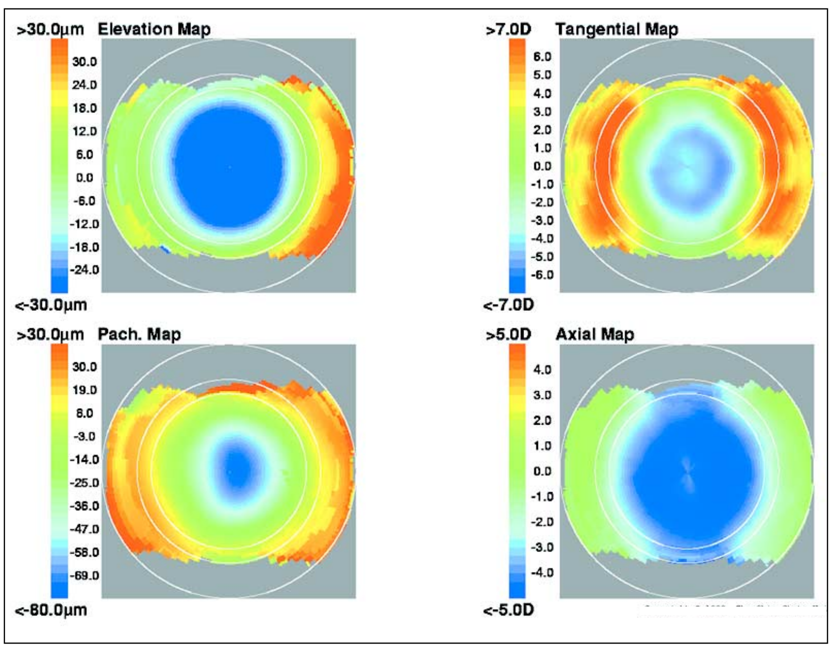

Figure 8. Average difference maps between 1 month postoperative LASIK and preoperative state for 8 eyes of 4 patients. The white circles define three corneal regions. The central ablated region has radius 2.75 mm, the middle transitional region has radius 2.75 to 3.25 mm and the outer non-ablated region has radius 3.25 to 4.5 mm. Elevation (upper left) differences were calculated by fitting the two surfaces in the transitional region, and demonstrate persistent increased elevation in the outer zone. Average tangential differences (upper right) show persistent increased curvature in the outer region. Average pachymetry differences (lower left) show persistent increased pachymetry in the outer region. Average axial differences (lower right) are also given.

pachymetry, as expected. Outside the ablation zone, a statistically significant increase in pachymetry was found at both 1 day and 1 month, but not at 1 week. However, the one week data demonstrated an overall statistically significant dehydration relative to the preoperative state, which resolved by 1 month. The postoperative increase in thickness outside the ablation zone has also been measured using very high-frequency digital ultrasound techniques.[12]

The persistent increase in elevation, curvature and pachymetry outside the ablation zone are consistent with the proposed biomechanical model, and verify that “shape-subtraction” assumptions #1 and #2 are not valid. To verify that assumption #3 is not valid, the Summit ablation algorithms are necessary in order to determine how much of the measured shape changes are due to the ablation profile that was cut, and how much are due to the proposed biomechanical response. This work is currently underway and preliminary data have been reported.[3] In addition, clinical evidence has been presented that peripheral elevation increases are strongly correlated with central flattening in a series of 30 eyes after LASIK.[13] This demonstates once again that peripheral changes do affect central shape.

What impact does the biomechanical response have on the goal of aberration-free ablative corrections via wavefront-guided procedures? Ultimately, the impact is on variability of response and predictability of the result, both in terms of shape across a large portion of the cornea and vision measured in terms of wavefront error, not spheres and cylinders. Wavefront analysis provides data only on the end result. It cannot differentiate where the changes in the visual system occurred to produce the measured result. Consider the endpoint of refractive surgery. Is the final target corneal shape or visual performance? Clearly, the final target is visual performance. However, the mechanism to achieve improved performance is through changing corneal shape, and all factors which affect that shape must be taken into account. The preliminary evidence presented here indicates that final corneal shape (and thus vision) is a function of three factors: the ablation profile, the wound healing, and the biomechanical response of the cornea to a change in its structure. The last two cannot be characterized by a pure wavefront analysis approach, and must be characterized in order to achieve the ultimate goal of optimization and customization of visual outcomes.

The "shape-subtraction" model of refractive surgery does not predict all the corneal shape changes that occur after laser refractive surgery. Therefore, wavefront analysis alone cannot fully predict visual outcomes. A missing piece of the puzzle of corneal response is the biomechanical effect. What is the solution in order to produce an aberration-free outcome, or at least minimized aberrations? First, the biomechanical corneal response to laser refractive surgery should be characterized, in parallel to developing wavefront technology. Corneal topography offers a mechanism to measure the actual shape changes produced. With knowledge of the ablation algorithms, the biomechanical response can be separated from the shape change produced by the ablation profile. Topographic changes can also be linked to the measured wavefront to more fully characterize both the corneal shape and functional response. Ideally, the ultimate customized, "guided" procedure will use a combination of wavefront and corneal topographic analysis to provide a complete picture of corneal response and visual outcome. Predicting this complete response on an individual basis is one of the major challenges to the future of customized, aberration-reducing ablative procedures.

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