Changes in biomechanically-corrected intraocular pressure and dynamic corneal response parameters before and after transepithelial photorefractive keratectomy and femtosecond laser-assisted laser in situ keratomileusis

Hun Lee, MD\textsuperscript{1,2}, Cynthia J. Roberts, PhD\textsuperscript{3}, Tae-im Kim, MD, PhD\textsuperscript{2}, Renato Ambrósio Jr, MD, PhD\textsuperscript{4}, Ahmed Elsheikh, PhD\textsuperscript{5}, David Sung Yong Kang, MD\textsuperscript{6}

\textbf{Affiliation:}

\textsuperscript{1}Department of Ophthalmology, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, South Korea
\textsuperscript{2}The Institute of Vision Research, Department of Ophthalmology, Yonsei University College of Medicine, Seoul, South Korea
\textsuperscript{3}Department of Ophthalmology & Visual Science and Department of Biomedical Engineering, The Ohio State University, Ohio, USA
\textsuperscript{4}Rio de Janeiro Corneal Tomography and Biomechanics Study Group, Rio de Janeiro, Brazil
\textsuperscript{5}School of Engineering, University of Liverpool, Liverpool, United Kingdom
\textsuperscript{6}Eyereum Eye Clinic, Seoul, South Korea

\textbf{Acknowledgment of grant support:} This work was partially supported by a grant of the Korean Health Technology R & D Project, Ministry of Health & Welfare, Republic of Korea (HI14C2044) and by research fund of Catholic Kwandong University International St. Mary's Hospital (CKURF-201604900001).

\textbf{Conflict of interest:} Drs Ambrósio and Roberts are consultants for and Dr. Elsheikh has received research funding from Oculus Optikgeräte GmbH. Dr. David Sung Yong Kang is
consultant to Avedro Inc. The remaining authors have no financial or proprietary interest in the materials presented herein.

Correspondence and reprint requests to:
David Sung Yong Kang, MD, Eyereum Eye Clinic, Kangnam Center Building 7Floor 825-13, Yeoksam-dong, Gangnam-gu, Seoul 06232, Korea, Tel: 82-2-3420-2020, Fax: 82-2-3420-2030, E-mail: kangeye@eyereum.com
ABSTRACT

**Purpose:** To investigate the changes in biomechanically-corrected intraocular pressure (bIOP) and new dynamic corneal response (DCR) parameters measured by corneal visualization Scheimpflug technology (Corvis ST) before and after transepithelial photorefractive keratectomy (tPRK) and femtosecond laser-assisted laser in situ keratomileusis (FS-LASIK).

**Methods:** Medical records of 129 eyes of 129 patients undergoing tPRK (n=65) or FS-LASIK (n=64) were examined. Participants underwent a complete examination before and 6 months after surgery. Main outcome variables were bIOP and DCR parameters including deformation amplitude (DA) ratio 2 mm, stiffness parameter at first applanation (SP-A1), as well as Ambrósio relational thickness through the horizontal meridian (ARTh) and integrated inverse radius at highest concavity.

**Results:** There were no statistically significant differences in bIOP before and after tPRK ($P = 0.101$) or FS-LASIK ($P = 0.138$). DA ratio 2 mm and integrated inverse radius significantly increased, while SP-A1 and ARTh decreased after tPRK and FS-LASIK (all $P < 0.001$). Changes in DA ratio 2 mm and integrated inverse radius before and after tPRK were smaller than those before and after FS-LASIK (all $P < 0.001$). With analysis of covariance, with refractive error change or corneal thickness change as a covariate, changes in DA ratio 2 mm and integrated inverse radius were smaller in tPRK than FS-LASIK (all $P < 0.001$).

**Conclusions:** The Corvis ST showed stable bIOP measurement before and after tPRK or FS-LASIK. The changes in DCR parameters before and after surgery were smaller for tPRK compared to the lamellar procedure, FS-LASIK.

**Precis:** Corvis ST showed stable bIOP measurement after tPRK and FS-LASIK. Corneas after FS-LASIK were less resistant to deformation than those after tPRK based upon smaller
changes in new DCR parameters after tPRK.

**Introductory text**

Corneal biomechanics is the response of corneal tissue to an applied force, which involves interactions between the externally applied force, the intrinsic viscoelastic properties of the cornea and the intraocular pressure (IOP). Corneal biomechanical properties are known to influence the measurement of IOP alongside the central corneal thickness (CCT), and both CCT and biomechanical response parameters are recognized as important factors in the susceptibility to the development of glaucomatous damage.

Corneal visualization Scheimpflug technology (Corvis ST; OCULUS Optikgeräte GmbH, Wetzlar, Germany), which allows *in vivo* characterization of corneal biomechanical deformation response to an applied air puff, has become a useful instrument for evaluating biomechanical response parameters of the cornea clinically. The Corvis ST captures the dynamic process of corneal deformation caused by an air puff of consistent spatial and temporal profiles using an ultra-high-speed camera that operates at 4300 frames/sec to capture a series of 140 sequential horizontal Scheimpflug images of corneal deformation. The Corvis ST enables the calculation of a variety of dynamic corneal response (DCR) parameters to characterize biomechanical response by analyzing patterns of deformation at highest concavity (HC) and applanation, both during inward deformation (loading) and during outward recovery (unloading), which have been reported to be influenced predominantly by IOP, as well as CCT and age. Recently, new corneal biomechanical parameters have been
introduced, including deformation amplitude (DA) ratio 1 mm, DA ratio 2 mm, integrated
inverse radius, stiffness parameter at first applanation (SP-A1), and ambrósio relational
thickness through the horizontal meridian (ARTh). Additionally, the Corvis ST provides a
measurement of a biomechanically-corrected IOP (bIOP) that is intended to be free of effects
of changes in corneal geometric and material stiffness parameters.

While the Corvis ST has been previously used to measure changes in corneal
biomechanical response parameters after laser vision correction procedures such as
photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK), and small incision
lenticule extraction (SMILE), as well as collagen cross-linking (CXL), the stability of the
new bIOP measurements and the significance of the new DCR parameters have not yet been
studied. Moreover, knowledge remains limited with respect to understanding how corneal
biomechanical parameters are modified according to surgical techniques.

Therefore, in the present study, we aimed to assess the stability of the recently
introduced bIOP estimates, and evaluate the changes in the new DCR parameters obtained
from the Corvis ST after transepithelial PRK (tPRK) and femtosecond laser-assisted LASIK
(FS-LASIK) procedures.

Materials and Methods

We performed a retrospective, comparative, observational case series with the
approval of the Institutional Review Board of Yonsei University College of Medicine (Seoul,
South Korea). The study adhered to the tenets of the Declaration of Helsinki and followed
good clinical practices. All patients provided written informed consent for their medical
information to be included in the study.

Patients included in the study were older than 20 years of age and underwent tPRK
or FS-LASIK using standardized techniques performed by the same surgeon (DSYK)
between May 2014 and April 2015. We excluded patients with previous ocular or intraocular surgery, ocular abnormalities other than myopia or myopic astigmatism with a corrected distance visual acuity (CDVA) of 1.00 (20/20 Snellen) or better in both eyes, corneal endothelial cell density of less than 2000 cells/mm$^2$, cataract, ocular inflammation, infection, or moderate and severe dry eye. We also excluded patients with signs of keratoconus on Scheimpflug tomography (displacement of the corneal apex, decrease in thinnest-point pachymetry, and asymmetric topographic pattern). We retrospectively reviewed the medical records of 129 eyes of 129 patients that met the inclusion and exclusion criteria. Only one randomly selected eye from each patient was included in the analysis.

**Examinations and Measurements**

Before and 6 months after surgery, all patients underwent complete ophthalmic examinations, including uncorrected distance visual acuity (UDVA) and CDVA, manifest refraction, slit-lamp examination (Haag-Streit, Gartenstadtstrasse, Köniz, Switzerland), corneal volume (Pentacam; OCULUS Optikgeräte GmbH), IOP-NCT (noncontact tonometer; NT-530, NCT Nidek Co., Ltd., Aichi, Japan), and fundus examination. In addition, the DCR parameters were measured using the Corvis ST. All measurements were performed by the same investigator to eliminate possible inter-observer variability, and taken at approximately the same time of day. Each measurement was performed three times and the average value was used in the analysis. The Corvis ST automatically calculated applanation time, applanation length and applanation velocity during three distinct phases; first applanation (A1; the cornea was flattened for the first time in the inward direction), highest concavity, and second applanation (A2; the cornea was flattened for the second time during recovery from the highest concavity). The DA measured at HC, peak distance, radius, and CCT were also recorded.
New DCR parameters include the DA ratio 2 mm, integrated inverse radius, ARTh, and SP-A1. DA ratio 2 mm represents the ratio between the DA of the apex and the average of two points located 2 mm on either side of the apex. The integrated inverse radius came from the integration of the inverse radius values that represent the central concave curvature at the highest concavity. The Corvis ST provides data for calculating the rate of increase of corneal thickness from the apex towards nasal and temporal sides. Via the characterization of the thickness data on the horizontal Scheimpflug image, the Corvis ST enables the calculation of the new corneal thickness index, the ARTh. Lower ARTh indicates a thinner cornea and/or a faster thickness increase toward the periphery. The SP-A1 is defined as applied load divided by displacement, in an analogous manner to one dimensional stiffness. The applied load is the air pressure, calculated at first applanation, minus bIOP. The displacement is the distance the corneal apex moves from the pre-deformation state to A1.

Together with DCR parameters, the Corvis ST provides a new and validated bIOP estimate that is intended to offer an estimate of true IOP or the corrected value of measured IOP, which considers the biomechanical response of the cornea to air pressure including the effects of variation in CCT and material behavior. The algorithm for bIOP is based on numerical simulation of the Corvis ST procedure, as applied on human eye models with different tomographies (including thickness profiles), material properties and true IOPs. The eye models were developed for analysis using the finite element method and designed to simulate important biomechanical features of the eye, including the cornea’s aspheric topography, the cornea’s variable thickness, low stiffness of epithelium and endothelium, the cornea’s weak inter-laminar adhesion, and the tissue’s hyperelasticity, hysteresis and age-related stiffening. The bIOP formula used in the Corvis ST was a modified algorithm of the published formula.
Surgical Techniques

Trans epithelial photorefractive keratectomy

Photoablation was performed using an excimer laser (Amaris 1050 Excimer Laser platform; Schwind eye-tech-solutions GmbH and Co KG, Kleinostheim, Germany), which uses a flying-spot laser with a repetition rate of 1050 Hz. Ablation profile planning was carried out using the integrated Optimized Refractive Keratectomy-Custom Ablation Manager software (version 5.1; Schwind eye-tech-solutions GmbH and Co KG). Mitomycin 0.02% was applied to all corneas for 20 seconds followed by thorough rinsing with chilled balanced salt solution (BSS). Postoperatively, 1 drop of topical levofloxacin 0.5% (Cravit; Santen Pharmaceutical, Osaka, Japan) was instilled at the surgical site, and a bandage contact lens (Acuvue Oasys; Johnson & Johnson Vision Care, Inc, Jacksonville, FL, USA) was placed on the cornea. Following surgery, topical levofloxacin 0.5% and fluorometholone 0.1% (Flumetholon; Santen Pharmaceutical) were applied 4 times per day for 1 month. The dosage was tapered over 3 months.

Femtosecond laser-assisted Laser in situ keratomileusis

The VisuMax femtosecond laser system with a repetition rate of 500 kHz was used to create the flap. The flaps had diameters of 8.1 mm and thicknesses of 100 µm with standard 90° hinges and 90° side-cut angles. The lamellar and side cuts were achieved with energies of 185 nJ. Stromal tissue ablation was performed with the Amaris 1050 Excimer Laser platform with a repetition rate of 1050 kHz. Flaps were repositioned after the excimer laser treatment and a bandage contact lens was placed on the cornea for 1 day. Topical fluorometholone 0.1% was used initially eight times daily and tapered for a period of 20 days. Topical levofloxacin 0.5% was used four times daily for 7 days.
Statistical analysis was performed using SPSS software version 22.0 (IBM, Armonk, NY, USA). Differences were considered statistically significant when the \( P \) values were less than 0.05. The results are expressed as the mean ± standard deviation. The Kolmogorov-Smirnov test was used to confirm data normality. To statistically compare preoperative and postoperative data between tPRK and FS-LASIK, we used independent \( t \)-test for continuous variables and \( \chi^2 \) test for categorical variables. We performed the paired \( t \)-test to evaluate the differences between preoperative and 6-month postoperative parameters including IOP-NCT, bIOP, Corvis-CCT, corneal volume, and DCR parameters in each group. Simple linear regression analysis was used to determine the relationship between changes (\( \Delta \)) in DCR parameters or bIOP, and \( \Delta \) manifest refraction spherical equivalent (MRSE), \( \Delta \)CCT, \( \Delta \) corneal volume, or \( \Delta \)ARTh in each group. Furthermore, we performed analysis of covariance (ANCOVA) to compare changes (\( \Delta \)) in DCR parameters between tPRK and FS-LASIK, with the \( \Delta \)MRSE, \( \Delta \)CCT, \( \Delta \) corneal volume, or \( \Delta \)ARTh as a covariate.

Results

Data were collected from 129 eyes of 129 normal healthy participants with mean age of 28.1±5.4 years (range, 20 to 41 years). Table 1 shows the preoperative characteristics of the two participant groups with no significant statistical difference between them as regards age, gender, preoperative sphere, cylinder, spherical equivalent, CCT, and optical zone.

Table 2 summarizes the changes in IOP-NCT, bIOP, Corvis-CCT, and corneal volume before and after tPRK or FS-LASIK. The bIOP was stable before and after tPRK and FS-LASIK (mean difference = 0.30±1.45 mmHg, \( P = 0.101 \) for tPRK, and mean difference = -0.26±1.41 mmHg, \( P = 0.138 \) for FS-LASIK). In each group, changes in bIOP before and after surgery were significantly smaller than those in IOP-NCT before and after surgery (all \( P \)
When combining the two forms of laser vision surgery, difference in bIOP before and after surgery was only $0.02 \pm 1.45$ mmHg ($P = 0.875$). These values were significantly smaller than those from IOP-NCT ($0.02 \pm 1.45$ mmHg versus $-2.33 \pm 1.54$ mmHg, $P < 0.001$).

Table 3 summarizes the changes in DCR parameters before and after tPRK and FS-LASIK. There were no significant differences in preoperative DCR parameters between tPRK and FS-LASIK groups. The differences in parameter values, as estimated pre and postoperatively, were significant in the two groups (all $P < 0.001$). The DA ratio 2 mm and integrated inverse radius significantly increased, while SP-A1 and ARTh significantly decreased after surgery. Results showed that $\Delta$DA ratio 2 mm and $\Delta$ integrated inverse radius were smaller in tPRK than FS-LASIK (all $P < 0.001$).

Figure 1 demonstrates the scatter plots and results for simple linear regression analysis between changes ($\Delta$) in DCR parameters or bIOP, and $\Delta$MRSE, $\Delta$CCT, $\Delta$ corneal volume, or $\Delta$ARTh between the two groups. The parameter showing the strongest relationships with $\Delta$MRSE, indicated by the $r^2$ values, was $\Delta$ integrated inverse radius, followed by $\Delta$ARTh, $\Delta$DA ratio 2 mm, and finally $\Delta$SP-A1, in tPRK group. For the FS-LASIK group, the parameter showing the strongest relationships with $\Delta$MRSE was $\Delta$DA ratio 2, followed by $\Delta$ integrated inverse radius and $\Delta$SP-A1. Further, the parameter showing the strongest relationships with $\Delta$CCT was $\Delta$integrated inverse radius, followed by $\Delta$ARTh, $\Delta$DA ratio 2 mm, and finally $\Delta$SP-A1, in tPRK group, while it was $\Delta$DA ratio 2, followed by $\Delta$SP-A1, $\Delta$ integrated inverse radius, and finally $\Delta$ARTh in the FS-LASIK group.

When comparing the changes in DCR parameters between the two groups with ANCOVA and $\Delta$MRSE, $\Delta$CCT, $\Delta$ corneal volume, or $\Delta$ARTh as a covariate, there were significant differences in $\Delta$DA ratio 2 mm and $\Delta$ integrated inverse radius (all $P < 0.001$; Table 4). $\Delta$DA ratio 2 mm and $\Delta$ integrated inverse radius were significantly smaller in tPRK than FS-LASIK (all $P < 0.001$). No significant differences were noted in $\Delta$SP-A1 or $\Delta$ARTh.
between the two groups.

**Discussion**

In the present study, we investigated the changes in bIOP and newly developed DCR parameters before and after tPRK and FS-LASIK. Most notably, the bIOP obtained from the Corvis ST was stable before and after laser vision correction surgery, without a clinically or statistically significant difference in the mean. Earlier work has shown that variations in CCT can introduce inaccuracies in IOP measurements using different forms of tonometry\textsuperscript{24,25}, and that corneal biomechanical properties may even have a greater impact on IOP measurements than CCT.\textsuperscript{3,7} In fact, the tangent modulus (a measure of material stiffness) has been reported to determine the relationship between the CCT and IOP measurement error in applanation tonometry, with stiffer corneas having the strongest relationship between CCT and IOP measurement error.\textsuperscript{3,7}

With laser vision surgery, in addition to the CCT reduction caused by tissue ablation, softening of tissue would be expected due to the separation of the flap in FS-LASIK. However, the fact that bIOP measurements remained almost unaltered after surgery is an indication that bIOP estimates are less influenced by changes in both CCT and material properties than the uncorrected IOP measurements.\textsuperscript{15} These results are compatible with an earlier study using a database involving 634 healthy eyes where application of the bIOP algorithm led to weaker associations of IOP measurements with both CCT (from $r^2 = 0.204$, 3.06 mmHg/100 microns to $r^2 = 0.005$, 0.04 mmHg/100 microns) and age (from $r^2 = 0.009$, 0.24 mmHg/decade to $r^2 = 0.002$, 0.09 mmHg/decade).\textsuperscript{22}

In the present study, postoperative changes in DA ratio 2 mm and integrated inverse radius after tPRK are significantly smaller than those for FS-LASIK. The original parameter DA is defined as the maximum amplitude when the cornea is deformed to its greatest concave
curvature by an air puff and is influenced by corneal stiffness.\textsuperscript{26} It is well known that thinner corneas have a tendency to demonstrate higher DA than thicker corneas with similar IOP.\textsuperscript{26} In a previous study investigating the differences in corneal deformation parameters after SMILE, laser-assisted subepithelial keratomileusis (LASEK) and FS-LASIK with adjustment for age, preoperative CCT and MRSE, postoperative DA in the FS-LASIK was significantly higher than in the LASEK.\textsuperscript{16} Considering that DA ratio 2 mm represents the ratio between DA at the apex and the average of two points located 2 mm on either side of the apex, our current results that changes in DA ratio 2 mm – after adjustment for changes in refractive error, corneal thickness, corneal volume, or ARTh – are significantly smaller in tPRK than FS-LASIK are in line with the previous study. Both studies indicate that the corneas after FS-LASIK were less resistant to deformation than those after surface ablations such as PRK and LASEK. Since PRK did not create a flap (as in LASIK), its effect on the corneal structural integrity is less than with the LASIK.\textsuperscript{27,28,29}

The major structural change in any type of laser vision correction is the tissue removed to generate the refractive effect, regardless of whether it is ablated from the surface or under a flap. Evidence is the similar change in the stiffness parameter, SP-A1 between the two groups. It is expected that this tissue removal generates the majority of the biomechanical response and its location at the surface or within the corneal depth have smaller effects on the biomechanics. The current study indicates that surface ablation has the smallest additional effect on corneal biomechanics, consistent with the literature and evidenced by the smaller changes in DA ratio 2 mm and integrated inverse radius, as discussed. Moreover, in case of the tPRK, there were strong relationships between new DCR parameters (\(\Delta\)DA ratio 2 mm, \(\Delta\)SP-A1, \(\Delta\)ARTh, and \(\Delta\) integrated inverse radius) and refractive error change or corneal thickness change, when compared with the FS-LASIK.

We performed the ANCOVA with corneal thickness change as a co-factor because
corneal thickness is known to be an important factor affecting the biomechanical response of
the cornea. In our study, corneal thickness change was found to be a moderate, but
significant confounder. In terms of IOP, we showed that bIOP obtained from the Corvis ST,
which is already adjusted for corneal thickness and corneal biomechanical response, was
stable before and after tPRK and FS-LASIK, demonstrating no significant difference. Thus,
we did not include changes in bIOP as a co-factor during the ANCOVA analysis.

The present study had limitations in its retrospective design and the relatively short
follow up time of 6 months. While the study presented significant evidence on the stability of
bIOP and validity of DCR parameters, a larger sample size and longer follow up would allow
a more thorough biomechanical comparison between laser vision surgery procedures. This
will be done within a prospective controlled comparative paired-eye study comparing several
laser vision surgeries.

In summary, we demonstrated the reliability of the bIOP estimates obtained by the
Corvis ST through the stability of its measurement following surface ablation or lamellar
procedure. This result indicated the reduced effect of changes in corneal thickness and
material behavior on bIOP measurements, compared to uncorrected IOP estimates. Most
notably, changes in corneal structural integrity in tPRK are significantly less than those in FS-
LASIK. The study also showed that new DCR parameters, such as DA ratio 2 mm, SP-A1,
ARTh, and integrated inverse radius, can be helpful as reliable measures of the biomechanical
changes in the cornea caused by laser vision surgery.

References

mechanical spectroscopy of the cornea for measurement of its viscoelastic properties


**Figure captions**

Figure 1. Scatter plots and results for simple linear regression analysis between changes in
dynamic corneal response parameters or biomechanically-corrected intraocular pressure, and changes in refractive error change, corneal thickness change, corneal volume change, or ambrósio relational thickness through the horizontal meridian change between transepithelial photorefractive keratectomy and femtosecond laser-assisted laser in situ keratomileusis. tPRK, transepithelial photorefractive keratectomy; FS-LASIK, femtosecond laser-assisted laser in situ keratomileusis; DA, deformation amplitude; MRSE, manifest refraction spherical equivalent; CCT, central corneal thickness; ARTh, ambrósio relational thickness through the horizontal meridian; SP-A1, stiffness parameter at first applanation; bIOP, biomechanically-corrected intraocular pressure.