

# Interaction between diurnal variations of intraocular pressure, pachymetry, and corneal response to an air puff: Preliminary evidence

Miguel A. Ariza-Gracia, PhD, David P. Piñero, PhD, José F. Rodríguez, PhD, Rafael J. Pérez-Cambrodí, OD, PhD, Begoña Calvo, PhD

In recent years, devices that measure the corneal biomechanics in clinical practice have been developed and released.<sup>1</sup> All the devices are based on analysis of the corneal deformation response to an air puff. However, this deformation is influenced not only by

the biomechanical properties of the cornea, but also by the intraocular pressure (IOP) and the corneal thickness. Therefore, IOP and corneal thickness should be considered when analyzing the results obtained with the devices.<sup>2</sup>

Submitted: October 8, 2014.

Final revision submitted: December 4, 2014.

Accepted: December 6, 2014.

From the Engineering Research Institute of Aragón (Ariza-Gracia, Rodríguez, Calvo), University of Zaragoza, and Bioengineering (Rodríguez, Calvo), Biomaterials and Nanomedicine Online Biomedical Research Center, Zaragoza, and the Department of Ophthalmology (Piñero, Pérez-Cambrodí), Medimar International Hospital and the Department of Optics (Piñero), Pharmacology and Anatomy, University of Alicante, Spain.

Supported by the European Union's Seventh Framework Program managed by Research Executive Agency under Grant Agreement number FP7-SME-2013 606634 (POPCORN Project) and the Spanish Ministry of Economy and Competitiveness (DPI2011-27939-C02-01).

Corresponding author: David P. Piñero, PhD, Oftalmar, Department of Ophthalmology, Medimar International Hospital, C/Padre Arrupe, 20, 03016 Alicante, Spain. E-mail: dpinero@oftalmar.es.

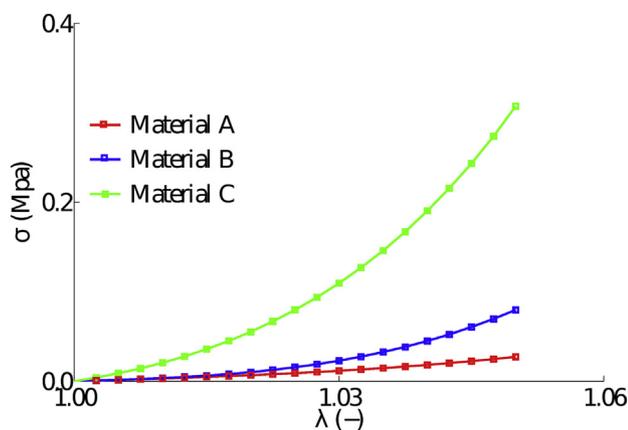
Because IOP and corneal thickness vary during the day in every individual, they are expected to have a clinical relevance to measurements of the corneal biomechanical properties. Kida et al.<sup>3</sup> found that corneal hysteresis (CH) measured with a dynamic bidirectional applanation device (Ocular Response Analyzer, Reichert Technologies) showed an inconsistent 24-hour variation, with no evidence of being influenced by 24-hour changes in IOP. A similar finding was reported by Shen et al.<sup>4</sup> However, González-Méjome et al.<sup>5</sup> found that changes in CH measured with the same device correlated well with changes in IOP, suggesting that diurnal IOP variations could be related to changes in corneal biomechanics. Likewise, Lau and Pye<sup>6</sup> suggested that diurnal variations in central corneal thickness (CCT) and corneal resistance factor (CRF) measured with the dynamic bidirectional applanation device may significantly affect the tonometry measurements.

This case report shows preliminary numerical results about the interaction between pachymetric and

IOP diurnal changes in 1 healthy eye and its potential relationship to corneal deformation during air puff. Numerical simulations correspond to 3 levels of corneal stiffness. The main objective of this analysis was to show how the IOP fluctuations during a short period of time might generate different results when the mechanical corneal behavior is analyzed by a device based on the use of an air-puff load (eg, non-contact tonometry). This variability might lead to inconsistent clinical decisions. Currently available devices for measuring the corneal biomechanical properties in clinical practice are based on analysis of the corneal response to an air puff, and we should know the limitations of the technology that we use in our daily routine. For this purpose, a topography system providing consistent elevation and pachymetric measurements<sup>7</sup> was used as well as a patient-specific finite element model of the patient's cornea.<sup>8,9</sup>

## CASE REPORT

Corneal geometry, CCT, and IOP in a 50-year-old subject were recorded 5 times during the same morning; ie, corneal topography, pachymetry, and Goldmann applanation tonometry (1 mm Hg steps) were measured. Corneal topography and pachymetry were measured using a Scheimpflug photography-based system (Pentacam, version 1.14r01, Oculus Optikgeräte GmbH). This system provides reproducible and repeatable corneal thickness measurements in 1  $\mu\text{m}$  steps. With the available topographical data, a patient-specific finite element model of the patient's cornea was built taking into account 3 levels of corneal stiffness (Figure 1). A simulation of noncontact tonometry was then performed to obtain the high-concavity displacement of the corneal apex when an air load was applied. Noncontact tonometry is the basis of the currently available devices that measure corneal biomechanical properties in clinical practice, such as the dynamic bidirectional applanation device and the dynamic Scheimpflug analyzer device (Corvis, Oculus Optikgeräte GmbH).



**Figure 1.** Stress versus stretch curves corresponding to the 3 levels of corneal stiffness simulated and evaluated: low (*material A*), intermediate (*material B*), and high (*material C*) stiffness. The curves were obtained in uniaxial Cauchy experiments of pig corneas and adjusted by the Gasser-Holzapfel-Ogden model.

**Table 1.** Diurnal changes in IOP, CCT, and simulated high concavity displacement assuming a medium corneal stiffness (material B).

Variable	8:15 AM	10:00 AM	11:30 AM	13:00 PM	14:30 PM
IOP (mm Hg)	10	11.5	10	10	9
CCT ( $\mu\text{m}$ )	505	501	509	516	512
U (mm)	1.199	1.170	1.175	1.150	1.185

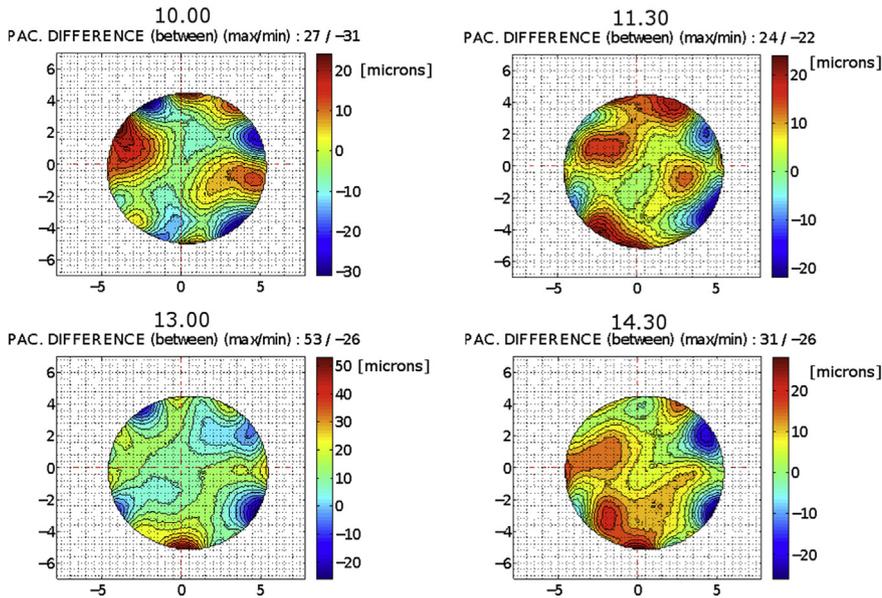
CCT = central corneal thickness; IOP = intraocular pressure; U = high concavity displacement

Table 1 summarizes the results of the diurnal corneal monitoring in the evaluated eye. As shown, the CCT and the IOP varied during the evaluation period. Similarly, as shown in Figure 2, there were localized differences in corneal thickness over some corneal areas and not only at the center. According to the results in Table 1, a close relationship between IOP, CCT, and numerical high-concavity displacement seems to exist with the corneal response at different moments of the day. Simulations with a cornea of intermediate stiffness revealed that the apex displacement due to the air puff was maximal when the IOP and the CCT were lower than their median values (Figure 2). When IOP was maximal and pachymetry was minimal, a median corneal displacement was achieved; the displacement was minimal when pachymetry was maximal and IOP was around its median value. Therefore, interplay between the pachymetry, the IOP, and the corneal displacement in response to an air puff is present, with more significant influence of pachymetry over IOP for the level of corneal displacement obtained in the simulations.

Characterizing corneal biomechanics by analyzing the corneal displacement in response to an air puff seems to be subject to some level of variability depending on the time of day at which the measurement is taken (Figure 3). A diurnal variation of approximately 30% was found for IOP, whereas a variation close to 4% was found for pachymetry. Numerical simulations revealed a corneal displacement variation of about 5%. Our simulations also indicate larger variability when a cornea of low stiffness is considered (Figure 3).

## DISCUSSION

There is an increasing interest in corneal biomechanics due to the development of new refractive surgery techniques aimed at modifying corneal properties, as well as to the development of a wide variety of surgical options for corneal ectasia management.<sup>1</sup> For this reason, significant research in corneal biomechanics has been done during the past few years, with important efforts made to develop a device for noninvasive in vivo measurement of the biomechanical properties of the human cornea. The use of an air puff as a load to apply on the cornea and analysis of the deformation induced by this type of load is the basis of the 2 currently available devices for characterizing the corneal biomechanical properties in clinical practice. Despite the ability to identify some cases in which a biomechanical alteration is present, there is a significant limitation in the



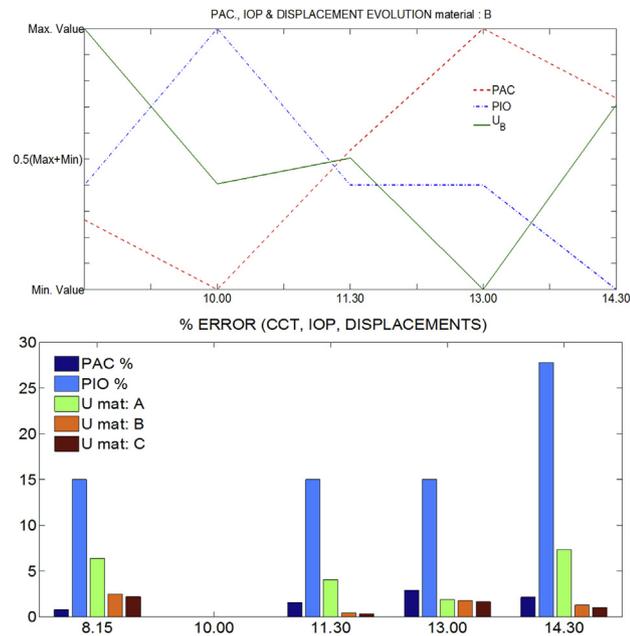
**Figure 2.** Topographic maps showing changes in pachymetry using the first measurement taken (8:15 AM) as a reference.

sensitivity of measurements that detect corneal biomechanical alterations.<sup>1</sup> The main factors in this are the use of nonstandardized and not well understood parameters for characterizing the corneal biomechanics

and the potential coupling of corneal thickness and IOP with these parameters.

The dynamic bidirectional applanation device measures the CH parameter, which is the difference between 2 pressure values recorded during a bidirectional air-puff applanation. According to simulations performed with a viscoelastic model (a 3-component spring and dashpot model) to analyze the impact of changing viscosity and elasticity on CH, low CH could be associated with high elasticity or low elasticity depending on the viscosity.<sup>10</sup> Furthermore, CH has been shown to be moderately correlated with IOP and CCT.<sup>11</sup> The dynamic Scheimpflug analyzer device is a noncontact tonometer that enables monitoring the corneal reaction to an air impulse by means of a high-speed Scheimpflug camera (4330 frames/sec).<sup>1</sup> The device measures biomechanical parameters such as deformation amplitude or first applanation time.<sup>1</sup> These parameters have been shown to be correlated with IOP and pachymetry. Huseynova et al.<sup>12</sup> found a low but significant correlation between IOP and the deformation amplitude of the cornea ( $r = -0.36$ ,  $P < .0001$ ), applanation time ( $r = -0.54$ ,  $P < .0001$ ), and applanation velocity ( $r = -0.118$ ,  $P < .0001$ ). Unfortunately, their study did not show a correlation between CCT and the deformation amplitude of the cornea.

Our preliminary results support the observation of a weak correlation between IOP and the maximum deformation amplitude of the cornea. However, our results also point to a clear interplay between IOP and CCT on the maximum corneal displacement when subjected to an air puff. The case report shows that in a healthy cornea, the variability in the maximum



**Figure 3.** Top panel: Changes in IOP (dashed blue line), apex pachymetry (dashed red line), and high-concavity displacement (green line) assuming a medium level of corneal stiffness (material B). All displayed values have been normalized by using the minimum and maximum values to evaluate trends. Bottom panel: Differences in pachymetry (dark blue bars), IOP (light blue bars), and high-concavity displacement (material A, green bars; material B, orange bars; and material C, brown bars) during the monitoring period using the time point registering the highest IOP value (10:00 AM) as a reference.

corneal displacement can reach 5% during the day depending on the level of stiffness of the cornea evaluated. This variation was close to the observed variation in corneal pachymetry (between 3% and 4%), while the observed variation in IOP was larger than 25%.

The variation in maximum corneal displacement that occurs during the day may limit the diagnostic ability to detect small biomechanical alterations from the corneal deformation in response to an air impulse, as may happen in the initial stages of keratoconus. Therefore, the time at which measurements are taken with air puff-based devices must be recorded and taken into consideration. In this case, less variability was observed from 10:00 AM to 1:00 PM. This agrees with results in studies of IOP variability in the circadian cycle in healthy subjects.<sup>13</sup> However, a larger number of patients is required to confirm this observation. In addition, the study should consider different types of corneas, not only healthy ones. Glaucoma patients do not follow this circadian pattern and have more IOP variability.<sup>13</sup>

In conclusion, the corneal deformation response to an air puff is dependent on IOP and pachymetry and not only on the biomechanical properties of the cornea. Therefore, this deformation by itself cannot be considered a parameter that accurately characterizes the biomechanical behavior of a specific cornea. Diurnal changes in IOP and corneal thickness are able to induce some variability in the air puff-based corneal deformation that can potentially lead to inaccurate clinical decisions. Additional studies are required to confirm this preliminary evidence, particularly studies that include eyes with well-known biomechanical alterations (advanced keratoconus) and with significant 24-hour changes in IOP.

## REFERENCES

1. Piñero DP, Alcón N. In vivo characterization of corneal biomechanics. *J Cataract Refract Surg* 2014; 40:870–877
2. Kling S, Bekesi N, Dorronsoro C, Pascual D, Marcos S. Corneal viscoelastic properties from finite-element analysis of in vivo air-puff deformation. *PLoS One* 2014; 9(8):e104904. Available at: <http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0104904&representation=PDF>. Accessed December 16, 2014
3. Kida T, Liu JHK, Weinreb RN. Effect of 24-hour corneal biomechanical changes on intraocular pressure measurement. *Invest Ophthalmol Vis Sci* 2006; 47:4422–4426. Available at: <http://www.iovs.org/cgi/reprint/47/10/4422>. Accessed December 16, 2014
4. Shen M, Wang J, Qu J, Xu S, Wang X, Fang H, Lu F. Diurnal variation of ocular hysteresis, corneal thickness, and intraocular pressure. *Optom Vis Sci* 2008; 85:1185–1192. Available at: [http://journals.lww.com/optvissci/Fulltext/2008/12000/Diurnal\\_Variation\\_of\\_Ocular\\_Hysteresis,\\_Corneal.12.aspx](http://journals.lww.com/optvissci/Fulltext/2008/12000/Diurnal_Variation_of_Ocular_Hysteresis,_Corneal.12.aspx). Accessed December 16, 2014
5. González-Méijome JM, Queirós A, Jorge J, Díaz-Rey A, Parafita MA. Intraoffice variability of corneal biomechanical parameters and intraocular pressure (IOP). *Optom Vis Sci* 2008; 85:457–462. Available at: [http://journals.lww.com/optvissci/Fulltext/2008/06000/Intraoffice\\_Variability\\_of\\_Corneal\\_Biomechanical.17.aspx](http://journals.lww.com/optvissci/Fulltext/2008/06000/Intraoffice_Variability_of_Corneal_Biomechanical.17.aspx). Accessed December 16, 2014
6. Lau W, Pye DC. Associations between diurnal changes in Goldmann tonometry, corneal geometry, and ocular response analyzer parameters. *Cornea* 2012; 31:639–644
7. Lackner B, Schmidinger G, Pieh S, Funovics MA, Skorpik C. Repeatability and reproducibility of central corneal thickness measurement with Pentacam, Orbscan, and ultrasound. *Optom Vis Sci* 2005; 82:892–899. Available at: [http://www.oculus.de/ch/downloads/dyn/sonstige/sonstige/lackner\\_pachymetry.pdf](http://www.oculus.de/ch/downloads/dyn/sonstige/sonstige/lackner_pachymetry.pdf). Accessed December 16, 2014
8. Alastrué V, Calvo B, Peña E, Doblaré M. Biomechanical modeling of refractive corneal surgery. *J Biomech Eng* 2006; 128:150–160
9. Pinsky PM, Datye DV. A microstructurally-based finite element model of the incised human cornea. *J Biomed* 1991; 24:907–922
10. Glass DH, Roberts CJ, Litsky AS, Weber PA. A viscoelastic biomechanical model of the cornea describing the effect of viscosity and elasticity on hysteresis. *Invest Ophthalmol Vis Sci* 2008; 49:3919–3926. Available at: <http://www.iovs.org/cgi/reprint/49/9/3919>. Accessed December 16, 2014
11. Touboul D, Roberts C, Kérautret J, Garra C, Maurice-Tison S, Saubusse E, Colin J. Correlations between corneal hysteresis, intraocular pressure, and corneal central pachymetry. *J Cataract Refract Surg* 2008; 34:616–622
12. Huseynova T, Waring GO IV, Roberts C, Krueger RR, Tomita M. Corneal biomechanics as a function of intraocular pressure and pachymetry by dynamic infrared signal and Scheimpflug imaging analysis in normal eyes. *Am J Ophthalmol* 2014; 157:885–893
13. Agnifili L, Mastropasqua R, Frezzotti P, Fasanella V, Motolese I, Pedrotti E, Di Iorio A, Mattei PA, Motolese E, Mastropasqua L. Circadian intraocular pressure patterns in healthy subjects, primary open angle and normal tension glaucoma patients with a contact lens sensor. *Acta Ophthalmol* 2014 Apr 10 [Epub ahead of print]