This guest editorial is one of a series looking back at landmark articles published in the JCRS. This special series commemorates the 25th anniversary of the joint Journal of Cataract & Refractive Surgery. This issue: Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. J Cataract Refract Surg 2005;31:156–162.

The publication of Dave Luce’s visionary article on corneal hysteresis (CH), a new biomechanical parameter produced by the ocular response analyzer (ORA), not only sparked a completely new line of inquiry but also made corneal biomechanics relevant for the clinician. The ORA was the first clinical tool that allowed studies of biomechanics in multiple subspecialties across the globe, from keratoconus and refractive surgery to glaucoma. Prior to 2005, ocular biomechanics were analyzed with ex vivo models and computer simulations. After 2005, clinicians developed new collaborations with basic scientists and engineers as they sought to understand how biomechanics affected disease development and progression in a pressurized, fluid-filled shell and how biomechanical response to surgical interventions affected outcomes. Since 2005, nearly 800 clinical articles that directly investigated CH in cross-sectional and longitudinal studies have been published. Many biomechanical technical articles have also been published including advanced algorithms based on deep learning and artificial intelligence, all of which advance our understanding in this important field.

Ocular biomechanical assessment quantifies the response to an applied load. That load can be destructive, as in ex vivo studies, or nondestructive to be of clinical value. For the ORA, an air puff is used to deform the cornea, making it function also as a noncontact tonometer. It is important to understand what CH represents and what it does not. It does not correspond to stiffness or elastic modulus, as is often misinterpreted in the literature. It does not represent elastic resistance to deformation. Low CH can be associated with a more compliant cornea, as in keratoconus, or with a stiffer cornea, as with aging or higher intraocular pressure (IOP). The inverse relationship with IOP is well documented, such that CH is reduced as IOP increases. CH is a viscoelastic parameter that represents the different pathways between loading and unloading, such that the applanation pressure inward is greater than the unloading applanation pressure in the outward direction due to energy dissipation in the viscoelastic material. For example, a stiffer eye with higher IOP is less capable of dissipating energy, resulting in lower CH. Both viscous and elastic responses contribute to CH, and different proportions can result in similar CH. This is likely the reason that CH is not different 1 year after crosslinking (CXL) the keratoconic cornea, despite evidence of stiffening in the infrared and pressure signals. Both the first and second applanation pressures increase after CXL, without a change in the difference between them, which is the formula for CH (Figure 1). The elastic changes that represent stiffening are masked by the viscous changes that are also induced with CXL. Analysis of the pressure and infrared signals or waveform of the ORA provides additional important information regarding biomechanics of response, as illustrated with the CXL example. Custom signal analysis was first reported in

![Figure 1. Ocular response analyzer examination from a keratoconic subject, prior to CXL in red, and 1 year after CXL in blue. Note that both the loading Peak 1 and unloading Peak 2 are substantially greater post-CXL, indicating substantial stiffening; in addition, the blue post-CXL pressure curve is greater than the red pre-CXL pressure curve, also consistent with stiffening. However, inward applanation pressure, P1, and outward applanation pressure, P2, both increased such that the difference between them is not substantially altered. Since CH is P1–P2, there is no change in CH despite obvious indications of stiffening. CH is affected by both elastic and viscous modifications to the tissue, and in the case of CXL, the elastic modifications are masked by the viscous modifications. CH = corneal hysteresis; CXL = corneal crosslinking; FWHM2 = Full Width Half Maximum of Peak 2; Time1 = 1st applanation time; Time2 = 2nd applanation time](https://doi.org/10.1097/j.jcrs.0000000000000626)
comparing contralateral eyes after a refractive procedure, one of which was stable and one of which was unstable with evolving iatrogenic ectasia. The unstable eye is in the top row with the corresponding ORA examination on the right. The contralateral stable eye is in the bottom row with the corresponding ORA examination on the right. Note the corneal hysteresis is quite similar between both eyes. However, the amplitudes of Peak 1 and Peak 2 are substantially lower in the top row unstable eye, consistent with evolving iatrogenic ectasia indicated by the corresponding tomography showing increased central elevation on both the anterior (upper left) and posterior (upper right) surfaces, increased curvature (lower left) and corresponding decreased pachymetry (lower right). ORA = ocular response analyzer

Figure 2. Orbscan corneal tomography 2 years after bilateral LASIK in the left column, adapted from Kérautret et al. The unstable eye is in the top row with the corresponding ORA examination on the right. The contralateral stable eye is in the bottom row with the corresponding ORA examination on the right. Note the corneal hysteresis is quite similar between both eyes. However, the amplitudes of Peak 1 and Peak 2 are substantially lower in the top row unstable eye, consistent with evolving iatrogenic ectasia indicated by the corresponding tomography showing increased central elevation on both the anterior (upper left) and posterior (upper right) surfaces, increased curvature (lower left) and corresponding decreased pachymetry (lower right). ORA = ocular response analyzer.

Figure 3. Box plot analysis of the 11 significantly different waveform-derived values from the ocular response analyzer, between eyes with a scleral buckle to treat retinal detachment and the untreated fellow eyes, using the dataset from Taroni et al. All values contained a component of the unloading phase of the air puff–induced deformation, including the 3 standard parameters (IOPcc, CRF, and CH) in the top row, which were calculated from the inward and outward applanation pressures and the remaining 8 waveform parameters were associated with Peak 2. No waveform parameters associated with Peak 1 during the loading phase were significantly different between the fellow eyes. It is proposed that this is driven by the significantly stiffer sclera in the treated eyes, which drove a faster recovery from concave to convex. CH = corneal hysteresis; CRF = corneal resistance factor; IOPcc = corneal-compensated intraocular pressure.
Investigators have reported that low CH is predictive of glaucomatous damage cross-sectionally and glaucomatous progression in longitudinal studies. However, an important question that arises with these associations is how a biomechanical parameter of the cornea is connected to damage at the optic nerve? It has been suggested that the biomechanical response of the cornea may be a surrogate for the biomechanics at the back of the eye. However, there is recent evidence that the sclera contributes to the measured corneal response. In a comparison of contralateral eyes of 18 subjects, where one eye received a scleral buckle to treat retinal detachment, it was reported that the treated eyes with much stiffer sclera, resulted in a significantly lower CH than the fellow eyes with no treatment. There was no statistically significant difference in IOP measured with Goldmann applanation tonometry between eyes. In analysis of the ORA waveform using custom software, it was found that 2 signal features were different, including a shorter Time2 indicating an abbreviated recovery, and smaller Full Width Half Max2 of the second peak indicating greater velocity in the recovery or unloading phase. Figure 3 shows the result of further analysis using the 38 waveform-derived parameters developed by the manufacturer. Of the 11 significantly different values between treated and untreated eyes, 3 were standard reported parameters that included both loading and unloading applanation pressures, and 8 were waveform parameters that were all associated with the second peak in the unloading phase. Specifically, a stiffer sclera resulted in increased aspect2, which is the second peak aspect ratio (height/width) and the length of this peak’s perimeter (path2). The greater aspect ratio included a lower peak width (w2) and higher slopes of peak rise and fall (uslope2 and dslope2), all indicating rapid corneal movement, and lower area under the second peak (p2area). In other words, the stiffer sclera drove a faster recovery of the concavity to the natural convex shape.

The scleral influence on corneal response to an air puff is consistent with ex vivo and modeling studies, which demonstrate that a stiffer sclera will resist fluid displacement as the cornea becomes concave, thus limiting corneal deformation. This can be misinterpreted as a stiffer corneal response. Conversely, a more compliant sclera may allow greater deformation, which might be misinterpreted as a more compliant cornea. The scleral contribution will be greater as deformation increases, which explains why those components of the signal associated with unloading are the ones involved with interpreting scleral response. It is proposed that the sclera is the connection between CH and glaucomatous damage at the optic nerve.

These studies lead us to a new interpretation of CH that actually represents ocular hysteresis. The cornea is the point at which the load is applied and the response measured; however, the entire eye is involved in dissipating the energy and contributing to the reported parameters. This response is not confined to the cornea, and it is anticipated the specific involvement of the sclera will generate many additional clinical biomechanical studies with a focus on dissecting the components of the waveform that indicate specific ocular structures.

Unfortunately, Dave Luce passed away in 2017. It is unlikely that he could have realized the broad scope of his invention when the concept of corneal hysteresis was published in the first JCRS special issue on corneal biomechanics in 2005. In the current year of 2021, there is no end in sight as to how CH and other new biomechanical parameters may impact patient care and ultimately preserve vision.

Acknowledgments
Atieh Yousefi Koupaei, PhD, performed the statistical analysis of the ocular response waveform parameters in Figure 3.

REFERENCES

Disclosures: C.J. Roberts is a consultant for Oculus Optikgeräte GmbH and Ziemer Ophthalmic Systems AG.

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