Ocular Response Analyser — a New Diagnostic Tool to Measure Corneal Biomechanical Properties and Intraocular Pressure

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Corneal biomechanical properties have been known to influence the outcome of ocular measurements and procedures for a wide range of ocular diseases. The assessment of corneal biomechanical properties has been a challenge and, for this reason, measurement of the geographical parameters of the cornea, namely corneal thickness and topography, has formed the mainstay of understanding the basis of various ocular pathologies. A newly marketed instrument, the Reichert ocular response analyser has been developed to improve the accuracy of intraocular pressure measurement by uniquely measuring and integrating corneal biomechanical data into its intraocular pressure estimates.

Key words: Cornea, Corneal topography, Intraocular pressure, Tonometry, ocular


Introduction

Although Goldmann applanation tonometry (GAT) measurement of intraocular pressure (IOP) is widely accepted as the gold standard, it has been extensively documented that corneal biomechanical properties such as corneal curvature, axial length, and central corneal thickness (CCT) meaningfully influence GAT IOP measurements.1-14 While numerous formulae and nomograms have been designed to compensate for these variations in GAT, researchers have found that their collective influence on GAT varies considerably between individuals and no methods have been entirely successful in addressing the influence of these variations on measuring IOP accurately.11-23

Corneal biomechanical properties have been known to influence the outcome of ocular measurements and procedures for a wide range of ocular diseases. The assessment of corneal biomechanical properties has been a challenge and, for this reason, measurement of the geographical parameters of the cornea, namely corneal thickness and topography, has formed the mainstay of understanding the basis of various ocular pathologies. A newly marketed instrument, the ocular response analyser (ORA; Reichert Ophthalmic Instruments, Buffalo, USA) has been designed to improve the accuracy of IOP measurement by uniquely measuring and integrating corneal biomechanical data into its IOP estimates.24,25

The ORA uses a dynamic bi-directional applanation process to measure the biomechanical properties of the cornea, including corneal thickness, and the IOP.

Method of Operation

The ORA uses a rapid air pulse to apply force to the cornea and an advanced electro-optical system to monitor the deformation. The precisely metered collimated-air-pulse causes the cornea to move inwards, past applanation into a slight concavity. The air pump shuts off milliseconds after applanation and, as the pressure decreases, the cornea gradually recovers its normal configuration. In this process, it passes once again through an applanated state.

In this process, which lasts for a few milliseconds, the applanation detection system monitors the cornea. Two independent pressure values are derived from the inward and outward applanation events. Due to the dynamic nature of the air pulse and because of energy absorption, or damping, in the cornea, there is a delay in the inward and outward applanation events, resulting in two different pressure values.

The average measure of these two applanation events provides a repeatable Goldmann-correlated IOP measurement (IOPg). The difference between the 2 pressure values is corneal hysteresis (CH).24 The CH measurement helps in understanding the biomechanical properties of the cornea and their influence on the IOP.
measurement process, and provides a basis for the measurement of 2 additional parameters, namely corneal-compensated IOP measurement (IOPcc) and corneal resistance factor (CRF).

The GAT makes ‘static’ measurements in the eye. The technique derives IOP from the force measured during a steady state of applanation of the cornea. However, the ORA makes a ‘dynamic’ measurement, monitoring the movement of the cornea in response to a rapid air impulse. It is this dynamic nature of the ORA measurement that makes possible the capture of other useful data about the eye.

Finally, the morphological signal that is produced from the ORA measurement is a unique ‘signature’ for the eye being measured. These waveforms, although not completely understood, contain valuable information (Figure 1).

**Corneal Biomechanical Properties: an Overview**

**Cornea as a Viscoelastic Structure**

Elastic materials are those for which the strain (deformation) is directly proportional to the stress (applied force), independent of the duration or the rate at which the force is applied (for example, a steel beam).

Viscous materials are those for which the relationship between strain and stress depends on time or rate (for example, pushing a spoon into a jar of honey). The resistance to the applied force depends primarily on the speed at which the force is applied (greater speed = greater resistance).

Structures that are said to be ‘viscoelastic’ contain characteristics of both types of material. In these systems there is a component of static resistance and a component of dynamic resistance. The response of such a system to an applied load depends not only on the magnitude of force and the rate at which it is applied, but also on its material properties.

Human corneal tissue is a complex viscoelastic structure. Hysteresis is the term coined by Sir James Alfred Ewing in 1890 for the property of physical systems that do not instantly follow the forces applied to them, but react slowly, or do not return completely to the original state.

**Corneal Hysteresis**

CH, which is the difference in the inward and outward pressure values obtained during the dynamic bi-directional applanation process employed by the ORA, is a result of viscous damping in the cornea, for example, the ability of the tissue to absorb and dissipate energy.\[^3,22,24\]

\[
CH = P1 - P2.
\]

CH measurement has been found to be independent of the radius of the curvature of the cornea, corneal astigmatism,

Figure 1. Morphological signal or the signature of the ocular response analyser. Reproduced with permission; © Reichart Inc.
visual acuity, or axial length, and is independent of IOP in normal eyes. CH increases with increasing CCT, but the correlation is moderate.26,27

CH has been found to be significantly lower in eyes with high myopia than in normal eyes, reflecting the compromised aspect of the cornea in such eyes.28 Low CH has been noted in eyes with narrow retinal arterioles.29

Corneal Resistance Factor
CRF is an indicator of the overall ‘resistance’ of the cornea. It is a measure of the cumulative effects of both the viscous end elastic resistance encountered by the air jet while deforming the corneal surface.3,22,24 CRF is derived from specific combinations of the inward and outward applanation values using proprietary algorithms:

\[
CRF = P_1 - (0.7 \times P_2).
\]

CRF is strongly correlated with GAT readings because the tonometer must overcome the static resistance of the cornea. CRF is also significantly correlated with CCT and GAT, but not with IOPcc.3,24 Low CRF has been noted in eyes with narrower retinal arterioles.29

Corneal-compensated Intraocular Pressure
IOPcc is a pressure measurement that uses the new information provided by the CH measurement to provide an IOP value that is less affected by corneal biomechanical properties. IOPcc has been developed using clinical data and a proprietary algorithm:

\[
IOP_{cc} = P_2 - (0.43 \times P_1)
\]

Therefore, IOPcc has essentially zero correlation with CCT in normal eyes and stays relatively constant post–refractive surgery.

Analyzing Measurement Signals
The ORA makes measurements by applanating the cornea with a puff of air and monitoring the shape of the cornea with an electro-optical detection system. The signal that is produced as a result of the measurement process is displayed, and should be analysed by the operator after each measurement. Operators should understand the signals and the signature in total to ensure reliable results when making measurements. Repeated measurements on the same eye should produce similar looking signals.

The green curve represents the pressure of air on the cornea (Figure 2). The red curve indicates the raw signal of the applanation detection system. The blue curve is a filtered version of the red curve, designed to identify the ‘optimum point of applanation’ in less than ideal signals.

The optical signal collected during the inward and outward applanation events causes the two ‘spikes’ on either side of the pressure curve. The applanation pressure is determined by drawing a line down from the peak of each applanation spike to the intersection of the green pressure curve. These points are graphically indicated in the ORA software by blue squares. The outward applanation pressure will always occur at a lower pressure on the pressure curve than the inward applanation spike due to CH.

The interpretation of ORA values has to be done by studying the morphology of the waveforms in the signature or the signal obtained. The features that need to be considered are:

- amplitude and regularity (noise) of the 2 applanation spikes
- distance between the 2 applanation spikes
- height of the pressure spike
- shape of the peak in the pressure spike (sharp or plateau).

The pressure curve will always be fairly symmetrical. The height of the curve will vary depending on the amount of pressure required to applanate a particular eye. Eyes with high IOP will have a higher steeper curve. The applanation signal curves, particularly the raw signal curve, may vary considerably in appearance from measurement to measurement. Ideally, the peak-amplitude (height) of the applanation signals (spikes) will be above the green curve. Both spikes should have a clearly defined and relatively well-centred high point (peak).

Characteristic Features of a Normal Signal
The characteristic features of a normal signal are:

- IOPcc and IOPg are close and in the normal range
- CH and CRF are close and in the normal range

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Figure 2. Ocular response analyser signal and waveforms. Reproduced with permission; © Reichart Inc.
Ocular Response Analyser

Table 1. Normal values of corneal hysteresis and corneal resistance factor.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of eyes</th>
<th>Corneal hysteresis Average (SD)</th>
<th>Corneal resistance factor Average (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pepose et al, 2007</td>
<td>66</td>
<td>9.70 (1.80)</td>
<td>9.50 (1.90)</td>
</tr>
<tr>
<td>Ortiz et al, 2007</td>
<td>165</td>
<td>10.80 (1.50)</td>
<td>11.00 (1.60)</td>
</tr>
<tr>
<td>Shah et al, 2006</td>
<td>207</td>
<td>10.70 (2.00)</td>
<td>10.30 (2.00)</td>
</tr>
</tbody>
</table>

The characteristic features of a keratoconus signal are:
- low amplitude peaks with sharp thin peaks
- ‘noisy’ raw signals that cause less repeatable signals
- characteristic ‘bounce’ in the P2 raw signal
- less repeatable signals than in normal eyes (Figure 3).

The characteristic features of a subclinical keratoconus signal are:
- signals look nearly normal
- characteristic but mild bounce in the P2 raw signal
- CH and CRF below normal range

The variations in the measurements depend on the signal quality, which is the most important factor. In a normal eye with a good signal, IOPcc and IOPg vary by 3 mm Hg between measurements and CH and CRF vary by 2 mm Hg between measurements.

Corneal Pathologies and Corneal Biomechanical Properties

Keratoconus

Measurement of corneal biomechanical properties of the cornea has the potential to identify various corneal conditions. Corneas that exhibit low CH are those that are less capable of absorbing (damping) the energy of the air pulse. Such eyes can be thought of in simple terms as having a ‘soft’ cornea. Low CRF indicates that the overall rigidity (resistance) of the cornea is less than normal. CH and CRF are significantly reduced in eyes with keratoconus and Fuchs’ dystrophy. It has been shown that CRF measurement is useful for identifying patients who have form fruste keratoconus or who have pellucid marginal degeneration. Due to the fact that CH and CRF provide a more complete characterisation of corneal biomechanical properties than CCT and topography, preoperative knowledge of these new measures could help in identifying patients at greater risk of developing postoperative complications such as ectasia.

The characteristic features of a keratoconus signal are:
- low amplitude peaks with sharp thin peaks
- ‘noisy’ raw signals that cause less repeatable signals
- characteristic ‘bounce’ in the P2 raw signal
- less repeatable signals than in normal eyes (Figure 3).

Figure 3. Ocular response analyser signal in an eye with keratoconus. Reproduced with permission; © Reichart Inc.

Abbreviations: CCT = central corneal thickness; CH = corneal hysteresis; CRF = corneal resistance factor; IOPcc = corneal-compensated intraocular pressure; IOPg = Goldmann-correlated intraocular pressure.
- thin CCT
- IOPcc higher than IOPg.
  
  The characteristic features of an advanced keratoconus signal are:
  - history of photorefractive keratectomy, LASIK, or other surface ablation procedures and suspicious topography
  - low amplitude peaks with sharp thin peaks
  - very noisy raw signals
  - characteristic bounce in the P2 raw signal
  - thin CCT
  - CH and CRF totally unreliable
  - IOPcc higher than IOPg.

**Post–refractive Surgery**

Currently, CCT is the primary factor used for screening candidates for refractive surgery. Patients with thinner corneas are considered to be at higher risk of developing post–LASIK corneal ectasia. Since CH is only weakly correlated with CCT, its measurement may be useful for excluding patients who are at risk of developing post–LASIK ectasia. Therefore, it is possible that in the future, CH and CRF will replace CCT as the primary screening tool for refractive surgery in addition to topography.

CH and CRF have potential uses in post–LASIK follow-up. CH and CRF are considerably reduced following refractive surgery as a result of the complex biomechanical changes induced. The post–LASIK reduction in CH does not correlate with the amount or percentage of corneal tissue removed or with the optical zone or patient age. This reduction in CH and CRF is not primarily a function of corneal thinning, but rather a weakening of the structure related to the creation of the flap. It has been postulated that CH measurements will be useful for customizing ablation algorithms to better predict and control LASIK outcomes.

Since IOPcc is independent of CCT in normal eyes and stays relatively constant post–refractive surgery, its measurement provides an accurate assessment of the IOP in the eye after LASIK and circumvents the need for recording the GAT IOP and correcting the same for CCT by using various algorithms, none of which have been accurately validated. Since the IOPcc has no correlation with CCT, it facilitates IOP measurements in post–refractive surgery eyes that are more consistent with preoperative tonometry values.

The characteristic features of a post–LASIK signal are:
- low amplitude signals with sharp and thin peaks
- rapid P2 signal falloff with pronounced ‘ricochet’ bounce
- low CCT
- IOPcc higher than IOPg and close to the normal value
- low CH and CRF
- fewer repeatable signals than in normal eyes (Figure 4).

**Figure 4.** Ocular response analyser signal in an eye pre– and post–refractive surgery. Reproduced with permission; © Reichart Inc.

**Abbreviations:** CCT = central corneal thickness; CH = corneal hysteresis; CRF = corneal resistance factor; IOPcc = corneal-compensated intraocular pressure; IOPg = Goldmann-correlated intraocular pressure.
The characteristic features of a post–photorefractive keratectomy signal are:
- low amplitude signals with fewer sharp and thin peaks than those obtained after LASIK but that are more noisy than after LASIK
- rapid P2 signal falloff with pronounced ricochet bounce
- low CCT
- IOPcc higher than IOPg and close to the normal value
- low CH and CRF
- fewer repeatable signals than in normal eyes.

The characteristic features of an ectasia signal are:
- very low amplitude signals with sharp thin peaks
- P2 signal bounce
- lots of noise
- low CCT
- IOPcc higher than IOPg
- low CH and CRF
- fewer repeatable signals
- suspicious or abnormal topography (Figure 5).

The ORA can be used to study the changes in corneal biomechanical properties following collagen cross-linking in eyes with ectasia. In a presentation at the meeting of the European Society of Cataract and Refractive Surgeons, it was reported that there were no statistically significant differences in most waveform parameters analysed (MA Woodward; 2009; Unpublished data). However, there were significant changes in CRF and IOP-related ORA parameters after cross-linking. While this was a report of a small sample of 23 eyes, there is sufficient scientific justification for use of the ORA to study the changes in corneal biomechanical properties following such procedures.

The characteristic features of immediate post-keratoplasty signal are:
- messy signal due to immediate movement of the cornea
- very low amplitude signal
- low CRF and CH
- IOPcc higher than IOPg (Figure 6).
Corneal Biomechanical Properties and Glaucoma

Corneal Hysteresis and Corneal Resistance Factor in Glaucoma

The Ocular Hypertension Treatment Study (OHTS) has raised the importance of CCT in diagnosing and managing glaucoma. Studies have shown that low CCT (thin cornea) may be an independent risk factor for the development and progression of the disease. It is now believed that corneal parameters other than CCT may play a role in the pathogenesis, as well as aid in the diagnosis and management, of glaucoma.

In a normal eye, there is no correlation between CH and IOPg. However, in a typical glaucomatous eye, there is a negative correlation between the 2 parameters. The eyes with severely elevated pressures have much lower than average CH and a much wider range. Kirwan et al reported that CH was significantly lower in eyes with congenital glaucoma than in normal eyes. CH in patients with primary open angle glaucoma (POAG) with acquired pit-like changes in the optic nerve head was significantly lower than in those who did not have such structural changes of the optic disc. CH has been described as the cornea’s ability to damp IOP and buffer fluctuations in the IOP. Thus, eyes with higher amounts of CH are thought to have more capacity to cushion short-term and long-term increases in IOP compared with eyes with lower CH. Conversely, when a cornea cannot absorb IOP increases, as might occur in an eye with lower CH, the result could be increased stress (force) and strain (deformation) on the optic nerve and peripapillary tissues. Consequently, low damping capacity might be expected to increase the risk of developing glaucomatous optic neuropathy. These findings may reflect IOP-independent mechanisms involved in the pathogenesis of glaucomatous optic nerve changes. It is also believed that low CH may be the result of corneal remodelling in response to glaucomatous damage.

Congdon et al reported that CH is independently related to glaucoma progression. The CH measurement may give clinicians a new tool to evaluate glaucoma treatment efficacy and to determine adequacy of treatment, monitor achievement of desirable IOP control, and determine which patients may need to be treated more aggressively. However, eyes with glaucomatous damage have higher CRF than CH. High CRF in these eyes is indicative of stiffening of the cornea due to sustained elevated pressure.

Corneal-compensated Intraocular Pressure in Glaucoma

To date, no factor used to correct for CCT in IOP measurement has been completely satisfactory. Many of these correction factors have evolved based on the changes in CCT and IOP observed after corneal refractive surgery. Besides corneal thinning leading to reduced IOP as determined by GAT, other factors such as rigidity, bio-elasticity, connective tissue composition, hydration, curvature,
Ocular Response Analyser

and deformability changes influence the corneal architecture, and these are not completely accounted for by correction factors. This is probably why these factors cannot be applied to IOP determination in patients with glaucoma. IOPcc provides IOP assessment that is less affected by corneal properties, including CCT, and remains essentially unchanged after LASIK.3,9,24

The characteristic features of POAG (uncontrolled) signal are:
• high amplitude signals with sharp and thin peaks
• noisy raw signals
• IOPcc and IOPg elevated
• low CH
• CRF greater than CH (Figure 7).

The characteristic features of POAG (controlled and stable) signal are:
• high amplitude signals that are smooth
• less noise
• IOPcc and IOPg well controlled
• CH and CRF in the normal range.

The characteristic features of POAG (uncontrolled and blind) signal are:
• signals of low amplitude
• noisy and lumpy signals
• IOPcc and IOPg elevated
• very Low CH
• high CRF.

The characteristic features of OHT signal are:
• signals are of high amplitude
• smooth signals with noise
• CCT increased
• IOPg higher than IOPcc
• CH and CRF increased (Figure 8).

The characteristic features of normal tension glaucoma signal are:
• signals are of low amplitude with sharp peaks
• signals have some noise
• CCT decreased
• IOPcc higher than IOP
• CH and CRF decreased (Figure 9).

It is noteworthy that the signals obtained from eyes with normal tension glaucoma look similar to signals obtained from patients with Fuch’s dystrophy and keratoconus, and those post-LASIK, reinforcing the theory that glaucomatous damage, in some manner, presents itself via the cornea.

Atypical Measurements
As emphasised, the accuracy of the measurements depends on the characteristic signal obtained with which the values have to be correlated. It should be remembered that, on occasions, atypical measurements may be obtained in eyes with corneal surface irregularities, ectasia, and thinning. The features of an atypical signal are:

Figure 8. Ocular response analyser signal in an eye with ocular hypertension. Reproduced with permission; © Reichart Inc.
Abbreviations: CH = corneal hysteresis; CRF = corneal resistance factor; IOPcc = corneal-compensated intraocular pressure; IOPg = Goldmann-correlated intraocular pressure.
measurement that will help in its identification are:
• signals are usually less repeatable than normal
• there are highly variable numeric measurement values.

In such a situation, we can obtain best values by:
• taking a series of measurements
• look for the best signal possible
• obtaining at least 2 signals that look similar and yield similar numeric results
• deleting obviously bad signals
• obtaining average values of good results.

Sources of Error
If the IOPg recorded by the ORA is significantly lower or higher than the GAT readings, it may be due to:
• calibration errors in the GAT
• poor operator technique
• recordings done in a biased population such as those with glaucoma or post-refractive surgery.

Contraindications for the Ocular Response Analyser
The following are considered absolute contraindications for performing ORA in an individual:
• presence of corneal ulcer
• immediately following trauma or keratoplasty.

Conclusions
If invention and the role of geometric parameters such as corneal topography and CCT marked the first paradigm shift, then invention and the knowledge of the role of corneal biomechanical properties form a second major paradigm shift in the understanding of ocular diseases and outcomes following various therapeutic interventions such as refractive surgery and collagen cross linking. Nevertheless, further refining and understanding of various ORA parameters and their role in the pathogenesis of ocular diseases is needed, which will pave the way for a more physiological approach to the treatment of various eye disorders.

References
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