Screening of Forme Fruste Keratoconus with the Ocular Response Analyzer

Cedric Schweitzer,1 Cynthia J. Roberts,2 Asbraf M. Mabmoud,2 Joseph Colin,1 Sylvie Maurice-Tison,1 and Julien Kerautret1

PURPOSE. To evaluate the performance of the Ocular Response Analyzer (ORA) in the screening of forme fruste keratoconus (FFKc).

METHODS. A retrospective comparative study was conducted involving 180 eyes. ORA preoperative data were analyzed for 125 normal control eyes (64 patients) undergoing laser in situ keratomileusis (LASIK) without corneal ectasia after 24 months of follow-up and 55 case eyes with unilateral keratoconus from a database (BCVA of 1.0, KISA index <60%). All eyes were matched in four groups of central corneal thickness (CCT): group 1, <500 μm; group 2, 500 to 559 μm; group 3, 540 to 579 μm; and group 4 >580 μm. Corneal hysteresis (CH), the corneal resistance factor (CRF), the air pressure curve, and the infrared signal were compared between FFKc and normal eyes in each group.

RESULTS. The mean CH was 9.1 ± 1.8 mm Hg for FFKc and 10.3 ± 1.9 mm Hg for control eyes (P < 0.001), and the mean CRF was 9.2 ± 1.8 and 11.1 ± 2.2 mm Hg (P < 0.001), respectively. Sensitivity in each group was as follows: group 1, CH < 9.5 mm Hg (91%) and CRF < 9.5 mm Hg (81%); group 2, CH < 10.5 mm Hg (91%) and CRF < 10 mm Hg (87%); group 3, CH < 11.5 mm Hg (79%) and CRF < 11 mm Hg (74%); group 4 had two cases of FFKc, and the difference was not significant. Air pressure levels at inward and outward applanation and the maximum air pressure level were significantly lower and shorter in time in FFKc (P < 0.001), whereas the shape of the infrared signal was more variable.

CONCLUSIONS. The ORA provides additional information in the screening of FFKc, with an accurate analysis of the corneal biomechanical properties according to CCT, air pressure, and infrared curves. (Invest Ophtalmol Vis Sci. 2010;51:2403–2410) DOI:10.1167/iovs.09-3689

Since the development of corneal photoablation with the excimer laser in refractive surgery, many studies have reported the safety and the ability of this technique for the correction of ametropia, with good anatomic and visual results.1–3 Corneal ectasia represents one of the rarest but also one of the most feared complications with an incidence of 0.2% to 0.66% in the literature.6,7

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case group, the quantitative KISA index, as published by Rabinowitz and Rasheed,20 to screen FFKc. The KISA index quantifies the topographic features of keratoconus and was initially derived as follows:

\[
\text{KISA(\%)} = \frac{1}{100 \times 300} \times (K) \times (\text{SRAX}) \times (\text{AST})
\]

Central keratometry (K) was generated by averaging the diopteric power points on rings 2, 3, and 4 of the videokeratographs. The inferior-superior diopteric asymmetry value (I-S) is calculated by subtracting the mean corneal curvature from the maximum corneal curvature in the corneal curvature map (skewed radial axes) as an expression of irregular astigmatism occurring in keratoconus. A KISA index greater than 100% was considered early keratoconus; less than 60%, normal; and between 60% and 100%, suspected keratoconus.

All eyes underwent a corneal biomechanical properties analysis with the ORA. All ORA measurements were obtained with the same calibrated instruments after checking for good alignment of the eye and the probe, as recommended by Reichert Laboratories. We studied the mean value of a series of four measurements without anesthesia, and data were analyzed with the Reichert software (ver. 3).

The case group of FFKc came from our keratoconus database (containing data for 640 patients in July 2008 and including normal fellow eyes) and comprised 55 fellow eyes of 55 (8.6%) patients with unilateral expression of keratoconus. We took the normal fellow eye for analysis. Keratoconus diagnosis was made on the basis of a clinical examination and on the corneal topography with a KISA index higher than 100%. The fellow eye was considered normal when best spectacle corrected visual acuity (BSCVA) was 10/10 (Monoyer scale) and the KISA index on corneal topography was less than 60%, without a suspect pattern. Eyes with rigid contact lenses, with central corneal thickness (CCT) less than 470 μm or a corneal curvature greater than 47 D were excluded.

The control group came from our database of patients who had undergone refractive surgery by LASIK since October 2006 (beginning of a systematic preoperative examination with the ORA). All patients underwent a clinical evaluation including visual acuity measurement and a corneal examination (Orbscan; Bausch & Lomb) every 6 months after surgery. We selected eyes presenting with an unchanged postoperative visual acuity or spherical equivalent, a stable keratometry of the two main axes, and an unchanged power and axis of astigmatism without skewed radial axes for more than 24 months. This concerned 125 eyes of 64 patients. We recorded the preoperative ORA data for analysis. This control group was selected to ensure the safety and the biomechanical stability of such corneas, to decrease the risk of FFKc, and to define safe ORA values.

In published data, CH and the corneal resistance factor (CRF), measured with the ORA, had positive and moderate correlations with the CCT.21–26 The mean CCT, measured with Orbscan, was 530 ± 32 μm in the case group and 553 ± 39 μm in the control group. For the analyses of CH and CRF, eyes were matched in four groups of homogeneous CCT values and a sufficient number of eyes: group 1, CCT < 500 μm; group 2, 500–539 μm; group 3, 540–579 μm; and group 4, ≥580 μm (see Table 1). The wide range of CCTs in each group was similar between the case and control eyes. The CCT group 4 included too few cases in comparison with the number of control eyes, and therefore the results of this group must be interpreted cautiously.

We studied CH and CRF between the case and control eyes in each CCT group. We analyzed the following results from the infrared signal: peak amplitude 1 (inward), peak amplitude 2 (outward), width of peak 1 at half the maximum value (fwhm1), and width of peak 2 at half the maximum value (fwhm2). We also analyzed the air pressure curve (P1 inward pressure level, Pmax maximum pressure level, and P2 outward pressure level, in arbitrary units, and time T1 at the first peak, T2 at the second peak, and time of Pmax, in milliseconds).

Comparison between two groups was made by ANOVA or Wilcoxon test when variables deviated from a normal distribution (analyses performed with Epi Info software ver. 3.3.2, http://www.cdc.gov/epiinfo/ provided in the public domain by the Centers for Disease Control and Prevention, Atlanta, GA). Results were considered statistically significant at P < 0.05. The biomechanical engineering department of The Ohio State University performed analyses of the infrared signal and of the air pressure curves.

Informed consent was obtained from each patient in accordance with the tenets of the French ethics committee and the Declaration of Helsinki.

**RESULTS**

The mean age was 31.1 ± 9.9 years in the case group and 34.8 ± 9.5 years in the control group. In the case group, the sex ratio (male to female) was 3.58, and the mean KISA index was 17.7% ± 14.9%. In the control group, the ratio was 0.88, and the mean follow-up was 26.1 ± 2.3 months.

**Corneal Hysteresis**

There was a positive and moderate correlation between CH and CCT in each group (Tables 1, 2). There was a significant difference (1.2 mm Hg; P < 0.001) between the case and control groups. In each CCT group, there was a difference in mean CH of between 0.5 and 1.1 mm Hg. There was a signific-

**Table 1. CCT Groups**

<table>
<thead>
<tr>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Mean CCT</td>
</tr>
<tr>
<td>Group 1, &lt;500 μm</td>
<td>11</td>
</tr>
<tr>
<td>Group 2, 500–539 μm</td>
<td>23</td>
</tr>
<tr>
<td>Group 3, 540–579 μm</td>
<td>19</td>
</tr>
<tr>
<td>Group 4, ≥580 μm</td>
<td>2</td>
</tr>
</tbody>
</table>

n, number of eyes; mean CCT is expressed in micrometers ± SD.

**Table 2. Correlation Coefficients between CH, CRF, Parameters of the Infrared, and Air Pressure Curves and CCT**

<table>
<thead>
<tr>
<th>R Cases</th>
<th>R Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH</td>
<td>0.3274 (P &lt; 0.001)</td>
</tr>
<tr>
<td>CRF</td>
<td>0.44234 (P &lt; 0.001)</td>
</tr>
<tr>
<td>P1</td>
<td>0.43515 (P &lt; 0.001)</td>
</tr>
<tr>
<td>P2</td>
<td>0.22183 (P = 0.001)</td>
</tr>
<tr>
<td>Pmax</td>
<td>0.43844 (P &lt; 0.001)</td>
</tr>
<tr>
<td>Time P1</td>
<td>0.39859 (P &lt; 0.001)</td>
</tr>
<tr>
<td>Time P2</td>
<td>0.27186 (P &lt; 0.001)</td>
</tr>
<tr>
<td>Time Pmax</td>
<td>0.36454 (P &lt; 0.001)</td>
</tr>
<tr>
<td>DID</td>
<td>-0.19441 (P = 0.004)</td>
</tr>
<tr>
<td>Peak 1</td>
<td>0.36666 (P &lt; 0.001)</td>
</tr>
<tr>
<td>Peak 2</td>
<td>0.20203 (P = 0.003)</td>
</tr>
<tr>
<td>Fwhm 1</td>
<td>0.13831 (P = 0.04)</td>
</tr>
<tr>
<td>Fwhm 2</td>
<td>0.07290 (P = 0.2873)</td>
</tr>
</tbody>
</table>

**Table 3. CH Comparison**

<table>
<thead>
<tr>
<th>Total</th>
<th>CCT 1</th>
<th>CCT 2</th>
<th>CCT 3</th>
<th>CCT 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>11.2</td>
<td>8.6</td>
<td>8.3</td>
<td>9.7</td>
</tr>
<tr>
<td>Controls</td>
<td>10.3</td>
<td>9.5</td>
<td>9.6</td>
<td>10.1</td>
</tr>
</tbody>
</table>

P < 0.001 P = 0.01 P < 0.001 P = 0.05 P = 0.21

Data are expressed as mean mm Hg ± SD.
significant difference in CCT groups 1 and 2 between the cases and controls. The CCT group 3 showed a difference of 0.5 mm Hg between the cases and controls, but it was not significant. The number of cases in CCT group 4 was too low to generate meaningful statistics (Table 3).

**Corneal Resistance Factor**

There was a positive and moderate correlation between CRF values and CCT in each group (Table 2). There was a significant difference of 1.9 mm Hg ($P < 0.001$) for the mean CRF between the case and control eyes. There was a significant difference in mean CRF, which ranged from 1.4 to 1.8 mm Hg, between the case and control eyes in each CCT group ($P < 0.001$ for CCT groups 1, 2, and 3, and $P < 0.05$ for group 4; Table 4).

**Air Pressure Curve**

The level pressure at inward ($P_1$) and outward applanation ($P_2$) and the maximum level pressure ($P_{\text{max}}$) were significantly different between the case and control eyes ($P < 0.001$), with lower results for the cases (Table 5). $P_1$, $P_2$, and $P_{\text{max}}$ correlated positively with CCT, with comparable correlation coefficients for case and control eyes (Table 2).

The times of the air pressure levels $P_1$, $P_2$, and $P_{\text{max}}$ were lower in the cases, with a significant difference between the case and control eyes ($P < 0.001$; Table 6). The different times correlated positively with CCT for both groups (Table 2).

The mean damping-induced delay (DID), representing the necessary time to deform cornea during outward applanation, was significantly shorter for the cases ($P = 0.04$). The DID correlated negatively with CCT for case and control eyes (Tables 2, 6).

**Infrared Signal Curve**

The analysis of the infrared curve at inward applanation showed a significant difference between the case and control eyes. There was a lower intensity of the mean peak 1 and a thinner mean width of peak 1 at half the maximum (fwhm1) in the case than in the control eyes ($P < 0.001$; Table 7).

The mean intensity of peak 2 was significantly lower in the cases ($P < 0.03$), but there was no significant difference in the mean width of peak 2 at half the maximum value (fwhm2) between both groups. We could see, however, a wider spread of peak 2 and fwhm2 in the case than in the control eyes.

In our study, the populations of case and control eyes were comparable in age, but the sex ratio was different between both groups. The cases were predominantly male, the sex ratio being 1.94 (male to female) in the whole keratoconus database.

In published research, keratectasia after LASIK has been shown to occur after a mean follow-up of 14 and 16 months.6,7 To select eyes with a low probability of presenting with a corneal biomechanical instability, the control eyes came from the preoperative database of patients undergoing LASIK with a follow-up of more than 24 months. In this group, the mean values of CH and CRF were close to published data for the whole population.22–24,26–30

Keratoconus is a progressive, bilateral, and asymmetric corneal dystrophy.1–5,12,13 Hence, we expect the normal eye of patients with unilateral expression of keratoconus to present with a latent biomechanical instability, which we define as a forme fruste of keratoconus. Topographic KISA scores to screen keratoconus were very low in our case group. Rabinowitz and Rashed considered a KISA score of between 60% and 100% as FFKc and a score less than 60% as normal.

**Screening of Forme Fruste Keratoconus**

Results for screening FFKc were more accurate when eyes were matched in the CCT groups. For example, with a CCT less than 500 μm (group 1), a CH less than 9.5 mm Hg had a sensitivity of 91% (Fig. 5). Group 2 showed the same sensitivity for a CH less than 10.5 mm Hg (Fig. 6). For a CCT of more than 540 μm (group 3), a CH of 11.5 mm Hg had a sensitivity of 79% (Fig. 7).

According to the receiver operating characteristic (ROC) curves, CRF seems to be a better parameter to screen FFKc. A CRF less than 9.5 mm Hg for group 1, less than 10.5 mm Hg for group 2, and less than 11.5 mm Hg for group 3 had a sensitivity of 81%, 96%, and between 74% and 89%, respectively.

Group 4 did not have a sufficient number of cases for analysis.

**DISCUSSION**

In our study, the populations of case and control eyes were comparable in age, but the sex ratio was different between both groups. The cases were predominantly male, the sex ratio being 1.94 (male to female) in the whole keratoconus database. To our knowledge, however, in the literature, there is no reported difference in viscoelastic properties in vitro or in ORA values between men and women. Therefore, this difference probably did not influence the results of the study.22–24,26–30

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**CH and CRF Receiver Operating Characteristic Curves**

| Cases       | $7.64 \pm 0.41$ | $12.43 \pm 0.38$ | $18.52 \pm 0.32$ | $0.78 \pm 0.27$ |
| Controls    | $8.11 \pm 0.50$ | $12.77 \pm 0.35$ | $18.69 \pm 0.26$ | $0.74 \pm 0.25$ |

Data are expressed in mean milliseconds ± SD.

| Cases       | $705.5 \pm 167$ | $549.6 \pm 189$ | $11.5 \pm 3.8$ | $11.6 \pm 5.4$ |
| Controls    | $788.2 \pm 124$ | $574.8 \pm 157$ | $12.3 \pm 3.5$ | $11.4 \pm 4.4$ |

Data are expressed in arbitrary units ± SD.
Although the CCT measurements with US pachymetry is less variable, we chose Orbscan II slit lamp biomicroscopy to allow a good repeatability and reproducibility of measured values with an acoustic factor of 0.92 and to ensure low intra- and interobserver variations.33–36 In published data, CH and CRF had a positive and moderate correlation with CCT, but there were no measurements of the same biomechanical parameters.33–36 We found similar moderate correlation coefficients with CCT in our study. Hence, we chose to match our case and control eyes in four groups of similar CCT to eliminate the difference of 23/26 Hg in the mean CCT of cases and controls that could influence CH and CRF mean values of the study, to improve the sensitivity of ORA values, and to reduce the influence of CCT on measured parameters. We determined the size of each CCT group so that it provided a sufficient number of cases and control eyes for statistical analysis. Control and case eyes matched in four groups of CCT had similar mean values, and value-scattering was homogeneous.

CH was different between the cases and controls in each CCT group, but CRF seemed to be a better parameter for screening FFKc, with a significant difference of 1.1 to 2.2 mm Hg between the cases and controls, CH having smaller differences. This confirms the different viscoelastic behavior of corneas presenting with FFKc. However, in our study, those parameters did not discriminate enough between both groups. Kerautret et al.37 reports a case of unilateral keratectasia after LASIK with similar values of CH and CRF, but the shape of the infrared and air pressure curves was different in the contralateral eyes. In our study, the shape of the air pressure curve was different between the case and control eyes. At comparable central corneal thickness, corneas of the case group were applanated faster and at lower pressures for inward and outward applanation pressures than corneas of the control group. Moreover, the shape of the infrared curve was different between the case and control eyes and seems to provide qualitative data on the biomechanical properties of corneas. The higher the infrared signal intensity and the tighter the width at half the maximum value, the more the cornea is applanated regularly with a shorter delay. In our study, at inward and outward pressure, FFKc corneas seemed to be applanated less regularly and with a longer delay. There was no significant difference in the full width at half the maximum at outward pressure applanation (fwhm2) between the groups, but the range of the values in the case group was wider than that in the control group. There is probably a less predictable infrared signal reception at outward applanation for case corneas, meaning that such corneas are more flexible and dissipate the infrared beam at the corneal apex. Moreover, the infrared signal is less dependent on CCT in the control group than in the case group, suggesting a quite similar corneal response to air pressure in this group. CCT could be a more important parameter in corneas presenting a latent biomechanical instability; such corneas seemed to be more flexible when narrower than expected for control corneas.

FIGURE 1. Infrared signal analysis: fwhm1, fwhm2 (milliseconds) comparison between the cases and controls. Box plot: median and quartiles; minimum and maximum values.

Elasticity refers to how a material deforms in response to an external stress and returns to its original shape along the same stress-strain pathway when the imposed stress is removed. Hysteresis is a viscoelastic property defined as the difference in elastic behavior under loading and unloading stresses, with the material regaining its original shape along a different stress-strain pathway.

The ORA is the first device to allow exploration of the biomechanical properties of the cornea in vivo. CH, supposed to represent its viscoelastic properties, is calculated as the difference of the two pressure values inducing inward and outward applanations. The analysis of the air pressure and infrared curves at inward and outward applanation provides more information on the corneal biomechanics that are not
considered at this moment by the ORA software. At inward applanation, peak1, fwhm1, \(P_1\), and time \(t_1\) are parameters representing the elastic behavior of the cornea under loading; whereas, at outward applanation, peak2, fwhm2, \(P_2\), time \(t_2\), and DID indicate the elastic behavior of the cornea under unloading. These parameters show the deformation of the cornea, not just its shear strength, represented by hysteresis.

In keratoconic eyes, there is a decrease in the diameter of collagen fibrils associated with an alteration of the regular orthogonal arrangement of the collagen fibril layers above all in the center of the cornea. Moreover, there is a decrease of proteoglycans in the extracellular matrix. Thus, these histologic alterations modify the elastic response of the cornea to an external stress and could precede morphologic deformations.\(^3\) \(^8\)–\(^4\) \(^1\) The analysis of the corneal elasticity in normal and keratoconic eyes could allow a screening of early biomechanical changes of the cornea.

CH and CRF have to be interpreted according to the CCT, and CRF seems to be the better parameter for screening FFKc. On ROC curves, CH and CRF alone do not allow the screening of such corneas with good sensitivity and specificity; but these curves could be helpful in determining the risk of having a silent biomechanical instability of the cornea according to CH and CRF sensitivities in a CCT group.

Many studies report methods of screening FFKc in the preoperative examination for corneal refractive surgery, but none is totally efficient. The analysis of topographical data remains the most used and the most described method of screening such corneas. Wilson et and Klyce\(^4\) \(^2\) and Rabinowitz\(^4\) \(^3\) described suspect topographical patterns on the mapping of the corneal anterior surface. Irregular astigmatism, asymmetric bowtie, skewed radial axes, or abnormal anterior corneal surface steepening were considered suggestive of FFKc.\(^4\) \(^2\)–\(^4\) \(^4\)

Other studies described a quantitative analysis of the corneal topography. A central keratometry value of more than 47.2 D or a difference of more than 1.4 D between the inferior and the superior average keratometry values of five points at 30° intervals, 3 mm from the center of the cornea were also considered suggestive.\(^5\) \(^5\)–\(^4\) \(^7\) Finally, the KISA index, associating all the values of this parameter, was produced.\(^2\) \(^0\)

Moreover, an elevation of the posterior surface of the cornea by more than 40 \(\mu\)m, analyzed by Orbscan or Pentacam (Oculus, Wetzlar, Germany) suggests FFKc.\(^4\) \(^8\)–\(^5\) \(^1\) Tanabe et al.\(^5\) \(^2\) described suspect corneas as having greater indices than normal corneas on videokeratography analysis. Moreover, on wavefront analysis, there was a more significant amount of high-order aberrations as third-order coma aberrations for such corneas.\(^5\) \(^3\)–\(^5\) \(^4\)

All these devices indicate, directly or indirectly, corneal morphology, but none explore its biomechanical properties. Most surgeons recommend for safety a residual stromal bed of more than 250 \(\mu\)m to limit biomechanical weakness after a photoablative procedure.\(^6\) \(^1\)–\(^6\) \(^6\)–\(^1\) \(^6\) The reproducibility of photoablation with an excimer laser and a better predictability of the corneal flap thickness with a femtolaser allow better prediction of the residual stromal bed (RSB) thickness.\(^5\) \(^8\)–\(^6\) \(^2\) However, analysis of corneal morphology during the preoperative examination and respect to the anatomic guidelines during the photoablative procedure are necessary but not sufficient. Many publications report a keratectasia with a residual stromal bed of more than 250 \(\mu\)m, revealing an FFKc that could affect 49% of eyes.\(^1\) \(^5\) \(^6\)–\(^6\) Some other publications report a corneal stability after photoablation with a shallower RSB.\(^6\) \(^7\)–\(^6\) \(^9\) There is a difference between each cornea in biomechanical properties and a difference in biomechanical behavior after photoablation. The corneal photoablation changes the intra-
stromal strength and modifies its viscoelastic properties; keratctasia results in a deformation of the central cornea by a viscoelastic phenomenon. These results highlight the need to develop a device exploring the corneal biomechanical properties. The development of a corneal biomechanical score to categorize each cornea and an improved predictability of biomechanical weakening induced by a photoablative procedure according to ametropia could optimize the management of patients in refractive surgery.

In our study, the case group had a high risk of keratoconus with no suspect sign on corneal topography. There was a difference in viscoelastic response to air pressure between both groups, although the corneal topography was similar. This study confirms the relevance of the examination of corneal biomechanics. The ORA seems to provide a qualitative analysis of corneas and could be helpful in screening for FFKc in association with the analysis of corneal morphology. The analysis of the air pressure curve and of the infrared signal is probably the next step in the development of the ORA, carrying more information about the biomechanical properties of the cornea. A wide study of both these signals in the whole population and an analysis of its association to CH and CRF is needed. Further studies are necessary to confirm these results and to observe the corneal topography and the ORA parameters over time for both groups.

References