Surgical Incision Alters the Swelling Response of the Human Cornea

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The ocular characteristics and responses were examined in patients who had undergone extracapsular cataract extraction (ECCE), intracapsular cataract extraction (ICCE) and penetrating keratoplasty (PKP) in one eye only. In each of the three groups, corneal sensitivity (the inverse of corneal touch threshold), oxygen uptake rate, and endothelial cell density were lower in the operated eye than in the normal healthy fellow eye. For the subjects as a whole, the differences in ocular characteristics between the two eyes were proportional to the angular size of the corneal incision, with ECCE patients (33° incision) showing the least differences and PKP patients (360° incision) showing the greatest differences. Five patients from the ICCE group were subjected to an osmotic stress test. There was no statistically significant difference in the corneal swelling response between the operated eye (5.1%) and the unoperated eye (4.7%), indicating that surgically induced scar tissue does not restrict the swelling properties of the cornea. When subjected to a hypoxic stress test, all three groups manifested less corneal edema in the operated eye (ECCE —0.7%, ICCE —4.0%, and PKP —3.3%). The reduction in hypoxic corneal swelling could not be attributed to removal of the crystalline lens since a similar reduction was seen in the PKP group who had phakic eyes. The corneal swelling response correlated inversely with the corneal touch threshold and directly with epithelial oxygen uptake, but did not correlate with endothelial cell density. These results indicate that corneal surgery has an effect on the physiologic characteristics of the corneal epithelium that is proportional to the angular size of the incision, and that the reduction in hypoxic swelling response is related to the changes induced in the epithelium. This implies a possible neurologic input to corneal epithelial metabolism. Invest Ophthalmol Vis Sci 26:864–868, 1985

Several studies have established that the cornea of the aphakic eye swells less with a hypoxic stimulus than does that of a paired normal eye.1–3 The corneal oxygen uptake rate of an aphakic eye is also reduced in comparison to the phakic eye, indicating reduced epithelial metabolic activity.4 These findings at least partly explain why an aphakic cornea tolerates contact lens wear successfully even though the oxygen availability to the cornea with such thick plus lenses is very low.5,6

Several hypotheses could explain why cataract surgery reduces the corneal edema response to hypoxia: (1) removal of the lens favorably alters metabolite levels in the aqueous humour; (2) partial denervation of the cornea reduces epithelial metabolic activity, resulting in less corneal need for oxygen; (3) the ability of the endothelium to function is altered; and (4) a local mechanical effect of corneal incision, eg, scar formation, prevents the cornea of the operated eye from swelling as much as that of the normal eye.

To determine which of the above hypotheses might explain the reduced hypoxic swelling response in the aphakic eye, we compared the ocular characteristics and responses of patients who had undergone various types of unilateral surgery: extracapsular cataract extraction (ECCE), intracapsular cataract extraction (ICCE), and penetrating keratoplasty (PKP).

Materials and Methods

Subjects

All the subjects had undergone a planned surgical procedure without complications. None of the subjects had any previous history or signs of other ocular disease. The subjects agreed to participate in this study after the nature of the procedures were fully explained.
Twelve subjects underwent ECCE, four patients using suction only while eight patients underwent phacoemulsification using the Kelman procedure. A small posterior capsulotomy was done in these latter eight cases. The mean angular incision size for patients in this group was $33^\circ$ (mean arc length of 3.5 mm). The average age of patients was 46 yr (range 17–80 yr). The average time after surgery was 19 mo (range 8–70 mo). The corrected visual acuity was 20/25 on average in the aphakic eye (range 20/60 to 20/20) and 20/40 in the phakic eye, (range 20/200 to 20/20).

Twenty patients underwent ICCE. The mean angular corneal incision size was $170^\circ$ (mean arc length of approximately 19 mm). The average age of these patients was 63 yr (range 36–79 yr). The average time after surgery was 40 mo (range 3–210 mo). Corrected visual acuity was on average 20/25 (range 20/60 to 20/20) in the aphakic eye and 20/30 (range 20/200 to 20/20) in the phakic eye.

Eight subjects had a unilateral PKP: one patient, as a result of herpetic corneal opacification; and seven patients, as a result of keratoconus. All patients had a penetrating corneal graft, 8 mm in diameter with an angular size of $360^\circ$. All eyes were phakic. The average age of the patients was 33 yr (range 28–38 yr) and the average time after surgery was 14 mo (range 6–31 mo). The mean corrected visual acuity of the operated eye was 20/30 (range 20/50 to 20/20) and of the fellow eye 20/20 except for two patients with 20/25.

The mean age of the patients and time since surgery varied between the groups. However these factors are not considered to be significant as the difference between the eyes within each group far exceeded the differences between the control eyes in the different groups.

Surgery in ECCE and PKP groups was performed in the same hospital by one surgeon. Surgery in the ICCE group was conducted by three surgeons using the same technique.

Materials

Contact lenses: The lenses used in the hypoxic stress test were 38% water content hydroxyethyl methacrylate (HEMA) with parallel front and back surfaces (Hydron material, special order), and were relatively thick (mean central thickness $0.284 \pm 0.015$ mm). The mean diameter of those lenses was $13.36 \pm 0.07$ mm. All lenses were fitted tight with movement of less than 0.2 mm on blinking.

Methods

Corneal thickness: The Payor-Holden micropachometer, consisting of the Haag-Streit Pachometer adapted to a Rodenstock Model 2000 biomicroscope, was used to monitor central corneal thickness changes. The design and operation of the system has been previously described. A typical standard deviation of 10 readings of corneal thickness taken at a measurement session was $\pm 4 \mu m$ ($\pm 0.8\%$).

Corneal oxygen uptake rate: Corneal oxygen uptake rate was measured using a procedure originally described by Hill and Fatt. An oxygen sensor (Radiometer E5057/0) 8 mm in diameter with a 25-\(\mu\)m diameter cathode sensor was used. It is covered with a 12.5-\(\mu\)-thick polypropylene membrane and applied directly to the anterior cornea. The sensor current was amplified by a Radiometer amplifier (PHM 73) linked to a microcomputer (Apple II Plus). The sensor was calibrated at 34°C using air-saturated water (155 mmHg \(pO_2\)) and nitrogen-saturated water (0 mmHg \(pO_2\)). Corneal oxygen uptake rate was determined by recording the time required for the oxygen tension in the membrane to drop from 140 to 100 mmHg. The result is expressed in mmHg per second. The average variability (SD) for three readings taken at a measurement session was $\pm 0.13$ mmHg/sec.

Endothelial cell density: Central corneal endothelium was photographed with a noncontact specular microscope. Cell density was determined by outlining the area of 30–40 cells depicted in each of three to five photographs (a total of 100–200 cells for each eye). The area was measured with the aid of a digitizer connected to a microcomputer. Mean cell density was then determined.

Corneal touch threshold: Corneal sensitivity was measured was a Cochet-Bonnet esthesiometer, which consists of a 0.12-mm diameter nylon monofilament encased in a cylinder. The esthesiometer was mounted on a triaxial holder so that its position and movement could be controlled in the x, y, and z meridians in an arrangement similar to that used by Milloidot. The length of the monofilament can be varied from 6.0 to 0.5 cm. This range corresponds to pressures of 11–200 mg/mm² (cross-sectional area of the filament, 0.0113 mm²). To obtain a measurement, the experimenter viewed the cornea and filament at close range. The esthesiometer was moved slowly toward the cornea at a constant velocity until visible bending of the filament occurred. The subject was asked to tap on the table if touch was felt. Presence or absence of the blink reflex was also noted. The esthesiometer was first set at maximum thread length of 6.0 cm and the length was then decreased by 0.5-cm increments until the patient felt three of six stimuli. This filament length was recorded as the value corresponding to the corneal touch threshold.
measurements were taken on both eyes of each subject. After these measurements, each subject wore the thick HEMA lens in each eye for 2 hr with the eyes closed. At the end of the 2-hr period, the lenses were removed and corneal thickness remeasured.

Osmotic stress test: Five of the unilateral ICCE aphakics returned for the osmotic stress test. Both eyes of each subject were immersed in air-saturated hypotonic saline (0.3% saline) in sealed goggles for 30 min. The flow rate of the solution through the goggles was maintained at a steady rate and the temperature maintained at 37°C. Ten central corneal thickness measurements were taken immediately before and after the osmotic stress test.

### Results

The baseline ocular characteristics of all subjects are listed in Table 1. Although the ICCE and PKP patients were examined on average 40 and 14 mo after surgery, respectively; the operated cornea was slightly thicker than the control cornea: 12 μm for the ICCE patients and 47 μm in the PKP group. The difference in corneal thickness between the individual’s two eyes in the ECCE group was not statistically significant (Student's two-tailed paired t-test). The corneal oxygen uptake rate was reduced in the operated eye of all patients (Table 1); the mean reduction was 6.8% in ECCE group, 10.7% in ICCE group, and 16.2% in PKP group. Central corneal touch threshold was also reduced in the operated eye in each group. The reduction in endothelial cell density was 10% with ECCE, 20% with ICCE, and 46% with PKP (Table 1).

When both eyes of all patients were subjected to the same hypoxic environment the unoperated eye swelled less (Table 2). The difference in the swelling response between the two eyes was statistically significant for all groups (Student's two-tailed paired t-test). The difference was, however, small in ECCE group, and 16.2% in PKP group. Central corneal touch threshold was also reduced in the operated eye in each group. The reduction in endothelial cell density was 10% with ECCE, 20% with ICCE, and 46% with PKP (Table 1).

Both eyes of five patients of ICCE group were subjected to an osmotic stress test. There was no
significant difference between the swelling of the operated and unoperated cornea (Student's two-tailed paired t-test, P > 0.10), the mean corneal swelling responses being 5.1% and 4.7%, respectively (Table 3).

Statistically significant correlations were found between the angular size of the incision and corneal touch threshold (0.828), endothelial cell density (—0.647), oxygen uptake rate (—0.327), hypoxic swelling response (—0.399) and the percentage difference in hypoxic swelling between the two eyes (—0.423) (Table 4). For all measured characteristics, the greater the angular size of the incision the greater was the effect. Percentage corneal swelling correlated with the indicators of corneal epithelial function (eg, reduced sensitivity and oxygen uptake rate), but did not correlate with endothelial cell density (Table 5).

**Discussion**

It is evident from the results that the greater the angular size of the incision the greater is the reduction in corneal sensitivity, indicating incomplete neural regeneration despite the long postoperative period. These results are in agreement with other corneal sensitivity studies after ICCE11 and PKP,12 which showed only partial recovery after 2–3 yr. Recent histochemic evidence indicates that nerve regeneration is both limited and slow in humans after PKP with only epithelial nerve leashes being observed.13 Greater and more rapid regeneration of stromal nerves occurs in rabbits following penetrating incisions14 that may indicate a species difference. The depth of an arcuate incision may also influence neural recovery. Recovery is more complete 60 days following nonpenetrating incisions than penetrating incisions.14

Our results indicate that removal of the crystalline lens does not cause the reduction in corneal oxygen uptake rate or hypoxic corneal swelling response that occurs in aphakic eyes. ICCE has a more pronounced effect on the observed parameters than does ECCE despite the fact that the lens has been removed in both groups. PKP also causes a marked reduction in corneal swelling and oxygen uptake rate in phakic eyes (Table 2).

No statistically significant difference in corneal swelling was observed between the operated and unoperated eye when the osmotic stress test was performed on five ICCE patients (Table 3). Clearly, the cornea of the aphakic eye is capable of swelling equally with the normal eye. Therefore, the reduction in swelling response seen with the hypoxic stress test has a metabolic rather than a physical etiology, eg, mechanical restriction of corneal swelling.15

To examine whether the reduction in swelling response was primarily associated with the altered ability of either the epithelium or the endothelium to function we investigated the association between swelling response and the indicators of epithelial function (corneal touch threshold and oxygen uptake rate) and endothelial cell density (cell/mm²). No correlation was found between corneal swelling response and endothelial cell density (Table 5), but the amount of corneal swelling correlated with both corneal touch threshold and oxygen uptake rate (Table 5). These results indicate that a change in the epithelium's ability to function plays a role in the reduced hypoxic corneal swelling response.

Corneal stromal edema after epithelial hypoxia is due to stromal lactate accumulation and osmotic swelling.16 The reduced corneal hypoxic swelling re-

### Table 3. Mean corneal swelling response to osmotic stress of ICCE patients

<table>
<thead>
<tr>
<th></th>
<th>Total cornea (%)</th>
<th>Total cornea (µm)</th>
</tr>
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<tbody>
<tr>
<td>Aphakic eye</td>
<td>5.1 ± 1.4</td>
<td>26.5 ± 8.3</td>
</tr>
<tr>
<td>Phakic eye</td>
<td>4.7 ± 2.3</td>
<td>24.3 ± 12.1</td>
</tr>
<tr>
<td>Difference</td>
<td>0.4 ± 1.8</td>
<td>2.1 ± 8.8</td>
</tr>
<tr>
<td>t value† (df = 5)</td>
<td>0.44</td>
<td>0.48</td>
</tr>
<tr>
<td>P</td>
<td>0.10</td>
<td>0.10</td>
</tr>
</tbody>
</table>

* Values mean ± standard deviation.
† Student's two-tailed paired t-test.

### Table 4. Correlations* of changes in corneal function with the angular size of corneal incision

<table>
<thead>
<tr>
<th>Equation</th>
<th>Correlation coefficient</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTT = 29.1 + 0.54 × IS</td>
<td>r = 0.828</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>ECD = 2934 – 3.34 × IS</td>
<td>r = –0.649</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>DCS = –13.3 – 0.071 × IS</td>
<td>r = –0.423</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>CS = 10.5 – 0.011 × IS</td>
<td>r = –0.399</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>O₂ = 3.98 – 0.001 × IS</td>
<td>r = –0.327</td>
<td>P &lt; 0.01</td>
</tr>
</tbody>
</table>

IS: angular size of corneal incision (degrees); CTT: corneal touch threshold (mg/mm²); ECD: endothelial cell density (cells/mm²); DCS: % difference in corneal swelling (%) between an individual's two eyes; CS: corneal swelling (%); O₂: corneal oxygen uptake (mmHg/sec).

* Pearson correlations; least-squares method of analysis.

### Table 5. Correlations* between corneal swelling and indicators of epithelial and endothelial functions

<table>
<thead>
<tr>
<th>Equation</th>
<th>Correlation coefficient</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS = 10.9 – 0.021 × CTT</td>
<td>r = –0.537</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>CS = 0.7 ± 2.3 × O₂</td>
<td>r = 0.363</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>CS = 8.0 ± 6.6 × 10⁻⁴ × ECD</td>
<td>r = 0.137</td>
<td>P &gt; 0.10</td>
</tr>
</tbody>
</table>

CS: corneal swelling (%); CTT: corneal touch threshold (mg/mm²); O₂: corneal oxygen uptake (mmHg/sec); ECD: endothelial cell density (cells/mm²).

* Pearson correlations; least-squares method of analysis.
sponse in the healed postsurgical cornea could perhaps be attributed to an increased endothelial permeability to lactate. If endothelial cell damage results in long-term increases in endothelial permeability, when hypoxia occurs there could be a greater efflux of lactic acid into the aqueous resulting in less edema. However, Bourne and Brubaker demonstrated that endothelial permeability to fluorescein is reduced with reduced endothelial cell density in PKP. The osmotic effects of lactate should therefore be increased rather than decreased if endothelial cell permeability is reduced. In fact, we found no correlation between reduction in hypoxic edema response and change in endothelial characteristics.

We therefore propose the following hypothesis: Corneal incision reduces metabolic activity because the epithelial nerve supply is interrupted. During hypoxia the reduced demand for oxygen results in a lower production of lactate; the stromal accumulation of lactate is therefore lower and so the cornea swells less rapidly. This implies that in the human cornea there is a neural influence on epithelial metabolic activity as suggested earlier by corneal denervation experiments in animals.

Key words: corneal incision, corneal swelling, corneal oxygen uptake, corneal touch threshold, corneal surgery

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References