Intracorneal Ring Segment Implantation Results in Corneal Mechanical Strengthening Visualized With Optical Coherence Elastography

Journal Article

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Publication date: 2022-07

Permanent link: https://doi.org/10.3929/ethz-b-000559372

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Originally published in: Journal of Refractive Surgery 38(7), <u>https://doi.org/10.3928/1081597X-20220608-01</u>

Funding acknowledgement:

174113 - Measuring local corneal biomechanical properties by multi-frequency vibrography: Moving towards an earlier diagnosis of pathologies and personalized computer simulations (SNF)

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31 Abstract:

32 **Purpose:** To quantify the mechanical impact of intracorneal ring segment (ICRS) implantation
 33 of different dimensions in an *ex vivo* eye model.

34 Methods: A total of 30 enucleated porcine eyes were assigned to ICRS implantation 35 (thickness 300 µm, angle 120°, 210° or 325°), tunnel creation only or virgin control. For 36 mechanical evaluation, each globe was mounted on a customized holder and intraocular 37 pressure (IOP) was increased in steps of 0.5 mmHg from 15 to 17 mmHg, simulating 38 physiologic diurnal IOP fluctuations. At each step, an optical coherence tomography volume 39 scan was recorded. Deformations between subsequent scans, as well as the locally induced 40 axial strains were analyzed using a vector-based phase difference method. The effective E-41 modulus was derived from the overall induced strain as a measure of global mechanical 42 impact.

43 **Results**: ICRS implantation increased the effective E-modulus from 146 and 163 kPa in virgin 44 and tunnel-only eyes to 149, 192 and 330 kPa in eyes that received a 5 mm optical zone ICRS 45 with 120°, 210° and 325° arc length, respectively; and to 209 kPa in a 6 mm optical zone ICRS 46 with 325° arc length. The most consistent effect was a shift towards positive strains in the 47 posterior stroma by 0.1 to 0.46 ‰ (factor 1.15 to 2.15) after ICRS surgery.

48 **Conclusions**: ICRS implantation reduces the overall tissue strain under the load of the IOP 49 and provokes posterior tissue relaxation. This effect is more dominant the longer the arc length 50 and the smaller the optical zone of the ICRS is. ICRS have not only a geometrical, but also a 51 mechanical impact on corneal tissue. This behavior might have clinical implications when 52 ICRS implantation is performed in biomechanically weakened keratoconus corneas.

53 Introduction:

54 Intracorneal ring segments (ICRSs) belong to the category of additive surgery and selectively flatten the cornea to correct optical errors like myopia¹, astigmatism², and especially corneal 55 56 ectatic diseases like keratoconus³. Commercially available ICRS are made of 57 polymethylmethacrylate and manufactured in different dimensions with a thickness between 58 150 and 350 µm, an arc length between 90° and 360°, an optical zone between 5- and 6-mm 59 diameter, a base width between 600 to 800 µm and a triangular, hexagonal or oval cross-60 sectional shape. Ophthalmic surgeons rely on experience and on nomograms supplied by the 61 manufacturers to select the most adequate ICRS for their patient. As a general rule, the thicker the ICRS and the smaller its optical zone, the larger is the achieved flattening effect^{4,5}. In this 62 63 context, short arc lengths better correct for astigmatism⁶ and long arc lengths better correct 64 for defocus. In keratoconus, the location of the cone with regard to a reference meridian and the keratoconus phenotype are additionally considered for ICRS selection.⁷ ICRSs may be 65 66 also successful in regularizing the corneal surface to facilitate contact lens fitting in severely 67 degraded corneas⁸.

While laser ablation surgery weakens the ocular shell, the mechanical impact of ICRS implantation is still not fully understood. Daxer et al⁹ proposed a model, in which the ICRS is considered to act as an artificial limbus leading to an overall strengthening of the cornea. On the other hand, numerical simulation studies suggest only a locally restricted mechanical impact, with negligible stress modifications in the corneal center ¹⁰ Although in clinical use for more than 2 decades¹¹, to date there are no published clinical data available to demonstrate a beneficial effect of ICRS implantation for keratoconus in terms of corneal biomechanics.

With the advent of new imaging approaches to assess mechanical characteristics noninvasively and with high spatial resolution, we have recently demonstrated using optical coherence elastography (OCE) that in an *ex vivo* eye model corneal strain distribution in the periphery of the ICRS remains unchanged, while the posterior stroma surrounded by the ICRS experiences a shift towards positive strains, ie relaxation.¹² This particular OCE set-up allows

80 to observe the mechanical response of ocular tissue under a close-to-natural loading 81 condition, which makes the interpretation of the derived strain maps directly comparable to 82 the post-surgical refractive outcome. While stress distribution is often assessed as a measure 83 of mechanical characterization, it is not directly accessible by imaging. However, OCE is able 84 to assess strain (ie., displacement), which is the immediate result (deformation) of the 85 interaction between the tissue and an applied stress field. Given that also theoretically strain 86 is directly related to stress - in an isotropic material linearly - the strain field is a meaningful 87 parameter to study.

88 Investigating changes in mechanical stress distribution as a consequence of ICRS 89 implantation is also relevant with regard to the refractive outcome, given that the corneal 90 stress-strain curve is non-linear. Local tissue relaxation thus would correspond to a local 91 weakening, which might be crucial when evaluating the long-term stability of the refractive 92 correction in degenerative diseases such as keratoconus. Usually, an additive surgery with 93 ICRS is performed in moderate to advanced cases of keratoconus. Several studies show 94 regularization of the corneal anterior surface of such cases and improvement of the corrected 95 visual acuity. On the other hand, predictability of these treatments still must be improved a 96 considerable, and the fact that mechanical effects are currently not taken into consideration might be one of the reasons ICRS surgery so far is less predictable^{11,13–15} than desired. 97

98 The purpose of the current study was to experimentally measure the axial strain field that is 99 induced after ICRS implantation of different dimensions and quantify the overall mechanical 100 impact of the surgery.

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102 Methods:

103 Implantation procedure

A total of 30 freshly enucleated porcine eyes were obtained from the local slaughterhouse (Zurich, Switzerland) and used within 8 hours. Eyes were collected from young adult pigs aged 6 to 8 months and had not been steamed. All eyes showed intact epithelium and were randomly divided into 6 experimental groups (n=5 per group) (see Table 1). Whereas group 1

108 eyes served as virgin control, in eyes of groups 2 to 6, a stromal channel was created under 109 a surgical microscope by means of a micrometer diamond knife (Duckworth & Kent Ltd., 110 United Kingdom) with an incision depth of 750 µm and a manual dissector (Mediphacos, Belo 111 Horizonte, Minas Gerais, Brazil) with a 5 mm optical zone in groups 2 to 5 and a 6 mm optical 112 zone in group 6. Eyes of groups 3 to 6 received an ICRS (Keraring, Mediphacos) with a 113 triangular cross-section, a thickness of 300 µm and different arc lengths of 120°, 210° and 114 325°, respectively, matching the optical zone of the stromal tunnel. This relatively high ICRS 115 thickness was chosen to guarantee a pronounced effect even in the porcine cornea, which is thicker than a human cornea (878 μ m¹⁶ vs 515 μ m¹⁷) for which the ICRS is designed for. 116

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118 Optical coherence elastography (OCE)

119 Imaging with a spectrometer based custom-built optical coherence tomography set-up with an 120 axial and lateral resolution of 3.9 and 12.4 µm in tissue, respectively, was performed during intraocular pressure (IOP) modulation similar as described earlier.^{18,19} OCT measurements 121 122 were performed 1 day after ICRS implantation. In the meantime, the eyes were stored in 123 plastic bags at 4°C. To compensate IOP reduction over night and leave time to reach an 124 equilibrium, approx. 45 min before elastographic assessment, the IOP of all eyes was adjusted 125 to 15 mmHg. A drop of PBS (phosphate-buffered saline) was applied on the corneal surface 126 immediately before measurement begin to prevent dehydration. For mechanical evaluation, 127 the IOP was increased in steps of 0.5 mmHg from 15 to 17 mmHg using a needle connected 128 to a water column and a syringe. At each pressure step, a volume scan consisting of 1000 x 129 100 A-scans spanning over an area of 11x11 mm was recorded. Large scale motion (more 130 than 1 pixel) between two subsequently recorded volume scans was computed using a cross-131 correlation approach. Subsequently, the axially induced corneal strain was determined by 132 calculating the axial gradient of the phase difference between the two scans, following a vector-based phase approach described before.^{18,19} In this context, axial direction refers to the 133 134 direction of the OCT beam, which coincided with the optical axis of the eye. Axial compressive strains are a sign of tissue compaction, and axial tensile strains indicate tissue expansion /
stretching. The measurement duration of a single cornea took 5 min.

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138 Data analysis

For a more consistent comparison between different samples, corneal thickness was normalized to 1. In order to evaluate the overall mechanical impact, the effective E-modulus E_{eff} was computed. It considers the overall strain amplitude $\Delta \varepsilon$ induced by the IOP change Δ_{iop} and the central corneal thickness T_{cct} :

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$$E_{eff} = \frac{\Delta_{iop}}{T_{cct} \cdot \Delta \varepsilon}$$

For statistical analysis, data demonstrated a normal distribution. Accordingly, subsequent
statistical comparisons relied on ANOVA and students t-test. A p-value of 0.05 was considered
to indicate a statistical significance.

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148 **Results:**

Corneal thickness was similar in all conditions (p=0.052 to 0.952), see Table 2. Tunnel depth in tunnel-only corneas was significantly (p=0.006 to 0.04) shallower than in corneas, in which an ICRS was implanted.

152

153 Optical coherence elastography

154 Figure 1 presents the enface view of the corneal structure and axial strain distribution. As 155 expected, the virgin and tunnel-only conditions demonstrate central tissue compression 156 (negative axial strain, blue color) in response to IOP increase, which slightly decreased in 157 amplitude towards the anterior stroma. In all corneas, in which an ICRS was implanted, a shift 158 towards positive strains (ie., relaxation, warmer colors) was observed in the posterior stroma 159 within the optical zone of the ICRS (white framed area in the posterior strain images). In the 160 anterior cornea, the same area seemed to experience a shift towards negative strains. The 161 size of this area did correlate well with the arc length of the ICRS.

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163 Figure 2 A summarizes the mean strain across the different conditions in the central cornea, 164 and in a 1 mm thick ring located interiorly adjoint to the ICRS. In general, the placement of an 165 ICRS tended to reduce the strain amplitude in the posterior stroma, both in the central and 166 ring region (blue and gray bars). This effect was stronger, the larger the arc length and the 167 smaller the optical zone of the ICRS was. ANOVA confirmed this trend and indicated with a 168 borderline significance of p=0.056 differences in the posterior central region based on the 169 different groups. At nearly all ICRS geometries, the increase in posterior strain was significant 170 compared to the virgin cornea, see **Table 3**. The effective E-modulus (black continuous line, 171 secondary y-axis) is a measure of the overall mechanical strength resulting after surgery. It 172 showed an increase after ICRS implantation, which was largest in the ICRS with the longest 173 arc length and smallest optical zone. Panels B and C present the strain profile as a function 174 of stromal depth in the central and ring region, respectively. While the most anterior corneal 175 layer demonstrated compression, the subsequent layer experienced relaxation and the 176 remaining posterior stroma similarly got compressed. This shape of the strain profile was 177 similar in all conditions and only the strain amplitude did vary.

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179

180 **Discussion**:

181 We compare for the first-time changes in axial corneal strain after ICRS implantation of 182 different dimensions and provide an interpretation of their global mechanical effect. We 183 confirm that localized corneal curvature changes are mostly restricted to within the optical 184 zone of the ICRS¹².

The posterior stroma demonstrated a consistent decrease in strain amplitude, which can also be interpreted as a shift towards positive strains. Interestingly, such a shift towards positive strains had previously been described in corneal regions subjected to corneal cross-linking treatment.¹⁹ Yet there, the shift could not be attributed to an overall decrease in strain amplitude, but rather to a shift in the strain profile. Independent of the underlying mechanism, 190 it seems that increasing the mechanical stability either by implanting a long-arc rigid ring 191 segment, or by directly stiffening the corneal tissue causes a spatially confined tissue 192 relaxation.

193 Recently, Daxer⁹ has introduced a strengthening factor to quantify the mechanical effect of the ICRS by considering it acts as an artificial limbus. It needs to be considered that this factor 194 195 is most accurate when evaluating the mechanical impact of a full (360° arc length) implant. In 196 the current study, we propose the effective E-modulus as a novel measure to quantify the 197 mechanical strengthening after ICRS implantation, also in implants of shorter arc lengths. A 198 particular advantage of the effective E-modulus is that is does not rely on theoretical 199 assumptions, but instead is directly related to tissue strain, and independent of corneal 200 thickness and the applied IOP. We showed that the effective E-modulus increases by up to 201 factor 2.25 in the 325° arc length ICRS with a 5 mm optical zone. This value comes close to the strengthening factor predicted by Daxer for a 360° ICRS suggesting that the two 202 203 parameters are comparable.

It is important to note that both, the effective E-modulus and the strengthening factor do not suggest an actual increase in tissue stiffness. The two parameters merely use mechanical denominations to describe the joint mechanical behavior of cornea + ICRS after surgery. Given the hyper-elastic nature of the natural corneal tissue, a decrease in tissue strain results rather in (minor) tissue softening than stiffening.

209 An additional point is that significant alterations of posterior stromal strain were identified at 210 210° and 325° arc length, but not at 120° arch length ICRS. Clinically, ICRS greater than 180° 211 arc length usually correct more defocus. The hypothesis is that such arcs from 180 degrees 212 on are able to exert forces on precisely contralateral areas of the cornea, thus flattening an 213 area larger than a specific single axis, and therefore correcting more defocus and less 214 astigmatism. Interestingly, significant increases in the estimated E-moduli were found 215 especially in these situations of 210° and 325° arc length, where a shift towards positive strains 216 was observed.

217 Tunnel depth was consistently shallower (33 to 60%) in the current study than typically 218 achieved in patients (70% to 75%). This can likely be attributed to the fact that porcine corneas 219 have been used in the current study and that the available diamond knife used for incision did 220 not allow for deeper tunnel creation. An unexpected observation was that tunnel depth in the 221 tunnel-only condition was persistently shallower than in eyes that received subsequent ICRS 222 implantation (p<0.05). We may speculate that is an artifact related to the measurement, as 223 tunnel depth in corneas with an ICRS was conducted once the ICRS was already in place, 224 and also because the cutting depth on corneas was initially set to be the same. A further 225 unexpected finding was a trend towards positive strains in the periphery of virgin corneas. This 226 effect likely can be attributed to the inclined corneal tissue with respect to the imaging beam. 227 In consequence, rather hoop strain than radial strain is measured, which naturally experiences 228 tissue extension upon IOP increase.

Opposite to the observations of our current and our previous¹² study, a recent numerical study 229 found that corneal stress after ICRS implantation¹⁰ relaxed in the anterior stroma, and 230 231 increased in the posterior stroma. The origin of this discrepancy likely emphasizes the 232 complex mechanical interactions in corneal tissue and demands for more sophisticated 233 mechanical models. On the other hand, one of the limitations of the current study is that 234 measurements were conducted in post-mortem tissue, which reportedly is subjected to 235 hydration artifacts arising from the degrading pumping efficacy of the endothelial cells. Thus, 236 the discrepancy might also result from a modified hydration state. A further limitation here is that porcine corneas are approx. 1.7 times thicker^{16,17} than healthy human corneas, and 237 238 approx. 2.2 times thicker than a keratoconic human cornea. Therefore, the strain amplitude 239 and strain pattern observed in the current study is likely not a realistic representation of a 240 typical clinical outcome, but rather gives an impression on the underlying working principle of 241 additive surgery. Future research is demanded to investigate the effect of ICRS implantation 242 directly in vivo in patients.

In conclusion, the current study quantifies the overall mechanical strengthening effect resulting after ICRS implantation of different dimensions and confirms a distinct effect in the anterior and posterior stroma. ICRS implantation reduces the overall tissue strain under the load of the IOP and provokes posterior tissue relaxation, that is more dominant in longer arc lengths and smaller optical zone ICRSs. ICRS have not only a geometrical, but also a mechanical impact on corneal tissue, which might impact the clinical behavior in eyes implanted with ICRS.

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252 Acknowledgement:

This study received funding from the Swiss National Science Foundation (Ambizione PZ00P2_174113 to SK). The authors thank Mediphacos (Belo Horizonte, MG, Brasil) for sponsoring the intrastromal ring segments and the surgical kit required for implantation.

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258 Author contributions:

EATN: designed the study, performed the ICRS surgery, data interpretation, revised themanuscript.

261 **FH**: provided surgical equipment and advise, revised the manuscript.

262 SK: conceived and designed the study, conducted the elastography measurements, data

263 processing and interpretation, drafted the manuscript, obtained funding.



266

267 Figure 1. Representative images of the different conditions (A) virgin – group 1, (B) tunnel-268 only – group 2, (C) 120° arc length ICRS with an optical zone of 5 mm – group 3, (D) 210° arc length ICRS with an optical zone of 5 mm – group 4, (E) 325° arc length ICRS with an optical 269 270 zone of 5 mm – group 5, (D) 325° arc length ICRS with an optical zone of 6 mm – group 6. At 271 each letter, the first panel presents the structural image together with the indicated location of 272 the stromal tunnel (dashed white line) and the ICRS (continuous white line). The second and 273 third panel present the mean axial strain distribution in the posterior and anterior stroma, 274 respectively. The white framed area in the posterior strain images indicates the region in which 275 a shift towards positive strains (i.e. relaxation) was observed.



Figure 2. (A) Mean axial strain in the central and ring region interior to the ICRS in the different conditions. The black line represents the effective E-modulus. Axial strain profile as a function of stromal depth in (B) the central and (C) the ring region - interiorly adjoint to the ICRS.

ant_center = anterior central region; post_center = posterior central region; ant_ring = anterior

ring region; post_ring = posterior ring region;

- **Table 1.** Summary of the different conditions analyzed in this study.

group	condition	optical zone (mm)	ICRS thickness (µm)
1	virgin	-	-
2	tunnel-only	5	-
3	1x120	5	300
4	1x210	5	300
5	1x325	5	300
6	1x325	6	300

Table 2. Summary of corneal and tunnel thickness in the analyzed groups

condition	thickness	tunnel depth	ratio
virgin	1180	-	-
tunnel-only	1174	391	0.33
1x120-SI5	1178	645	0.55
1x210-SI5	1257	636	0.51
1x325-SI5	1257	624	0.49
1x325-SI6	1191	708	0.60

Table 3. Statistical comparison of posterior stromal strain between different conditions. Bold

292 print indicates a statistical significant difference with p<0.05.

	virgin	tunnel- only-SI5	1x120-SI5	1x210-SI5	1x325-SI5	1x325-SI6
virgin tunnel-only-	-					
SI5	0.140	-				
1x120-SI5	0.662	0.532	-			
1x210-SI5	0.044	0.267	0.162	-		
1x325-SI5	0.017	0.082	0.115	0.917	-	

•••	1x325-SI6		0.024	0.216	0.124	0.933	0.822	-
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296	6 References:							
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