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

Intrastromal ring segment implantation results in corneal mechanical strengthening visualized with optical coherence elastography

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Word count: 2697

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Financial disclosure:
ET (none), FH (none), SK (none)

Abstract:

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

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

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

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

Introduction:

Intracorneal ring segments (ICRSs) belong to the category of additive surgery and selectively flatten the cornea to correct optical errors like myopia[1],astigmatism[2], and especially corneal ectatic diseases like keratoconus[3]. Commercially available ICRS are made of polymethylmethacrylate and manufactured in different dimensions with a thickness between 150 and 350 μm, an arc length between 90° and 360°, an optical zone between 5- and 6-mm diameter, a base width between 600 to 800 μm and a triangular, hexagonal or oval cross-sectional shape. Ophthalmic surgeons rely on experience and on nomograms supplied by the 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 context, short arc lengths better correct for astigmatism[6] and long arc lengths better correct 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 also successful in regularizing the corneal surface to facilitate contact lens fitting in severely degraded corneas[8].

While laser ablation surgery weakens the ocular shell, the mechanical impact of ICRS implantation is still not fully understood. Daxer et al[9] 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 decades[11], 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 non-invasively 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 to observe the mechanical response of ocular tissue under a close-to-natural loading condition, which makes the interpretation of the derived strain maps directly comparable to the post-surgical refractive outcome. While stress distribution is often assessed as a measure of mechanical characterization, it is not directly accessible by imaging. However, OCE is able to assess strain (ie., displacement), which is the immediate result (deformation) of the interaction between the tissue and an applied stress field. Given that also theoretically strain is directly related to stress - in an isotropic material linearly - the strain field is a meaningful parameter to study.

Investigating changes in mechanical stress distribution as a consequence of ICRS implantation is also relevant with regard to the refractive outcome, given that the corneal stress-strain curve is non-linear. Local tissue relaxation thus would correspond to a local weakening, which might be crucial when evaluating the long-term stability of the refractive correction in degenerative diseases such as keratoconus. Usually, an additive surgery with ICRS is performed in moderate to advanced cases of keratoconus. Several studies show regularization of the corneal anterior surface of such cases and improvement of the corrected visual acuity. On the other hand, predictability of these treatments still must be improved a 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.

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

Methods:

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 eyes served as virgin control, in eyes of groups 2 to 6, a stromal channel was created under a surgical microscope by means of a micrometer diamond knife (Duckworth & Kent Ltd., United Kingdom) with an incision depth of 750 μm and a manual dissector (Mediphacos, Belo Horizonte, Minas Gerais, Brazil) with a 5 mm optical zone in groups 2 to 5 and a 6 mm optical zone in group 6. Eyes of groups 3 to 6 received an ICRS (Keraring, Mediphacos) with a triangular cross-section, a thickness of 300 μm and different arc lengths of 120°, 210° and 325°, respectively, matching the optical zone of the stromal tunnel. This relatively high ICRS thickness was chosen to guarantee a pronounced effect even in the porcine cornea, which is thicker than a human cornea (878 μm[16] vs 515 μm[17]) for which the ICRS is designed for.

<u>Optical coherence elastography (OCE)</u>

Imaging with a spectrometer based custom-built optical coherence tomography set-up with an 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 were performed 1 day after ICRS implantation. In the meantime, the eyes were stored in plastic bags at 4°C. To compensate IOP reduction over night and leave time to reach an equilibrium, approx. 45 min before elastographic assessment, the IOP of all eyes was adjusted to 15 mmHg. A drop of PBS (phosphate-buffered saline) was applied on the corneal surface immediately before measurement begin to prevent dehydration. For mechanical evaluation, the IOP was increased in steps of 0.5 mmHg from 15 to 17 mmHg using a needle connected to a water column and a syringe. At each pressure step, a volume scan consisting of 1000 x 100 A-scans spanning over an area of 11x11 mm was recorded. Large scale motion (more than 1 pixel) between two subsequently recorded volume scans was computed using a cross-correlation approach. Subsequently, the axially induced corneal strain was determined by 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 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.

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}:

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

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.

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.

Optical coherence elastography

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

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

Discussion:

We compare for the first-time changes in axial corneal strain after ICRS implantation of different dimensions and provide an interpretation of their global mechanical effect. We confirm that localized corneal curvature changes are mostly restricted to within the optical zone of the ICRS[12].

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, it seems that increasing the mechanical stability either by implanting a long-arc rigid ring segment, or by directly stiffening the corneal tissue causes a spatially confined tissue relaxation.

Recently, Daxer[9] 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 is most accurate when evaluating the mechanical impact of a full (360° arc length) implant. In the current study, we propose the effective E-modulus as a novel measure to quantify the mechanical strengthening after ICRS implantation, also in implants of shorter arc lengths. A particular advantage of the effective E-modulus is that is does not rely on theoretical assumptions, but instead is directly related to tissue strain, and independent of corneal thickness and the applied IOP. We showed that the effective E-modulus increases by up to 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 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.

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

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

Opposite to the observations of our current and our previous[12] study, a recent numerical study found that corneal stress after ICRS implantation[10] relaxed in the anterior stroma, and increased in the posterior stroma. The origin of this discrepancy likely emphasizes the complex mechanical interactions in corneal tissue and demands for more sophisticated mechanical models. On the other hand, one of the limitations of the current study is that measurements were conducted in post-mortem tissue, which reportedly is subjected to hydration artifacts arising from the degrading pumping efficacy of the endothelial cells. Thus, 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 approx. 2.2 times thicker than a keratoconic human cornea. Therefore, the strain amplitude and strain pattern observed in the current study is likely not a realistic representation of a typical clinical outcome, but rather gives an impression on the underlying working principle of additive surgery. Future research is demanded to investigate the effect of ICRS implantation 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.

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.

Author contributions:

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

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

SK: conceived and designed the study, conducted the elastography measurements, data processing and interpretation, drafted the manuscript, obtained funding.

Figure, Tables and Captions

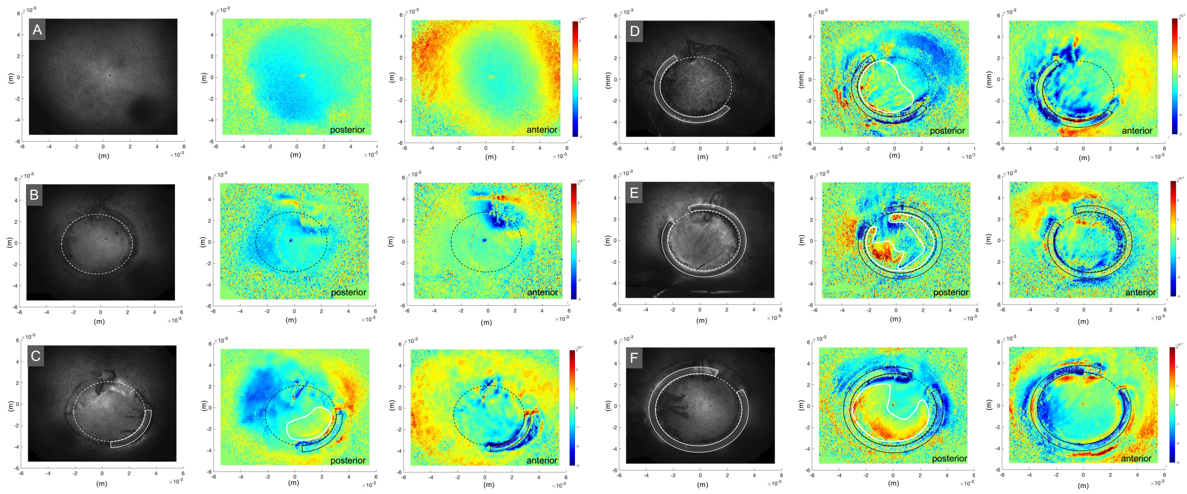

Figure 1. Representative images of the different conditions (A) virgin – group 1, (B) tunnel-only – group 2, (C) 120° arc length ICRS with an optical zone of 5 mm – group 3, (D) 210° arc length ICRS with an optical zone of 5 mm – group 4, (E) 325° arc length ICRS with an optical zone of 5 mm – group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

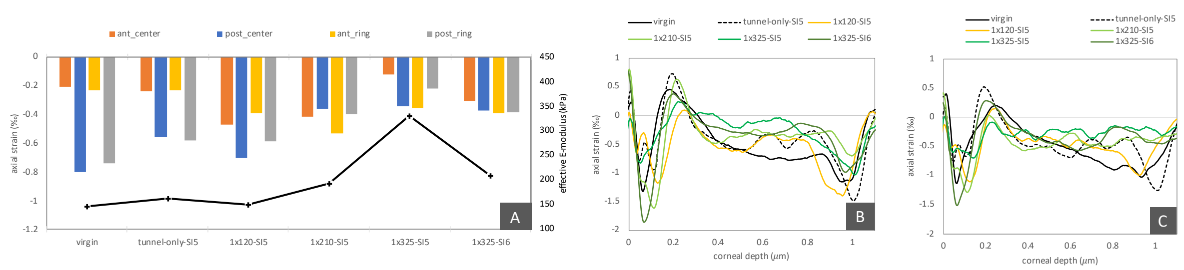

Figure 2. (A) Mean axial strain in the central and ring region interior to the ICRS in the different conditions. The black line represents the effective E-modulus. Axial strain profile as a function of stromal depth in (B) the central and (C) the ring region - interiorly adjoint to the ICRS.

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 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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