The Biomechanics of Keratorefractive Surgery

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Introduction

Corneal biomechanics is the study of the mechanical properties and responses of the cornea. The cornea's remarkable transparency and strength allow it to contain the intraocular pressure, serve as a protective layer and act as the major refracting surface of the eye. The shape of the cornea, and hence its refractive properties, is directly determined by its ultrastructural and biomechanical properties. In keratorefractive surgery the aim is to alter the cornea's refractive power by changing its shape. In the early days of laser vision correction it was assumed that the postoperative change in corneal shape was determined directly by the pattern of tissue ablation.[1] Now it is clear that this is an oversimplification because biomechanical and wound healing changes also influence final corneal shape.[2] This is illustrated by the hyperopic shift that typically occurs following phototherapeutic keratectomy, a procedure that a simple shape subtraction theory would predict to be refractively neutral.

Like all technical subjects biomechanics has its own language and this complicates understanding for the non-specialist. The purpose of this article is not to review biomechanical theory in general or even to describe all that is known about corneal biomechanics but rather to provide the reader with an understanding of the most clinically relevant concepts and principles so enabling an appreciation of how this important subject can impact on clinical practice.

Corneal Ultrastructure and Biomechanics

The cornea comprises 5 main layers of varying thickness. From anteriorly these are:

1. Epithelium (~50?m thick centrally)
2. Bowman's layer (uniform thickness of 8-9?m)
3. Stroma (480?m thick)
4. Descemet's layer (11?m at age 50; thickens with age at about 1.2?m per decade)
5. Endothelium (5?m thick)

Nearly all the biomechanical strength of the cornea is provided by its stroma comprised of multiple lamella running parallel to the corneal surface and containing parallel bundles of collagen fibres within a matrix. This matrix is composed of glycosaminoglycans covalently bound to core proteins to form proteoglycans and water. There are about 200 stromal lamellae averaging about 1.2 ?m thick and varying in width from 0.25 mm to greater than 1 mm.

In the anterior third of the stroma, lamellae are smaller than in its posterior two thirds and adjacent lamellae interweave to a certain extent.[3] This contrasts with a far more ordered array in the posterior two thirds of the stroma where lamellae are larger and there is minimal interweave (Figure 1).

It is important to distinguish these mechanical interlamellar connections from molecular corneal collagen cross links. The former are important for keratorefractive surgery since they couple mechanical forces between lamellae; the distribution of inter-weaving, sometimes referred to erroneously in the biomechanical literature as “cross-links” is shown in Figure 2. Increase in the number of the latter are thought to explain the increase in corneal stiffness that occurs with age and account for the increase in corneal stiffness following riboflavin-ultraviolet A treatment. Like all collagens, the basic structure of type I collagen, the predominant collagen in the stroma, is a triple helix. Relative to their diameter, individual collagen fibres are widely separated within the surrounding ground substance and it is more likely that corneal collagen cross links are within rather than between individual fibres.

The ends of stromal collagen fibres have never been seen on electron microscopy so individual fibres are generally assumed to traverse the cornea from limbus to limbus. In the central and paracentral cornea most fibres run either vertically or horizontally but there are an increasing number of obliquely orientated fibres as distance from the corneal centre increases (Figure 3).[4] In the central cornea, collagen fibre spacing is smaller than peripherally, a difference hypothesised to provide greater strength where the cornea is thinner.[5] There is some evidence that in the periphery some lamellae change direction to become concentric with the limbus.[6]

Basic Mechanical Concepts

Stress is a property of any material under load. An extensile load tries to separate atoms within a solid. This force is opposed by a large number of small internal stresses within the material, for example, inter-atomic bonds. Under the assumption that the load is uniformly distributed and the material homogeneous, the sum of all these stresses must equal the applied force and hence the mean stress is measured indirectly as the force or load per unit area or:

The deformation induced by stress is strain and is also conventionally expressed in relative terms as:

When most materials are stretched or compressed in one direction they narrow or expand in another. The ratio of these coupled changes, or equivalently the ratio of transverse to axial strain, is Poisson’s ratio. Biological tissues are assumed to be incompressible hence Poisson’s ratio is usually taken to be 0.5 in the cornea.

In elastic materials, such as a metal spring, a change in stress results in an instantaneous strain change. Below a certain maximum, the elastic limit, when the load is removed the object immediately returns to its original configuration. Beyond this limit permanent or plastic deformation occurs and at a certain point failure or material breakage results. Viscous materials such as honey undergo a continuing deformation for as long as the load is maintained. Viscoelastic materials, which include rubbers and nearly all biological materials, have an immediate elastic response to a change in load followed by an ongoing viscous response.

Viscoelasticity has several important consequences: First sustained loading results in progressive ongoing deformation, a process called creep. Second viscoleastic materials have a different stress-strain curve for loading and unloading. As a result they absorb energy during loading and emit energy, often as heat, during unloading, a phenomenon called hysteresis. The energy absorbed by the material due to hysteresis is dissipated as heat and can result in an accumulation of microdamage over time, a process called fatigue. Fatigue is responsible for the warming and then eventual cracking of rubber under cyclical loading. Both fatigue and creep have been implicated in the pathogenesis of mechanical failure in orthopaedic tissues and it is likely that the cornea is similarly susceptible.

Most biological materials are anisotropic so their mechanical properties vary according to the plane of measurement.   In the case of the cornea a load applied perpendicular to the corneal surface ('out of plane') will cause greater strain than a tangential ('in plane') stress because such a stress will tend to separate rather than stretch stromal lamellae (Figure 4). Consequently, it is relatively easy to perform a blunt lamellar dissection, especially in the posterior cornea, but a similar separation cannot be performed across the thickness of the cornea.

The ratio of stress to strain in a material is known as its Young's or elastic modulus defined as:

Unlike a spring in which, below its elastic limit, strain or displacement is directly proportional to load, the strain-stress relationships of biological tissues such as the cornea are non-linear (Figure 5). As a result, such materials do not have a single Young's modulus but can instead be described by their tangent or secant elastic moduli. The former is the gradient of the plot of strain against stress at the point in question and the latter is the average gradient to that point (Figure 6).

Stiffness, defined as:

is an absolute equivalent of the relative parameter Young's modulus dependent on overall load rather than stress. Although this absolute definition means that comparison of stiffness values between different materials is meaningless unless material geometry is known, stiffness is a useful way to compare the changes that occur in a particular object following surgery or to contrast materials with different geometries but the same mechanical function.

Two other constants relate to the strength of a material in addition to Young's modulus. The bulk modulus determines the compressibility of a material under uniform pressure. This is clearly unusual for the cornea so has little application to corneal biomechanics. The shear modulus is of greater significance since it represents the deformation of a material under a shearing force where the force acts parallel to one surface, the opposing surface being fixed. These forces apply in the cornea when collagen fibres are cut releasing tension and applying a shearing force via the interweaving of lamellae. In the human cornea it has been shown that shear deformation and hence shear strain is small. This may not seem obviously relevant but the in-plane biomechanical properties of the cornea theoretically are important when the corneal shape changes as a result of corneal weakening or when there are structural discontinuities, for example keratectomies, however created.

Laboratory Measurements

Broadly speaking, two main techniques have been used to study the mechanical properties of the cornea: strip extensiometry and inflation testing. In the former the mechanical response of the isolated tissue strips is quantified using a mechanical pulling machine and in the latter the effect of increasing intraocular pressure on corneal shape is characterised.

Although conceptually simple, these techniques have important limitations. Creation of corneal strips prior to testing by extensiometry necessarily involves severing many collagen fibres and changing the mechanical ground state of the cornea. Stretching and so straightening the cornea disrupts its normal architecture and affects the pattern of internal stress distribution. Being viscoelastic the cornea is particularly affected by changes in hydration and such variation is thought to have significant effects on its mechanical properties.

On top of these material factors, the relatively coarse resolution of most measuring devices means that grossly supraphysiological forces, often applied in a nonphysiological direction, are usually required for testing. Together these variables are believed to account for why measurements of corneal Young's modulus have varied over three orders of magnitude,[7-11] a range greater than is physiologically credible (Table 1). As a result the absolute values of corneal Young's modulus and other fundamental mechanical descriptors remain open to dispute although it does appear that the corneal stiffness is significantly reduced in keratoconus.[8]

Interlamellar cohesive strength testing (ICST) is a variant of extensiometry which involves quantifying the force required to complete a lamellar dissection. Whilst interpretation of the absolute values of ICST measurements is complicated by the same factors as extensiometry, it is possible that relative differences between regions of the cornea reflect genuine mechanical variation because they correlate with the ultrastructural differences in collagenous architecture described above. Specifically, it has been found that the stiffness of the peripheral cornea is approximately twice that of the central cornea along both the horizontal and vertical meridians[12, 13] and that the stiffness of the anterior third of the stroma is approximately twice that of its posterior two thirds.[14]

Following surgery the ends of severed collagen fibres do not reconnect and the cornea remains permanently weakened. This is evident clinically by fact that LASIK flaps have been relifted 11 years after surgery and that following blunt trauma eyes almost always rupture at the site of previous penetrating incisions. Comparing eyebank corneas from donors which had previously undergone successful LASIK with control corneas, the tensile strength (maximum stress when a material fails) of the central and paracentral part of the LASIK wound averaged just 2.4% of normal values and the mean peak tensile strength of the peripheral flap-wound interface was 28.1 % of normal 3.5 years postoperatively.[15]

Clinical measurements

One of the holy grails of anterior segment surgery is to develop a clinical device capable of measuring the properties of the in vivo cornea because this would enable correction of intraocular pressure measurements for biomechanical variation, identify patients at risk of complications of surgery and personalise treatment for those appropriate for surgery.

Dynamic corneal imaging (DCI) is a modification of corneal topography in which the change in the pattern of reflected mires following corneal indentation is analysed.[16] Although an innovative adaptation of a familiar technology, DCI remains in the prototype stage at present and this is to a large extent because the optimum means of data analysis is yet to be determined.

The only commercially available device that claims to measure the biomechanical properties of the in vivo cornea is the Ocular Response Analyser (Reichert).[17] This device, a modified pneumotonometer, detects the air jet pressure required for corneal applanation during both inwards and outwards corneal deformation. The mean of these two pressures is called the Goldmann-correlated IOP (IOPg) and the difference between them corneal hysteresis (CH). From these two measured parameters two related variables are derived, corneal resistance factor from CH and corneal compensated IOP from IOPg. It is argued that these derived values are relatively independent of confounding factors such as corneal thickness.

Although ORA CH values tend to be lower in both keratoconus and Fuch's endothelial dystrophy, this metric has yet be found of value as a diagnostic discriminator because there is overlap with the normal population. It is possible that this is due to ORA CH being defined as an absolute difference in applanation pressure, disregarding peak air jet pressure, rather than the conventional definition of hysteresis as the proportion of energy absorbed during a loading cycle.

Mathematical Models of the Cornea

In mechanical terms the eye is a pressure vessel with the cornea being part of the wall that contains the intraocular pressure. The simplest models of such situations are thin shell models, in some ways analogous to thin lens models in that the vessel wall is assumed to be of insignificant thickness compared to its radius. Such a model is the basis of the Imbert-Fick law underlying Goldmann applanation tonometry.

The assumptions on which thin shell models are based are an oversimplification because they assume that the cornea is of constant thickness and mechanically isotropic. Finite element analysis is a more complex analytical technique which uses a computer to predict the mechanical responses of structures when they are modelled as having multiple subunits.

Both thin shell and finite element models have been used to study the cornea but the uncertainty as to the fundamental mechanical constants of the cornea mean that the results obtained by them need be interpreted with caution. Similar concerns led to Jue & Maurice commenting on their first-order approximation to a simple structural model:
"Biological tissues are seldom regular enough in structure or consistent in mechanical properties to justify the loss in clarity of the relationships that result from more rigorous treatments."

Keratorefractive surgical procedures

Before the development of the excimer laser, incisional techniques were the mainstay of keratorefractive surgery. Both radial and tangential (arcuate) incisions were used with radial incisions being made to treat myopia and paired arc or tangential incisions to treat astigmatism.

Introduction of 193 nm argon-fluoride excimer laser into clinical practice in the late 1980s rapidly changed the paradigm of keratorefractive surgery by enabling highly controlled removal of corneal tissue and so modification of corneal curvature.[1] In photorefractive keratectomy (PRK), the prototype procedure, the excimer laser was used to ablate directly Bowman's layer and anterior stroma but interaction of molecules released by the regenerating epithelium and activated stromal keratocytes leads to a high incidence of haze and removal of the epithelium causes significant pain.

These complications of surface ablation meant that laser in-situ keratomileusis (LASIK), involving formation of a hinged lamellar flap which is replaced after the underlying stroma is ablated, rapidly became the most frequently performed laser vision correction procedure following its introduction in the early 1990s. Post-operative pain is less and visual recovery faster because surface disturbance is minimised. It has been estimated that 17 million LASIK procedures had been performed worldwide by 2004 and that more than 1 million are now performed each year in the USA alone.

Effects of surgery

With the dictum "so the force, so the extension" Hooke formalised the truism that objects deform in the direction of applied loads. Implicit in this description of the linear stress-strain relationship of most inorganic materials is the more general concept that the magnitude but not direction of displacement will increase if a structure under constant load is weakened. As a result pressure vessels will steepen and bulge in regions that are thinned or weakened.

This is what happens following radial keratotomy (RK). The wounds gape and the cornea bulges in the region where the incisions have been made and this results in secondary flattening of the cornea. The exact amount of flattening that occurs will obviously depend on factors such as incision depth, length, orientation, length and number. Careful observation suggests that not only does wound gape occur but also compression of anterior tissue between the wounds, meridian tissue elongation at and between wounds and little involvement of endothelial side tissue. The two points of note here relating to the biomechanical response are: additional incisions do not induce more flattening since there is already relaxation of anterior tissue between the wounds but further flattening will be caused if the depth of the incisions increases.

A paradox of excimer laser keratorefractive corneal surgery is that mid-peripheral and central steepening response is not seen postoperatively. Instead, both phototherapeutic keratectomy (PTK) and LASIK flap creation results in central corneal flattening and a hyperopic shift. The most widely accepted theory holds that the reason for this is corneal structural anisotropy.[2, 18] Surgery results in thickening of the stroma outside the ablation zone and it is argued that this process generates a centrifugal force that is transmitted to deeper stromal layers through interlamellar connections so pulling the central stroma flat.

This hypothesis is somewhat counterintuitive because it might be assumed that when load bearing collagen fibres are severed the load previously borne by these now mechanically inert fibres would be transferred to the underlying intact fibres resulting in a steepening and bulging of the central cornea. The outwards force postulated to cause biomechanical flattening by the hypothesis described above cannot be measured and it is possible that the flattening that undoubtedly does occur is non-mechanical in nature and caused, for example, by changes in epithelial thickness or stromal hydration or during wound healing.

It is also important to appreciate that current generation clinical instruments are not well suited to the measurement of biomechanical change. As well as the fact that non-mechanical factors contribute to postoperative change in anterior corneal shape, the utility of Placido ring videokeratography is further limited by the most central curvature values being obtained by extrapolation rather than direct measurement. With the exception of very high frequency ultrasound systems, which claim an axial resolution of about 1 µm, most commercially available anterior segment imaging instruments have axial resolutions less than the changes in displacement of about 5 µm believed to be caused by surgery. For example, an axial resolution 8-18 µm is typical for anterior segment time domain optical coherence tomography and the resolution of instruments based on Scheimpflug and slit-scanning principles is even lower.

Measurement of IoP in the post Refractive Surgery Cornea

Corneal thickness and curvature often changes dramatically following excimer laser refractive surgery and this invalidates the assumptions on which Goldmann applanation tonometry (GAT) is based. Tables for correcting the measured value according to central corneal thickness do exist but these necessarily require a knowledge of this variable and are generally based on the non-refractive surgery population. As a result, these tables may not be generalisable to the post-surgical population. An alternative approach is to measure IOP using a device such as the ORA or Pascal dynamic contact tonometer which are believed to be considerably less affected by biomechanical variation than GAT.

Long-term mechanical stability

RK is now rarely performed because the 10 year Prospective Evaluation of Radial Keratotomy study showed that there is a continued hyperopic shift giving rise to its nickname the “gift that keeps on giving.” In the case of excimer laser keratorefractive surgery, all of the longest follow up studies of myopic and hyperopic PRK demonstrate refractive stability. In contrast, most long-term reports suggest a trend towards refractive instability following LASIK with those that do not tending to be complicated by high retreatment rates. More worryingly, LASIK surgery has been associated with occasional development of postoperative ectasia, a complication that is extremely infrequent following surface ablation.

These differences in stability can be accounted for by the differing number of collagen fibres cut in each type of procedure and the fact these load bearing fibres do not reconnect following surgery. RK involves multiple long and very deep incisions which necessarily sever many collagen fibres and a greater number of fibres are cut in LASIK than PRK because the depth of ablation is so much greater. It has been calculated that when 6.0 D of myopia is corrected 232,260,000 collagen fibres are severed during LASIK compared to 5,331,200 in PRK a 43.6 fold difference (Professor John Marshall, personal communication).

Biomechanical optimisation of surgery

To date efforts to capitalise on the mechanical superiority of surface ablation by controlling the wound healing response responsible for its principal complication haze have only met with limited success. Although less common than after PRK, haze remains a complication of so-called advanced surface ablation procedures such as epithelial laser assisted keratomileusis (epiLASIK) and laser epithelial keratomileusis (LASEK). Intraoperative application of mitomycin C is very effective but there are concerns as to the long-term effects of this treatment on keratocyte and endothelial cell density. Whilst work continues to overcome these problems attention has also been directed towards modifying the mechanical effect of intrastromal ablation.

The development of clinical femtosecond lasers mean that mechanical microkeratomes are no longer the only means of cutting LASIK flaps. Compared to the meniscus flaps cut by conventional mechanical microkeratomes, femtosecond laser flaps are technically more simple to create and have a more accurate, precise and uniform thickness. As a consequence femtosecond lasers can cut consistently shallower flaps than mechanical microkeratomes and do so with a very low risk of intraoperative complication. This technological advance has enabled sub-Bowman’s keratomileusis (SBK), LASIK performed under a 90 to 100 µm thick flap, to become reality. It has been suggested that SBK might combine the advantages of surface and intrastromal ablation with the drawbacks of neither and early results appear to support this claim.[19]

Whilst outside the scope of this review, the reader should also be aware that femtosecond laser technology can be used to trephine the cornea during corneal transplant surgery. Whereas with mechanical technology it is not practical to create donor tissue buttons with anything other than parallel sides, complex configurations are simple to cut with the femtosecond laser. Of these the top-hat configuration seems most promising and compared to conventional penetrating keratoplasty requires fewer sutures to be secured, causes less post-operative astigmatism, allows earlier suture removal and is more resistant to wound burst following IOP increase.

Biomechanical modification

Historically management of ectatic disorders has been based on a paradigm of refractive support in an attempt to avoid or at least delay the need for keratoplasty surgery. This is being challenged by the development of the minimally invasive corneal collagen cross linking procedure.[20] Taking less than an hour to perform and using the photosensitiser riboflavin this treatment results in an impressive increase in the stiffness of corneas in the laboratory and is effective in arresting, and sometimes reversing, the progression of keratoconus and post-LASIK ectasia.

Conclusion

The mechanical properties of the cornea are determined by its ultrastructure with nearly all its strength being provided by stromal collagen fibres. The greater number of interlamellar connections in the anterior third of the stroma and the more complex weave of lamellae in the peripheral cornea give these regions approximately twice the stiffness of the posterior stromal two thirds and central cornea.

In keratorefractive surgery, corneal shape is changed either indirectly by weakening the cornea or directly by selective tissue ablation. The former is the mechanism of the effect of radial and astigmatic keratectomy; excimer laser vision correction works through a combination of both mechanisms. A consequence of corneal structural and mechanical anisotropy is that the biomechanical impact of refractive surgical incisions is much greater than would be predicted by depth alone.

The dramatic changes in corneal thickness and curvature that often follow keratorefractive surgery invalidate the assumptions underlying Goldmann applanation tonometry. No commercially available clinical instrument is yet able to provide a clinical useful measure of corneal biomechanical properties and correct for this source of error although novel tonometers have been developed that are believed to be less influenced by such variation.

Our understanding of normal corneal biomechanical variation is likely to improve in coming years as research efforts continue. If a device capable of characterising the biomechanical properties of the cornea were to be developed this would enable true IOP to be calculated, patients at risk of complications of post-refractive surgery ectasia to be identified preoperatively, personalise treatment in those for whom it is appropriate and monitor the changes caused by therapeutic interventions such as corneal collagen cross-linking.

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Figure Captions

Figure 1. Scanning electron micrographs demonstrating the change in structure of the stroma. From top to bottom: Bowman's layer showing disorganised collagen fibres; anterior stroma demonstrating interweaving of collagen fibres within adjacent lamellae; posterior stroma showing perpendicular orientation of collagen fibres within adjacent lamellae and the absence of interweaving (EM sections courteousy of Professor John Marshall, St Thomas' Hospital).

Figure 2. Indication of the distribution of inter-weaving of collagen fibres between stromal lamellae.

Figure 3. Regional variation in probable collagen fibre orientation within stromal lamellae.

Figure 4. Stress can change with the direction in which it is measured since the cornea is anisotropic. Stress is commonly resolved into 3 orthogonal components: normal or cross-plane and two in-plane components: meridional and circumferential.

Figure 5. Stress-strain curves for the human cornea under loading from intraocular pressure and relaxation. The difference between the curves is known as hysteresis (see text). (Plotted from data after Hjordtal (1995) and fitted with a 3 term power series. Data points are mean ± SEM).

Figure 6. Illustrative non-linear strain-stress curve demonstrating both secant and tangent methods of measuring Young's modulus. Note also how Young's modulus changes with load.

Table Captions

E value MPa (IOP mm Hg)	Author	Method
6.8	Nyquist (1968)	Strip extensiometry
57 (2350)	Andreassen et al. (1980)	Strip extensiometry
4 (30)	Nash et al. (1982)	Strip extensiometry
0.37 (10)	Woo et al. (1972)	Intact cornea, in-plane
0.025	Sjontoft and Edmund (1987)	Intact cornea, in-plane
3.0 (6)	Hjortdal (1995)	Intact cornea, in-plane
0.027	Schwartz et al. (1966)	Intact cornea, normal (cross-plane)
0.030	Battaglioni and Kamm (1984)	Intact cornea, normal (cross-plane)

Table 1. Young's modulus measured for corneal strips and intact corneas. Note the wide variation in values and anisotropy between cross-plane and in-plane values. Values vary with load/stress because of the non-linearity in the stress-strain curve.