Tonometry: A Study in Biomechanical Modelling.

Appraisal and utility of measurable biomechanical markers.

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Abstract: Research Rationale

Goldmann Applanation Tonometry (GAT) is the recognised 'Gold Standard' tonometer. However this status is refuted by eminent authors. These contradictory views have driven the initial goal to assess, from first principles, the evolution of GAT and to experimentally evaluate its utility and corrections. Subsequently, an important caveat became the evaluation of Corneal Hysteresis and Corneal Resistance Factor.

Chapter 1. Biomechanical building blocks are defined and constitutive principles incorporated into continuum modelling. The Imbert-Fick construct is re-interpreted a simple biomechanical model. GAT corrections are also appraised within a continuum framework; CCT, geometry and stiffness. These principles enable evaluation of alternative tonometer theory and the evolving biomechanical markers, Corneal Hysteresis (ORA-CH) and Corneal Resistance Factor (ORA-CRF).

Chapter 2 appraises corneal biomechanical markers, CCT, curvature, ORA-CH and ORA-CRF in 91 normal eyes and the impact these have on three tonometers: GAT, Tonopen and Ocular Response Analyser (ORA). Tonopen was the sole tonometer not affected by biomechanics. CCT was confirmed the sole measurable parameter affecting GAT. ORA did not demonstrate improved utility. ORA-CH and ORA-CRF do not appear robust biomechanical measures.

Chapter 3 assessed agreement between GAT, the ORA measures and Tonopen. Tonopen is found to measure highest and raises the question should a development goal emphasise GAT agreement or improvement?

Chapter 4 assessed repeatability of the three tonometers and biomechanical measures keratometry, pachymetry, ORA-CH and ORA-CRF on 35 eyes. Coefficients of Repeatability (CoR) of all tonometers are wide. Effects assessed in Chapter 5 may be masked by general noise. ORA does not appear to enhance utility over GAT.

Isolation of corneal shape change via Orthokeratology (Chapter 5) demonstrate ORA-CH and ORA-CRF reflect, predominantly, a response to corneal flattening. It is proposed they do not significantly reflect corneal biomechanics.

After reviewing models for tear forces (Chapter 6), a refined mathematical model is presented. Tear bridge attraction is minimal and cannot explain under-estimation of IOP by GAT in thin corneas. CCT corrections and the Imbert-Fick rules are incompatible.

Chapter 7 summarises findings. The supremacy of GAT is likely to remain for some time, reflecting the sheer magnitude of overturning 60 years of convention, historical precedent, expert opinion as well as the logistical and educational difficulties of redefining standards and statistical norms.

Dedicated to

Captain James Stanley Frampton

&

Doreen Frampton

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List of Abbreviations

CC	Corneal Curvature
CCave	Average of Keratometry readings
CC..ave	Average of Keratometry readings in DTA (Chapters 2, 4)
CCave..Pre	Average of Keratometry readings pre-orthokeratology in DTA (Chapter 6)
CCave..Post	Average of Keratometry readings post-orthokeratology in DTA (Chapter 6)
CCT	Central Corneal Thickness
CCTus	Central Corneal Thickness via ultrasound pachymetry
CCTus..pre	Ultrasound pachymetry pre-orthokeratology (Chapter 6)
CCTus..post	Ultrasound pachymetry post-orthokeratology (Chapter 6)
CoR	Coefficient of Repeatability (Chapter4)
DCT	Dynamic Contour Tonometer
DTA	Decision Tree Analysis
GAT	Goldmann Applanation Tonometer
GAT..Pre	GAT pre-orthokeratology in DTA (Chapter 6)
GAT..Post	GAT post-orthokeratology in DTA (Chapter 6)
IOP	Intraocular Pressure
IOPGAT	GAT measured intraocular pressure in the GAT Equation
IOPT	Intracameral intraocular pressure in the GAT Equation
LoA	Bland-Altman Limits of Agreement
M'	Elasticity of the cornea pushing toward the tonometer
N'	Surface tension of tears pulling the tonometer probe toward the cornea
NCT	Non-Contact Tonometer
ORA-CH	Corneal Hysteresis as measured by the Ocular Response Analyser
ORA..CH	ORA measure of Corneal Hysteresis in DTA (Chapters 2, 4)
ORACH..Pre	ORA measure of Corneal Hysteresis pre-orthokeratology in DTA (Chapter 6)
ORACH..Post	ORA measure of Corneal Hysteresis post-orthokeratology in DTA (Chapter 6)
ORA-CRF	Corneal Resistance Factor as measured by the Ocular Response Analyser
ORA..CRF	ORA Corneal Resistance Factor in DTA (Chapter 2, 4)
ORACRF..Pre	ORA Corneal Resistance Factor pre-orthokeratology in DTA (Chapter 6)
ORACRF..Post	ORA Corneal Resistance Factor post-orthokeratology in DTA (Chapter 6)
ORA-IOPcc	Corneal Compensated IOP as measured by the Ocular Response Analyser
ORA..IOPcc	ORA measure of Corneal Compensated IOP in DTA (Chapter 4)
ORAIOPcc..Pre	ORA Corneal Compensated IOP pre-orthokeratology in DTA (Chapter 6)
ORAIOPcc..Post ORA	Corneal Compensated IOP post-orthokeratology in DTA (Chapter 6)
ORA-IOPg	GAT equivalent IOP as measured by the Ocular Response Analyser
ORA..IOPg	ORA measure of GAT equivalent IOP in DTA (Chapter 4)
ORAIOPg..Pre	ORA GAT equivalent IOP pre-orthokeratology in DTA (Chapter 6)
ORAIOPg..Post	ORA GAT equivalent IOP post-orthokeratology in DTA (Chapter 6)
P1	ORA traditional NCT IOP equivalent reading at initial inward applanation
P2	Second, outward applanation reading by ORA as cornea returns from concavity
Pre-OK	Referring to measures recorded prior to orthokeratology
Post-OK	Referring to measures recorded post orthokeratology

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Chapter 6

Chapter 1: Tonometry: A Study in Biomechanics

1.1 Tonometry: An Introduction

1.1.1 Current Recommendations, Clinical Best Practice and Literature Conflict

Community optometrists rely heavily on guidelines and protocols to direct their clinical decision making. Busy practitioners, unlikely to critically appraise research, rely on governing bodies to discriminate evidence and disseminate concise implementations. The 16 page 'Quick Reference Guide' (NICE 2009a) gives a synopsis of the recommendations, but not the critiqued supporting evidence, of the full NICE guidance on the diagnosis and management of chronic open angle glaucoma (NICE 2009b).

The NICE guidelines on glaucoma (2009b) represent current opinion on the diagnosis and management of chronic open angle glaucoma in Britain. This document, based largely on the evidence from the major longitudinal studies, synopsised by the European Glaucoma Society (EGS 2003), states patients should be offered Goldmann Applanation Tonometry (GAT) and Pachymetry as part of the diagnostic process. NICE (2009b) further emphasise GAT remains the 'Gold Standard' for tonometry, albeit with a correction for Central Corneal Thickness (CCT). CCT is well established as a strong predictive factor for conversion to frank glaucoma (Wolfs *et al*. 1997, Brandt *et al*. 2001, Gordon *et al*. 2002, Palmberg 2002, EGS 2003, EGPS Group 2007, OHTS Group & EGPS Group 2007).

Ruokonen *et al*. (2007) and Kerstein *et al.* (2011) suggest International Standard ISO 8612 for tonometers indicates new tonometers must be tested against the reference standard; GAT. This is not strictly accurate; the document stipulates true IOP cannot be measured without invasion of the globe (European Committee for Standardisation 2009). The choice of GAT as reference standard in ISO 8612 is qualified as representing the minimum requirement; by inference manometric calibration would be more appropriate. The classification of GAT as reference tonometer appears to reflect

a pragmatic expedient rather than choice of an ideal benchmark. Goldmann and Schmidt (1957, 1961) certainly referenced against manometric measures; a logical imperative if fundamental improvements on the existing reference, Schiőtz, were to be realised. Likewise, post GAT, the Dynamic Contour Tonometer (DCT), with its fundamentally different theoretical premise of the Law of Hydrostatic Pressure rather than the Imbert-Fick principle, was calibrated against manometric references, not to the ISO standard of GAT (Kanngiesser *et al.* 2005).

The Guideline Development Group of NICE did consider evidence to support the use of other tonometers, but the status of GAT as 'Reference Standard' was not disputed. The exercise was to consider whether other tonometers demonstrate acceptable agreement to GAT, rather than accuracy in measuring true intracameral IOP. Since no instrument can be assured to be perfectly accurate, such a comparison can suggest higher variability for the instrument being compared (Bland and Altman 1986). The group also cite 'Expert Opinion', lowest on the evidence hierarchy (Chung and Ram 2009), to support the continued use of GAT as the most precise instrument. Woolf *et al*. (1999) does suggest recommendations can be influenced by the experience of clinicians. Reliance on 'Expert Opinion' can therefore be detrimental (Kane1995) and may also reflect time constraints in preparing protocols (Woolf *et al.* 1999).

Could historical precedent, inclusion as reference tonometer in ISO 8612 and familiarity with GAT constrain innovation? Certainly, both GAT and its CCT corrections have been criticised.

Mark (2012) suggests as early as 1895 Koster showed the Imbert and Fick assumptions to be untenable. Markiewitz (1960) also challenged the 'Imbert-Fick Law' after the introduction of GAT, considering it without support of universal laws or principles. Whitacre and Stein (1993) state categorically acceptance of GAT is unwarranted. The authors suggest the 'Imbert-Fick Law' isn't a law, rather an explanation for tonometry where none of the assumptions are true. Brandt (2004) considers our ability to accurately measure IOP far weaker than imagined and we rely on a flawed measure on which to base clinical decisions.

Stodtmeister (2012) is also critical of the unconditional acceptance of GAT. The author speculates few people critically appraised the original papers. The biophysical and statistical details being forgotten, Stodtmeister suggests, GAT has become an unchallenged standard of measurement.

CCT correction nomograms have also been questioned (Hager *et al*. 2008, Boehm *et al.* 2008, Brandt 2004, Doughty and Zaman 2000). Proposed corrections range from 2mmHg to 7.1mmHg per 100µm of corneal thickness (Ehlers *et al*. 1975, Whitacre *et al*. 1993, Doughty and Zaman 2000, Tonnu *et al*. 2005, Kohlhaas *et al*. 2006). Indeed Brandt *et al*. (2001) indicate linear corrections could lead to a negative value of IOP in specific cases. Further, Brandt (2004) emphasises, since no nomogram proposed to adjust GAT readings for CCT has been validated, clinicians cannot use the data (Brandt 2004). Young (2014) certainly warns the desire to characterise the cornea with a single number is simplistic and unrealistic. While CCT is often presented as an independent parameter (Whitacre *et al.* 1993, Whitacre and Stein 1993, Herndon *et al*. 1997, Damji *et al.* 2003, Rask and Behndig 2006, Harada *et al.* 2008) it is more likely a measurable reflection of corneal biomechanics. Whitford *et al.* (2015) certainly suggest corneal biomechanics an expression of geometry, incorporating thickness and topography, and material stiffness, contingent on corneal microstructure.

The status of GAT as 'Gold Standard' (NICE 2009b) is incompatible with the contradictory opinions described (Markiewitz 1960, Whitacre and Stein 1993, Brandt 2004, Stodtmeister 2012). Casson *et al.* (2012) suggest it is prudent to be sceptical of any scientific paradigm and Śródka (2010) believes no assumption so obvious to nullify the need for testing. These polarised views have driven the primary goal of this dissertation to assess, from first principles, the evolution of GAT and then to test the GAT principles to evaluate the instrument's relevance and utility.

Tonometry reflects a mechanical and biomechanical challenge. Before any meaningful interpretation of literature or experimental evidence can be made, the building blocks of biomechanics and the methodologies of biomechanical modelling must be defined. Principles on which techniques are based must be critiqued within this framework. The origins of the 'Imbert-Fick' construct are certainly difficult to access, potentially allowing interpretative vagaries to creep into the literature.

1.1.2 Chapter Aims

To establish the constitutive principles of biomechanics and to incorporate these laws into continuum modelling philosophies. To clarify biomechanical nomenclature.

To understand corneal properties and the simplifications presented for modelling purposes.

To critique, from the original source material, the assumptions and conclusions driving the evolution of GAT.

To critique GAT corrections within a continuum framework; CCT, geometry and stiffness.

To appraise alternative tonometer theory biomechanically as well as evaluating the evolving biomechanical markers measurable *in vivo*; Corneal Hysteresis and Corneal Resistance Factor, as measured by the Ocular Response Analyser.

1.2 Mechanics and Biomechanics: The Building Blocks of Models

1.2.1 Models

Fung (1983, 1990) states, from molecules to organisms everything must obey the laws of mechanics. However, the complexities of biological multicellular tissues make the collective behaviour of tissue not apparent from the cellular scale (Tlili *et al*. 2015). The intricacies of organ ultrastructure and microstructure necessitate the reliance on phenomenological descriptors of the behaviours of interest (Humphrey 2002); Harada *et al.* (2008), for instance, suggest corneal biomechanics can be inferred via the measurement of CCT.

Consequently, Tlili *et al.* (2015) suggest biologists use the term 'model' to represent the behaviour of an archetypal organ of interest while physicists consider 'models' to represent analytical equations or numerical simulations. Further, modelling can be considered at the continuum or constitutive levels. A constitutive equation characterises the local properties of a material within the framework of continuum mechanics (Tlili *et al*. 2015). A purely constitutive approach reflects a 'bottom up' cell based approach (Tlili and colleagues 2015). Conversely, successful continuum models are artificial simulations of relevant mechanical variables of interest, on an intermediate scale and representing larger tissues.

Both approaches are important to understand physiology and pathophysiology complexities, allowing unification of theoretical ideas and experimental findings (Humphrey 2002). Theoretical *models*, based on mechanics unmeasurable *in vivo*, help predict tissue behaviour, target new experiments or simulate experiments not physically possible. Further, constitutive models allow the interpretation of *in vivo* experimental results suggesting which assumptions or parameters best describe those results.

Regardless of difficulties, Fung (1993) indicates the goal of biomechanics is to specify material behaviour at a constitutive level; although the author allows a broader definition of the term. Atoms and molecules are organised into cells, tissues, organs and organisms; biomechanically the smallest tissue volume considered is multicellular (Fung 1993). A constitutive equation, as defined by Fung (1993), describes the physical property of a tissue retaining independence of extraneous frames of reference; it remains

axiomatic under a range of normal conditions. In reality, the description of many mechanical principles as constitutive is not accurate, by necessity the scale and range of physical assumptions are minimised until a quasi-constitutive level of behaviour can be anticipated and experimental and modelling outcomes predicted. In general, Buzard (1992) suggests the endeavour is to ascertain the smallest homogenous component of a composite material.

This is valid for classical mechanics as well as biomechanics. Young and Budynas (2002) considering general mechanics, indicate it is customary to assume materials are elastic, isotropic, homogenous and infinitely divisible without change in properties; characteristics rarely true. The authors expand; structural materials are aggregates of crystals, fibres or cemented particles, the arrangement of which may be random or systematic. A random arrangement can only be considered isotropic if the part considered is large in comparison to its constitutive unit. A systematic arrangement will result in varying elastic properties and material strength depending on the direction of load.

Further, unlike classical mechanics living composites are, *in vivo*, under habitual levels of stress (Fung 1973, Elsheikh *et al*. 2013). To model these systems, morphology, material properties and function need amalgamation (Fung 1983). Evans and Avril (2012) explain it is difficult to measure constitutive properties of living tissues, making constitutive equations for most biological systems unknown (Fung 1993). Virtually by necessity a continuum approach is required.

1.2.2 Principles of Mechanics, Biomechanics and Physics

Fung (1990) stipulates the prerequisite of compliance with the axiomatic laws of physics and mechanics.

1.2.2.1 Force

$$\mathbf{F}=m\mathbf{a} \qquad \textbf{(1.2.1)}$$

Where:
F: Force
m: Mass
a: Acceleration

The term ‘ma’ (mass x acceleration) Newton called inertial force.

Force is a vector function and must be stipulated by both magnitude and direction. The net force acting on a surface, when the external force is acting obliquely, will represent only the component of total force acting normally to the surface.

Newton’s First Law of Motion: If the force acting on a particle is zero, velocity will remain constant. **(1.2.2)**

Newton’s Second Law of Motion: If the force acting on a particle is not zero the particle will accelerate. **(1.2.3)**

Newton’s Third Law: Inertial Force = External Force **(1.2.4)**

Equilibrium reflects a specific set of conditions of motion when there is no acceleration of any particle in the body. Buzard (1992) states this stability indicates all external forces applied to an object will be reflected by internal (inertial) forces set up within the material body. Simply put, Newton’s Third Law states: ‘to every action there is always an equal and contrary reaction’ (Thomson and Guthrie 1867).

1.2.2.2 Pressure

Pressure is related to a force acting normally on a unit area of a surface (Oxford Paperback Reference 2009), by the equation (Bird and Ross 2012):

$$P = \mathbf{F}/A \qquad \textbf{(1.2.5)}$$

Where:
F: Force acting on a body
A: Area over which the force is acting
P: Pressure

Fung (1993) states palpation is commonly used to estimate the pressure inside an elastic vessel such as a blood vessel, aneurysm or eyeball. The question Fung raises however is whether pressure, or resultant force, is being measured? A question not only applicable to digital tonometry but also GAT and its non-contact mimics.

1.2.2.3 Young-Laplace Equation

The Young-Laplace equation defines the relationship between internal pressure, surface tension and the curvature of a liquid surface (Fung 1993).

$$\Delta P = \sigma\left(\frac{1}{R_1} + \frac{1}{R_2}\right) \quad \textbf{(1.2.6)}$$

Where:
ΔP: Pressure difference across the fluid interface
σ: Surface tension
R_1 and R_2: Principle radii of curvature

Representing the pressure difference (ΔP) over an interface the equation applies specifically to a static fluid experiencing no outside forces (Verges *et al*. 2001). While σ is the surface tension of the fluid, the bracketed expression is a purely geometric factor for shape with the two principle radii (Skσæveland 2012). If the denser material is spherical the equation could be simplified to ΔP = 2σ/R (Bar-Meir 2013).

This equation undoubtedly underpins the qualifications ascribed to the Imbert-Fick Law. Surface Tension is the property of a liquid ensuring it adopts a form minimising its outer surface area (van Honschoten *et al*. 2010). While not universally agreed (Bar-Meir 2013), a traditional explanation for surface tension suggests, while an internal molecule experiences equal attraction in every direction created by the molecular forces in the encapsulating liquid, a surface molecule will interact with adjacent and internal molecules only, resulting in stronger attractions at the surface (Oxford Dictionary of Physics 2009).

While not an infinitely thin liquid surface, a membrane, in mechanical rather than biological terms, implies a thin structure offering negligible resistance to bending (Humphreys 2002); a quasi-constitutive behaviour with, intuitively, a level of error. The Young-Laplace equation is only valid if the membrane is so thin shear forces can be neglected (Fung 1993).

A shell, as opposed to a membrane, is defined as being relatively thin, in relation to the principle radius of the vessel, with no abrupt changes in thickness, slope or curvature (Young and Budynas 2002). If the shell thickness is less than one-tenth the smaller (inner) radius of the shell curvature it is defined a thin shell (Young and Budynas 2002) and a modified version of the Young-Laplace equation can be applied. The modified law does not apply to a thick walled shell, sometimes referred to as a 'wall' (Young and Budynas 2002). The ratio is the defining feature of the definition, an arteriole for instance,

with an inner radius/wall thickness ratio approaching 100% (Fung 1993) does not fulfil the definition of a thin walled shell. Buzard (1992) suggests the cornea can be considered a thin walled sphere, albeit with associated error; he suggests an error of 5% if the radius/thickness ratio is 15. A cornea with a Gullstrand-Le Grand standard eye radius of curvature of 7.8mm (external radius) (Fincham and Freeman 1980, Śródka 2009, 2013), and a shell thickness of 0.52mm (Ehlers *et al*. 1975) yields this ratio. The Gullstrand-Le Grand inner corneal radius of 6.49mm (Śródka 2009, 2013) and a corneal thickness of 0.52mm yields a shell thickness/inner radius proportion of 8%, fulfilling, at least in an idealised eye the prerequisites for the cornea to be considered a 'Thin Shell'. As categorised a 'Thin Shell' rather than a 'Membrane' implies bending and shearing forces cannot be neglected; an observation of relevance when considering applanation tonometry.

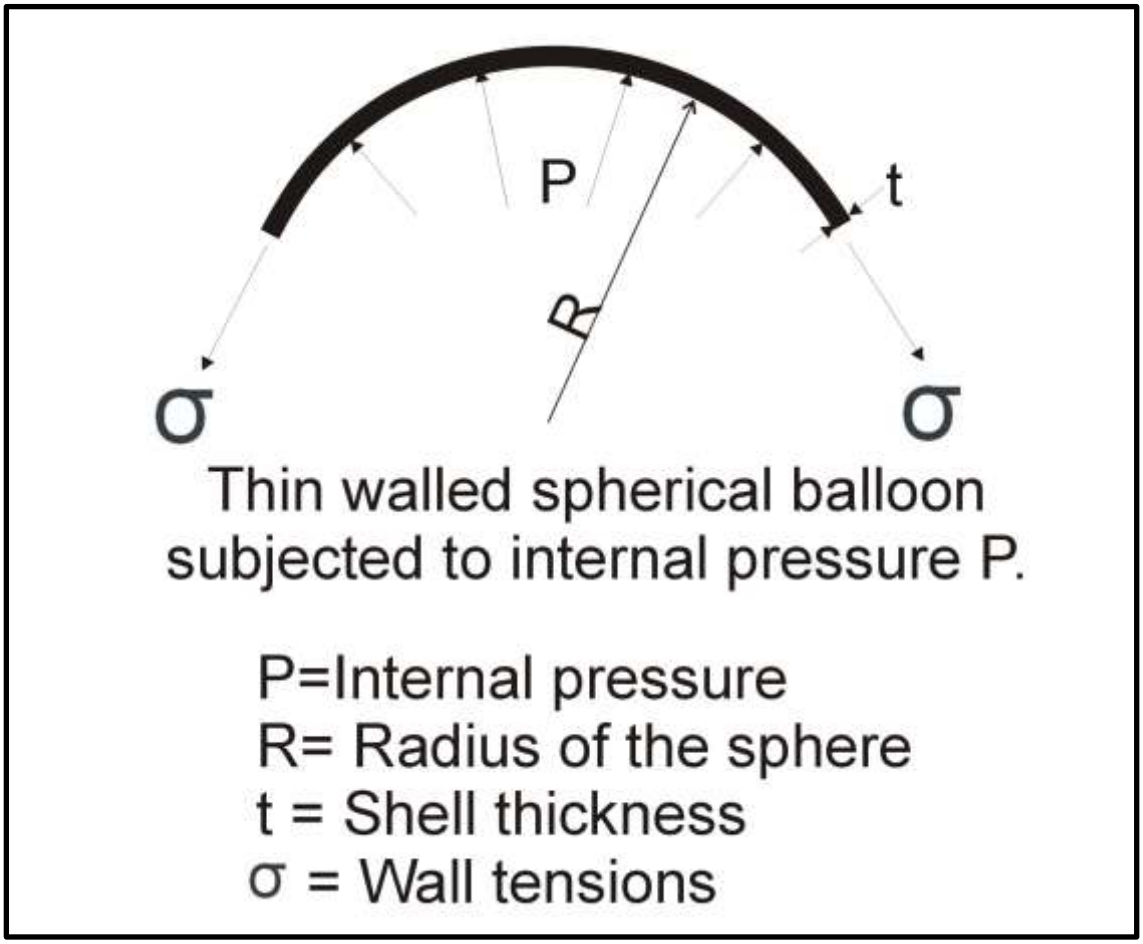


Figure 1.1 Membrane stress (Hoop Stress)

Purslow and Karwatowski (1996), present a modified equation as it applies to thin-shelled pressure vessels of homogenous, isotropic materials (Fig1.1) as:

$$\sigma = \frac{P.R}{2t}$$ **(1.2.7)** Hoop Stress for 'Thin' Shells

Where:

σ: Membrane (Hoop) stress. Stress (σ) = F/A (Applied Force/Cross Sectional Area)

P: Internal fluid pressure.
R: Radius of curvature of the shell.
t: Membrane thickness.

Buzard (1992) suggests the equation is used to estimate the stress at the surface of the cornea. Since this equation is a derivation of a law pertaining to infinitely thin fluid surfaces it is, as Buzard (1992) states, an approximation with the degree of error proportional to the shell thickness/radius ratio.

1.2.2.4 Stress

Stress uses identical notation to pressure. Bird and Ross (2012) describe stress as the force acting on a material causing a change in dimensions: the ratio of applied force to cross-sectional area of the material. On a constitutive level it more specifically is the measure of the internal forces in a body between individual particles as they resist separation, compression or sliding (Oxford Dictionary of Physics 2009).

Circumferential, or Hoop, stress acts parallel to the shell surface. For shells of revolution, for which a sphere is a specific case, Young and Budynas (2002) subcategorise hoop stress into meridional and circumferential. These subcategories are redundant for spheres, where meridian and circumference are equal but would apply to ellipsoids or cylinders. Depending on the direction of the force, in the case of a container external or internal, Hoop stress can be either 'tensile', extending the shape, or 'compressive' in response.

Shear, or bending, stress is created when the material is subjected to forces in opposite directions (Buzard 1992). Under these conditions there is a tendency to distort the material, as occurs in tonometry, or, if the stress is great enough actually shear the material. Young and Budynas (2002) suggest these forces can be created by loadings of the shell and supporting structure, creating boundary conditions.

Radial stress acts through the thickness of the wall (Young and Budynas 2002). If the shell walls are thin this stress can be ignored; the term 'membrane stress' implies a thin shell.

If the shell is thick, radial stress, in this case often termed 'Wall Stress' (Young and Budynas 2002), cannot be ignored and is not necessarily evenly distributed throughout the wall thickness but tends to be concentrated toward the inner surface (Fung 1993). This statement by Fung must presume the pressure exerted is internal in origin, blood pressure or intraocular pressure for example. If the primary stress considered is external in origin, as would be the case with applanation or indentation tonometry, then the radial stress, associated with the specific force, would be concentrated toward the outer surface.

1.2.2.5 Strain

Strain is the result of stress. If a material is loaded with a force (stress σ) then the material, if it is elastic, must change in length. Strain (ε) is the dimensionless (Bird and Ross 2012) ratio of the change in length of a material compared to its' original length (Battaglioli and Kamm 1984):

$$\varepsilon = \frac{\Delta L}{L} \qquad \textbf{(1.2.8)}$$

1.2.2.6 Young's Modulus and Material Stiffness

Young's Modulus, also termed Elastic Modulus, is the ratio of pressure applied to the change in length induced (Battaglioli and Kamm 1984, Buzard 1992):

$$E = \frac{Stress}{Strain} = \frac{F/A}{\Delta L/L} = \frac{FL}{A\Delta L} \qquad \textbf{(1.2.9)}$$

Battaglioli and Kamm (1984) explain, when the Elastic Modulus is high little deformation will occur and the reverse when Young's Modulus is small. Young's Modulus of Elasticity (E) is a measure of the intrinsic stiffness of a material (Hamilton and Pye 2008), while Battaglioli and Kamm (1984) indicate it is a measure of a material's strength. Material Stiffness is actually a slightly different metric to Young's Modulus, however the two are linked.

Stiffness, as defined by Bird and Ross (2012), can be expressed as:

$$Stiffness = \frac{Force}{Extension} = \frac{F}{\Delta L} \quad \textbf{(1.2.10)}$$

Where:
F is the tensile stress force
ΔL is the material extension resulting from the tensile force

Like Young's Modulus of Elasticity, within normal conditions, the material extension is linearly proportional to the force applied.

Since: E=σ/ε, σ=F/A and ε=ΔL/L Young's Modulus E can be written as:

$$E = \frac{FL}{A\Delta L} = \frac{F}{\Delta L} \cdot \frac{L}{A} = Stiffness \cdot \frac{L}{A} \quad \textbf{(1.2.11)}$$

Since F/ΔL is 'Stiffness' it follows Young's Modulus will be directly proportional to the material stiffness.

1.2.2.7 Modulus of Rigidity

'Modulus of Rigidity' or 'Shear Modulus' (G) represents, as described by Young and Budynas (2002), the elastic modulus in shear. Defined similarly to 'Modulus of Elasticity' (Buzard 1992):

$$G = \frac{Shear\ Stress}{Shear\ Strain} \quad \textbf{(1.2.12)}$$

1.2.2.8 Poisson's Ratio

Interconnected with Young's Modulus and Shear Modulus is Poisson's Ratio (υ). Young and Budynas (2002) define it as the ratio of lateral to longitudinal strain, assuming uniform and uniaxial longitudinal stress within the proportional limit.

$$Poisson's\ Ratio = \frac{Lateral\ Strain}{Longitudinal\ Strain} \quad \textbf{(1.2.13)}$$

Like many mechanical models, in a mathematically accurate sense, Poisson's Ratio is not a constitutive equation, qualifications for its acceptance are stipulated. The equation assumes material homogeneity (Buzard 1992). For incompressible, homogenous materials tensile load inducing lateral contractions of the material will result in longitudinal extension of twice that magnitude. Water (Buzard 1992) and, because of the water

content, soft tissue (Holsapfel and Ogden 2010), are, within normal parameters, homogenous, incompressible materials and as such will demonstrate a Poisson's ratio approaching 0.5.

In reality, all solids, liquids and gases are compressible. Pence and Gou (2015) suggest the constitutive treatment of many materials, including liquids, as incompressible is true under the expected mechanical loadings over standard time scales. This essential caveat ensures water and soft tissue are assumed constitutively incompressible.

1.2.2.9 Hooke's Law

An elastic material is one which obeys Hooke's Law stating stress is proportional to strain (Fung 1993). Young and Budynas (2002) indicate elasticity reflects a material's capacity to sustain stress without permanent deformation, when the stress is removed the material will return to its habitual dimensions. The loading/unloading curve is a straight line (Fig 1.2). The mechanical stress energy is stored reversibly as strain energy (Roylance 2001), allowing the material to revert immediately to its original dimensions on removal of the stress load, without loss of energy as heat.

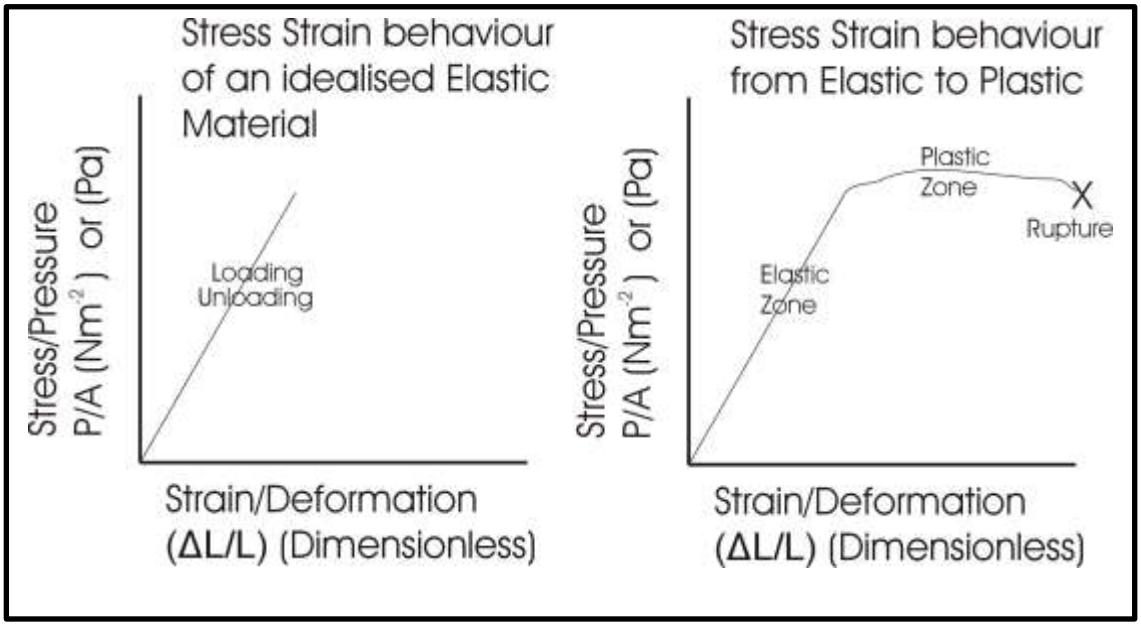


Figure 1.2 Stress/Strain graphs of elastic solids

Like all quasi-constitutive concepts caveats are imposed. The stress must not exceed the elastic limit of the material, if so the constitutive elements of the material are permanently altered and the material becomes plastic (Fig 1.2) and will finally fracture (Buzard 1992). Conversely, plasticity reflects a material's ability to sustain appreciable,

permanent deformation without rupture (Young and Budynas 2002). A brittle material, such as glass, will still have an elastic zone but will simply fracture at its elastic limit without demonstrating any plastic behaviour. Young and Budynas (2002) suggest plasticity also denotes the property of yielding or flowing under steady load. Sometimes called 'creep', plastic flow is due to sustained stress.

1.2.2.10 Boundary Conditions

Boundary conditions are extremely important to incorporate into modelled systems. Young and Budynas (2002) define boundary conditions as zones of stress at edges or ends of a member.

1. Buzard (1992) considers a plate supported at one end. Due to gravity the top edge will endure tensile stress while the bottom edge compressive. Somewhere in the middle, logically, the beam is under no stress. The transition is a boundary condition.
2. Another boundary condition occurs when a beam is flexed, as occurs with the cornea during applanation or indentation. The point of flexure creates a change in equilibrium with associated shear forces. During tonometry, for instance, the pressure profile in the peripheral cornea notwithstanding additional external loads will be different to the profile under the tonometer probe. Between these two zones is a boundary condition (Śródka 2010).
3. Edge dynamics also create boundary conditions. A flexible beam rigidly fixed at a supporting structure. This is a significant issue when testing any biological tissue *in vitro*. Asejczyk-Widlicka *et al.* (2011) stress the problems associated with many *in vitro* tissue testing. Uniaxial stretching, biaxial stretching, the use of corneal buttons or strips and the cutting and flattening of specimens are all associated with boundary conditions.
4. A boundary condition could also be created via radial stress.

1.2.2.11 Law of Hydrostatic Pressure

The final general mechanical principle to consider is the Law of Hydrostatic Pressure by Pascal which states: 'pressure exerted anywhere in a confined incompressible fluid is transmitted equally in all directions throughout the fluid such that the pressure ratio remains the same' (Kanngiesser *et al.* 2005, Robert 2007). In a static fluid the force is transmitted at the speed of sound throughout the fluid and acts at right angles to the surface (Oxford Dictionary of Physics 2009). In the absence of constraints, these internal

forces push toward a sphere, having the largest volume for a set surface area (Markiewitz 1960, Mark 2012).

1.2.3 Biological Systems

Living tissues consist of composite materials with correspondingly complex mechanical behaviour (Fung 1973). There is no natural state to serve as a unique reference for stress and strain measurements as the cells within a tissue, including the cornea (Elsheikh *et al.* 2013), exist under permanent stress and respond to stress variations by changing mass, metabolism, internal structure, production or re-absorption of proteins and extracellular structures (Fung 1993). Under physiological conditions the cornea is subject to circumferential stress caused by intraocular pressure and concentrated anterior stresses from external forces of the lids (Hatami-Marbini and Etebu 2013). Fung suggests modelling living tissue necessitates broadening the scope of constitutive equations. Classic continuum mechanics is of limited help as mechanics of rubber or metals have few, if any, counterparts in living tissues (Fung 1993, Roberts 2000); a vital caveat when considering the Imbert-Fick construct for tonometry.

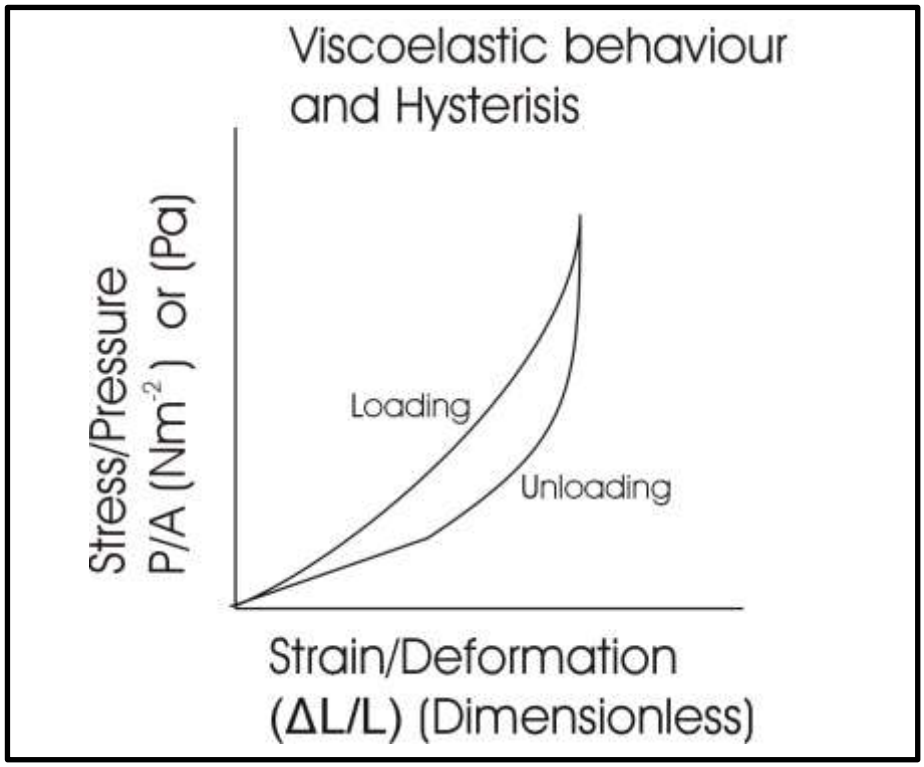


Figure 1.3. Viscoelastic deformation curve

Humphrey (2002) indicates most soft tissue demonstrates a non-linear, inelastic, heterogeneous, anisotropic character, varying with location, time frame and individual.

Viscoelasticity incorporates a number of phenomena (Fung 1993). If a body is stressed and the stress is maintained the body will continue to deform; this is creep. When a body is strained and the strain is maintained constant the corresponding stresses reduce; this is relaxation. Cyclic loading of a biological body will demonstrate a different stress-strain response during loading to unloading. Described as hysteresis (Fig 1.3) the constitutive equations are different for each phase. Further, loading and unloading are virtually strain rate independent (Fung 1973).

Young and Budynas (2002) considering hysteresis as a mechanical, rather than biomechanical phenomenon, suggest it is the result of dissipation of energy as heat during a stress cycle. Holzapfel and Ogden (2010) also assume the collagen fibres contribute to strain energy in extension but not in compression, perhaps explaining the hysteretic response.

Creep, Relaxation and Hysteresis together comprise viscoelasticity.

1.2 4 Corneal Structure

The cornea is the first cellular surface of the eye's optical system and, of the total 60 dioptres ocular power of a relaxed eye, contributes 43 to 45 dioptres (Piñero and Alcón 2014, Rio-Cristobal and Martin 2014).

The cornea has five categorised layers parallel to the external surface (Pandolfi and Manganiello 2006). Anterior to posterior: epithelium, Bowman's layer, stroma, Descemet's membrane and endothelium (Hatami-Marbini and Etubu 2013) (Figure 1.4).

Pandolfi and Manganiello (2006) suggest the stroma constitutes 90% of the corneal thickness, but more importantly this layer defines the mechanical behaviour of the cornea. Certainly all papers cited for corneal modelling solely consider the stroma.

Figure 1.4. Categorised Corneal Layers

Dias and Ziebarth (2013), Kotecha (2007) and Winkler *et al*. (2014) indicate collagen is the primary structural component of the cornea and sclera, lending structural integrity and mechanical strength. In soft tissues the collagen, aligned in a preferred direction, as in the transparent cornea, ensures the material is mechanically transversely isotropic (Holzapfel and Ogden 2010, Kwon *et al.* 2008). Morishige *et al.* (2006) indicates the stromal collagen is composed of Type I and IV collagen fibrils of 30 to 35nm diameter and organised in lamellae bundles of varying thickness. The central cornea consists of approximately 300 collagen layers increasing to 500 peripherally, explaining the increase in corneal thickness centrally to peripherally (Misson 2010). Maurice (1957) suggested corneal transparency is reliant on uniformly small diameter collagen fibrils, closely spaced (≈55nm) creating an optically homogenous matrix.

Regardless of this optical requisite lamellae are not absolutely evenly distributed, with branching and interweaving of lamellae bundles (Misson 2012). Misson (2012) suggests while microstructure of isolated volumes of stroma may appear uniform, there are variations anterior to posterior within the cornea.

Anterior stromal lamellae are more undulating, interwoven and branching (Morishige *et al*. 2006, Kamma-Lorger *et al*. 2010) as well as thinner and more densely packed with a more random orientation as they interconnect with Bowman's Layer (Kamma-Lorger *et al.* 2010, Dias and Ziebarth 2013). The posterior stroma contains thicker, more loosely packed lamellae of limbus to limbus orientation (Dias and Ziebarth 2013). Mid and peripheral stromal lamellae run parallel to the corneal surface. Dias and Ziebarth further suggest the presence of transverse lamellae within the anterior stroma provide additional rigidity within this zone, the posterior cornea is known to be mechanically weaker.

Studer *et a*l. (2010) and Whitford and colleagues (2015) generalise the overall stromal lamellae organisation. Central cornea has an orthogonal arrangement nasal/temporal and superior/inferior, circumferentially arranged fibrils in the limbus and corneal periphery (Shin *et al.* 1997) with transitional zones between (Fig 1.5).

Figure 1.5. Idealised corneal model showing preferentially aligned, collagen fibrils in the cornea and Limbus (Boote *et al.* 2006)

Linking internal anatomy to corneal morphology and function, Read *et al.* (2006) indicate the central cornea, on average, is a prolate ellipse, becoming significantly flatter in the periphery. The circumferential orientation of peripheral collagen may explain this flattening. Further, the authors note the peripheral cornea does not contribute to foveal vision but the shape, as it blends into the stroma, is of importance anatomically and mechanically. Carney *et al.* (1997) also hypothesise peripheral flattening may contribute to aberration control.

Extracellular matrix serves several functions (Humphrey 2002). It supports the tissue shape by providing structural strength and resilience, provides an active scaffold onto which cells can migrate and adhere, acts as an anchor for active substances such as proteases and growth factors and provides an aqueous environment for non-active diffusion. Biomechanically the proteoglycan extra cellular matrix soaks up initial loading (Anderson *et al*. 2004) and behaves elastically (Holzapfel and Ogden 2010).

1.2.5 Corneal Elasticity, Corneal Rigidity, Coefficient of Ocular Rigidity and Optical Self-Adjustment

1.2.5.1 Nomenclature Conflict

While Goldmann and Schmidt (1957, 1961) felt a design imperative for their new tonometer was the neutralisation of corneal elasticity they declared rigidity inconsequential. Schmidt (1959) states ocular rigidity, while profoundly affecting the Schiőtz instrument, is completely eliminated with GAT. This engenders conflict in the literature.

Amdur (1960) and Bayoumi *et al*. (2010), suggest the elimination of ocular rigidity proposed by Goldmann and Schmidt is due specifically to the reduced displacement of intraocular fluid compared to indentation (0.45mm^3 rather than 7-14mm^3 with indentation). The authors contend volume displacement in GAT is so small ocular rigidity has little effect on pressure readings. Conversely, Shah (2000) and Tamburrelli *et al.* (2005) describe the corneal component in the GAT model as 'corneal rigidity' resisting applanation, seemingly contradicting the statement of Goldmann and Schmidt (1957, 1961). Further, Lim *et al.* (2008) consider the well documented impact of CCT on GAT measurement (Ehlers *et al*. 1975, Whitacre *et al*. 1993, Brandt *et al*. 2001, Gordon *et al.* 2002, Palmberg 2002, EGS 2003, EGPS Group 2007, OHTS Group & EGPS Group 2007) reflects an *in vivo* surrogate marker of corneal rigidity.

The reduced displacement of fluid with applanation tonometry, while lessening artificial elevations in IOP, cannot explain the elimination of corneal rigidity as Goldmann and Schmidt (1957, 1961), Amdur (1960) and Bayoumi *et al*. (2010) claim. The interpretive conflict arises as Goldmann and Schmidt (1957), and others, are citing Friedenwald's 'Coefficient of Ocular Rigidity' while Shah (2000), Tamburrelli *et al.* (2005), Lim *et al.* (2008) and many modern authors, when using the term 'rigidity' are in fact describing 'corneal stiffness' rather than 'corneal rigidity' or 'Modulus of Rigidity'. Material 'stiffness' (Formula 1.2.10) is related to Young's 'Modulus of Elasticity' (Formula 1.2.9) via the relationship in Formula 1.2.11. Stiffness does not directly link to 'Modulus of Rigidity' which is a measure of a material's resistance to 'shear' forces (Young and Budynas 2002).

However, when the term 'rigidity' is used in ophthalmic texts it often represents a misinterpretation of Friedenwald's measure of globe distensibility as representing

material ‘stiffness‘. Laiquzzaman *et al.* (2006) consider Corneal Hysteresis, as measured by the Ocular Response Analyser, a more appropriate measure of corneal or ocular rigidity (*stiffness)* than previous complex formulae. The authors cited (Edmund 1987, Edmund 1988, Hartstein and Becker 1970, Foster and Yamamoto 1978, Hjortdal and Jensen 1995, Friedenwald 1937, Pallikaris *et al.* 2005) were all considering distension of the entire globe to inflation loading based on the original work by Friedenwald (1937). The Friedenwald coefficient cannot be compared to the ORA metrics. Ariza-Garcia *et al.* (2015) indicate non-contact air plenum induces a mechanical response to bending, whereas a corneal response to IOP variation represents membrane response to inflation loading.

Kalenak (1991) states the terms ocular or scleral rigidity have no place in physics, mechanics or ophthalmology. Friedenwald’s choice of name for his empirical and complicated concept has led, White (1990) suggests, to confusion and misappropriation of the term ‘rigidity’ within ophthalmology. Purslow and Karwatowski (1996) further state ‘Ocular Rigidity’ is one of the most confused areas of ophthalmology, propagated by inappropriate citation and misrepresentation as a true mechanical constitutive equation. Correct terminology is critical. As Dupps (2007) indicates, the precise descriptive words become shorthand for complex biological concepts. The wrong words are likely to confound rather than enlighten.

Within the next sections, authors’ descriptive terms will be used for citation accuracy. However, if, in the opinion of this author, an alternative descriptor is more biomechanically accurate, this term will be placed in parentheses and italics.

1.2.5.2 Friedenwald’s ‘Coefficient of Ocular Rigidity’

Liu and He (2009), quite precisely, describe Friedenwald’s coefficient as a measure of overall globe distensibility; an empirical concept, not a material property (Asejczyk-Widlicka and Peirscionek 2008).

Friedenwald (1937) considered three possible outcomes when a bolus of incompressible fluid is pumped into the eye filled with incompressible fluid. The first possibility could be rapid increase in outflow; discounted within the tonometry time frame. Outflow does increase but is not instantaneous, minutes can elapse as is the case with tonography (Dueker 1996, Toris and Camras 2007).

The scleral wall could expand. This is certainly the case, is a documented part of tonography (Dueker 1996) and Stein (2010) re-enforces the fundamental that, due to

incompressibility, the intraocular volume must increase by the same volume. Of significance when considering intraocular pressure variation is how much of this expansion is scleral as opposed to corneal. Friedenwald (1937) assumed eyeball expansion is primarily in the equatorial (scleral) zone. However, this investigator was indenting the eye with a Schiötz tonometer so the equatorial expansion would be anticipated.

The third possibility Friedenwald gives is compression of the intraocular vascular bed. Based on evidence from previous animal studies, Friedenwald felt small changes in intraocular volume would not affect blood volume to any extent. However marked dilatation or constriction of the intraocular vessels produces appreciable changes in ocular elasticity (Friedenwald's term). Certainly indentation tonometry will result in expulsion of blood (Patel 2010). Dastiridou *et al*. (2009) indicate 85% of total ocular blood volume is choroidal. An increase in IOP forces blood from the eye until this pressure exceeds arterial blood pressure (Eisenlohr *et al*. 1962). Higher levels certainly increase the risk of central retinal vein occlusion (Palmberg 2002). The choroidal bed is a primary area of ocular compression under excessive intraocular pressure load. The compressibility of the intraocular blood vessels will reflect the intravascular pressure itself (Solver and Geyer 2000), which will vary continuously as the volume within the vasculature changes. This in turn constantly changes the total intraocular volume (extravascular fluid and intravascular) and consequently IOP (Queirós *et al.* 2006). Intraocular pressure dampening may be as reflective of choroidal compression as shell elasticity.

Friedenwald did not differentiate between scleral expansion and compression of the vascular bed, but considered them, for his model, a single entity reflecting overall ocular elasticity (*distensibility*). Individual contributions of wall expansion and vascular compression cannot be ascertained from Friedenwald's single coefficient. Friedenwald's conclusions have been criticised, not least because of his use of enucleated eyes (Pallikaris *et al.* 2005). However the single most important criticism is the confusion the name of his coefficient has engendered. The Friedenwald's 'Coefficient of Ocular Rigidity' is a measure of the resistance of the complete globe to distending forces; a unique metric applying to the entire, and necessarily living, globe with functional vasculature. Friedenwald did strive to enforce the fact his coefficient was a new metric, not to be confused with a true mechanical law.

While so often misrepresented and contributing much confusion in the literature, Friedenwald's 'Coefficient of Ocular Rigidity' does reflect a continuum approach to IOP homeostasis of the entire eye.

1.2.5.3 Globe Distension: A response to inflation loading

Stark Johnson *et al*. (2007) suggest at low pressures eyes are very distensible; large volumes can be introduced into the eye with little change in intracameral IOP. The higher the pressure the less distensible the eye becomes. Once highly loaded very small increases in intraocular volume will induce large elevations in IOP (Stark Johnson *et al.* 2007). Biomechanics would predict this.

Considering a collagenous rabbit tendon (Fig 1.6), Fung (1993) demonstrated within normal physiological range (O to A), a relatively small increase in load will produce large deformations. A linear phase (A to B in Fig 1.6), outside normal ranges, is followed by non-linear disruption and final rupture. A similar curve for porcine corneal strips was also found by Elsheikh and Alhasso (2009). Collagen stiffens the tissue at higher loadings while the ground substance behaves as a Hookean material (Holzapfel and Ogden 2010). As the stress exceeds the elastic limit of the material the constitutive elements are permanently altered and the tissue becomes plastic and will finally fracture (Buzard 1992).

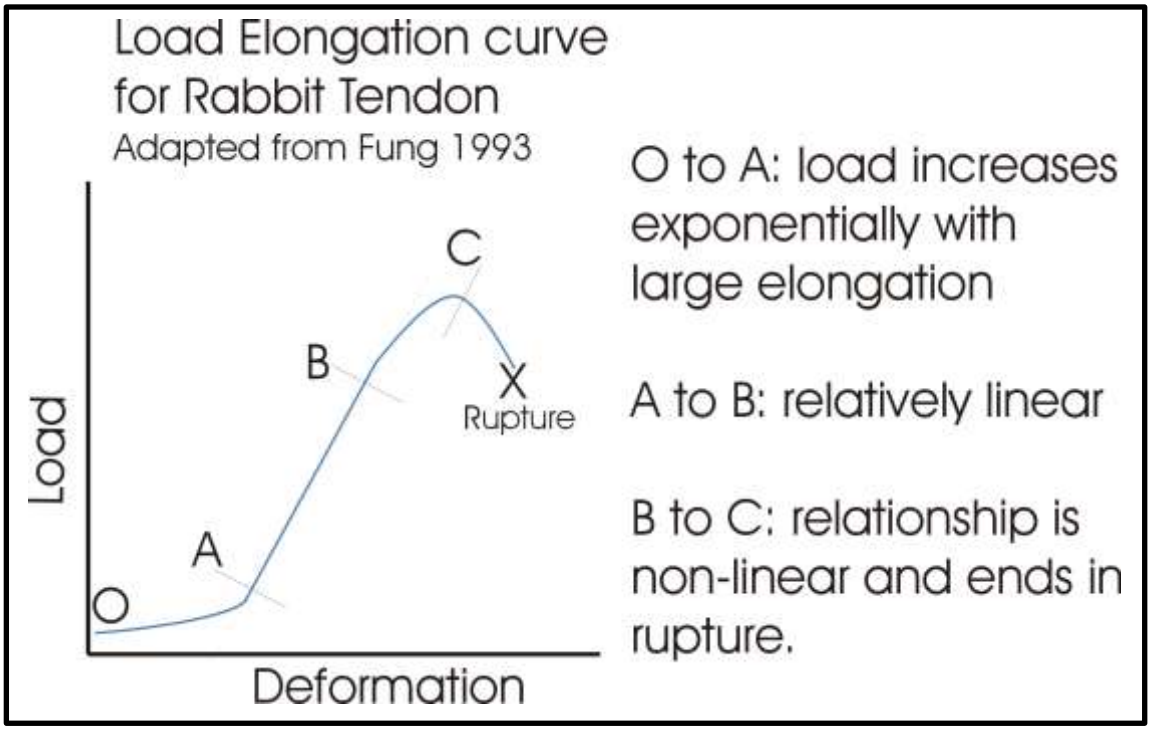


Figure 1.6. Load Elongation curve for rabbit tendon

Anderson *et al.* (2004), modelling the cornea, suggest a two phase response to loading. Initial loading is soaked up by the proteoglycan extra cellular matrix, with the collagen fibrils remaining loose with little contribution to overall performance. Hence large inputs of incompressible fluid will be successfully absorbed by expansion of the shell. As the volume continues to rise the collagen fibrils become taut and start to control tissue response as it becomes rapidly stiffer (Anderson *et al.* 2004). This was the conclusion drawn by Friedenwald (1937) to explain the observation initial large volumes of fluid can be introduced into an eye with meagre rises in IOP. The author speculates, as the length of individual scleral fibres extend the associated rise in IOP is substantial. Elsheikh and colleagues (2008a) demonstrated this effect during inflation tests on human corneas which showed hyper-elastic behaviour and low stiffness initially but exponentially increasing stiffness as inflation increased. Metzler *et al*. (2014) also established corneal stiffness increases with increasing IOP. Logically, as Buzard (1992) explained, tensile loading of incompressible materials results in lateral contractions and associated longitudinal extension; the shell will thin as it stretches.

Basing their experiments on the principles outlined by Friedenwald (1937), and interpreting the inflation results as a measure of 'ocular rigidity' *(stiffness)* creates, for Stark Johnson and colleagues (2007), a paradox. They acknowledge GAT measurements will be higher in rigid (*stiff*) corneas, but also consider thicker corneas inherently more rigid (*stiff*) than thinner ones. The conclusion reached is thinner corneas are more distensible and therefore should be more effective in buffering IOP fluctuations. If corneal/scleral elasticity is a primary dampener of IOP fluctuations, patients with thinner corneas should demonstrate greater resilience to IOP damage; an observation the evidence does not support (Wolfs *et al*. 1997, Brandt *et al*. 2001, Gordon *et al*. 2002, Palmberg 2002, EGS 2003, EGPS Group 2007, OHTS Group & EGPS Group 2007). In actuality the results of Stark Johnson and associates (2007) demonstrate a cornea thinned due to tensile stress and elongation will demonstrate high stiffness. A physiologically thin cornea under normal intraocular pressure load will have a significantly lower modulus of elasticity (Section 1.2.2.6).

1.2.5.4 Ocular Self-Adjustment: Function dictates form

Stark Johnson and colleagues (2007) suggest the cornea acts as a dampener for variations in IOP by its inherent elasticity, the upshot being associated changes in radius of curvature. This creates disconnect between ocular function and form. However the

authors removed the sclera posterior to the vortex veins as well as the vitreous, retina, uvea and lens from the post mortem eyes. Inflation tests assume the cornea/sclera to be part of a thin-walled pressure vessel complying with the modified Young-Laplace equation (1.2.7). The law of hydrostatic pressure presumes free movement of particles ensuring uniform distribution of pressure within the pressure vessel (Young 2007). In reality the eye comprises at least four sub-compartments, anterior chamber, posterior chamber, vitreous cavity and intra-vascular compartments. Schiőtz (1905), cannulating the vitreous space, did describe the vitreous as an obstacle to pressure variations. Further, aqueous is produced in the ciliary body, enters the posterior chamber, circulates through the pupil, and is drained via the trabecular meshwork (Krupin and Civan 1996). Aqueous dynamics, the potential barrier effect of the vitreous (Schiőtz 1905, Hernández-Verdejo *et al.* 2010) and variation in intraocular volume induced by the ocular pulse (Xu *et al.* 2011), would suggest IOP homeostasis reflects a response of the entire eye.

Asejczyk-Widlicka and Peirscionek (2008), using inflation tests, via the optic nerve of whole enucleated porcine eyes, reported, contrary to Stark Johnson *et al.* (2007), an increase in scleral curvature with no statistical change in corneal curvature.

This observation highlights an important aspect of ocular biomechanics: optical self-adjustment (Śródka and Iskander 2008). This hypothesised process ensures mechanical effects do not induce perceptible alterations to the optical properties. As Fung (1983) states biomechanics must reflect morphology, material properties and function. The evolutionary imperative; function must necessarily dictate geometry and form (Śródka and Iskander 2008, Śródka 2009). If geometry or form are not synchronized, as is evident in the development of ametropia, functionality must be affected (Carney *et al.* 1997, Grosvenor and Goss 1998). AlMahmoud *et al*. (2011) found a weak statistical correlation between corneal curvature and CCT, thicker corneas were also flatter. However, this relationship became highly significant when myopes were isolated while no significance was found for hyperopes. Further, if material properties and morphology are catastrophically altered, as with Acute Angle Closure Glaucoma (Ritch and Lowe 1996) or Congenital Glaucoma (Dickens and Hoskins 1996), the ocular function totally fails.

Piñero and Alcón (2015) indicate minimal changes in corneal shape can induce significant variations in optical properties, a concept emphasised by Asejczyk-Widlicka and Peirscionek (2008). Changes in equatorial dimensions in preference to optical length or corneal curvature, as advocated by Friedenwald (1937), are instinctively logical. IOP homeostasis must reflect a complex response of the living, entire globe.

1.2.6 Corneal Modelling Principles

Can the cornea be considered, for modelling purposes, a thin shell? Anderson *et al.* (2004) suggests thin shell assumptions lead to an estimated 4.3% loss in accuracy as compared to a model incorporating stacked elements. The supposition of constant corneal thickness also incurs an increase in predictive error of 2%. Gilchrist and colleagues (2012) do champion the use of generalised linear elastic models to yield simple, accurate models for non-linear elastic behaviour for moderate deformations. The authors rationalise the stance because physiological strains are small and variations in normal range can be in the order of 10%.

Further, Pandolfi and Manganiello (2006) suggest the stroma constitutes 90% of the corneal thickness and defines the mechanical behaviour of the cornea.

Grytz and Meschke (2010), critiquing their modelling assumptions, admit to considering the stroma in isolation; an accepted modelling orthodoxy. Anderson *et al*. (2004) indicate the constitution of the layers vary considerably; the epithelium, Bowman's layer, Descemet's and endothelium all possess higher in-plane stiffness compared to the stroma (Grytz and Meschke 2010). The exact contributions of the five layers may be impossible to quantify but Grytz and Meschke do highlight the potential modelling hazards of considering the cornea a homogenous thin shell rather than a five layered composite. Stromal structure, outlined in section 1.2.4, is not homogenous.

Hjortdal (1996) demonstrated strain effects to intraocular pressure loads varied across the cornea. The finite element model of Woo *et al.* (1972) suggests, as IOP increases some elements become highly stressed while others remain at low levels. Dias and Ziebarth (2013) indicate the posterior stromal elasticity is 39.3% stiffer than the anterior. Shin *et al.* (1997) also presented data indicating the strain distribution of the anterior cornea to be non-uniform. The authors speculate the heterogeneity of the collagen orientation is responsible. This view has been supported experimentally by Hjortdal (1996) who found differences in the elastic response of the cornea, central and paracentral cornea showed maximal stiffness in the meridional direction while the limbus was structurally stiffer circumferentially. Stromal anisotropy demonstrating horizontal to vertical stiffness ratio of 3 and horizontal to diagonal ratio of 10 was also reported by Pandolfi and Manganiello (2006), although it should be noted this was based on strip cut corneal specimens with profoundly manipulated geometry and induced boundary conditions. The authors surmise the variation must be due to regional differences in

collagen orientation within the ground substance. Sloan *et al.* (2014) found the shear modulus varied continuously throughout the cornea with a peak level well within the stromal. The authors suggest the cornea should not be characterised a transverse, isotropic material.

Contradictory evidence was presented by Elsheikh and Alhasso (2009). Controlling for variables by comparing right to left porcine corneal strips in vertical and oblique orientations these authors did not find significant differences in biomechanical behaviour of the stromal tissue in different anatomical directions and concluded an almost isotropic behaviour.

Regardless, the relatively systematic orientation of the collagen allows modelling assumptions more complex than the assumption of complete material homogeny. Holzapfel and Ogden (2010) observe the modelling of tissue as fibre reinforced elastic is well established. Glass *et al.* (2008) indicate the elastic modulus of the collagen fibrils is in the order of 1GPa while the ground substance is 100,000 times lower. The model needs to consider elastic modulus of the fibrils, the ground substance and mix ratio of fibrils and ground substance and the orientation of the fibrils.

In general, Buzard (1992) suggests, the endeavour is to ascertain the smallest homogenous component of a composite material property. In the case of the corneal stroma, the biologically assumed constitutive units would be a single homogenous group of collagen lamellae and a homogenous unit of the supporting matrix. This modelling philosophy reflects, what would appear, the most widely used modelling strategy: 'Finite Element Modelling'. Buzard (1992) indicates the 'finite elements' are chosen to represent easily analysed forms, forms which can be approximated to demonstrate predictable, homogenous responses. The level of assumed homogeny will reflect the model's predictive complexity.

So while modern, computer generated, modelling has a scientifically robust appearance, any modelled system is reliant on the assumptions and preconditions stipulated by the designer. While stressing the importance of numerical modelling in investigating the human cornea, Studer *et al.* (2012) highlight the inherent problems facing modellers. The authors present the methodologies of five studies, all utilised identical formulations for collagen fibres and matrix tissue as well as inverse modelling against experimentally attained inflation data. Regardless, differences in published material coefficients varied by 3 orders of magnitude. The authors hypothesise fitting a material model to a single set of experimental data is not sufficient.

While beneficial if a model can be solved quickly, it must also be reliable. It may be tempting to optimise for a single parameter, producing a mathematically sound result, but at the risk of possibly reflecting an inadequate constitutive model (Evans and Avril 2012). Anderson *et al*. (2004) stress if modelling internal eye dynamics, such as intraocular pressure homeostasis, whole eye models are essential. This increases model complexity and potential approximations. Asejczyk-Widlicka *et al.* (2011) modelled the cornea and sclera as a pressure vessel, defined by the authors as a closed structure filled with fluid and capable of expanding with increased volume. The advantage is measurement of tissue biomechanics in an intact state. Conversely, simplifications are necessary. The modified equation for thin walled shells of Young-Laplace assumes constant thickness, necessitating application of an average value for cornea and sclera. Further the ocular shell is treated as isotropic, radii of curvatures averaged and the vessel assumed spherical. All approximations increase inaccuracies (Asejczyk-Widlicka *et al*. 2011).

A limited knowledge, or deliberate simplification, of the complexities of underlying microstructure of living tissue can ensure researchers rely on over simplistic constitutive principles. This approach produces a 'closed' solution with the physical phenomenon being described by a discrete number of equations in which all variables are known; the result governed by those discrete numbers (Buzard 1992).

Modelling decisions often reflect financial and time constraints. Modelling the cornea as a two dimensional, homogenous material (Anderson *et al*. 2004) with limited finite element meshes, while simplifying the modelling process, will be less accurate (Piñerro and Alcón 2015). If only a single parameter is considered, elasticity of the cornea for instance, a global solution can be readily obtained and experimentation can support the model but, while solved will demonstrate inherent uncertainty (Evans and Avril 2012).

Inverse modelling helps optimise and amalgamate experimental findings with modelled forecasts. Ghaboussi *et al.* (2009) used a modelling anchor of a report by Johnson *et al.* (1978) of a young lady with CCT of 900µm and GAT readings of 30 to 40mmHg. A finite element model was created to simulate this clinical observation and then performance tested. Evans and Avril (2012) suggest an inverse approach ensures modelled simulations are refined in response to experimental results, with constant readjustment until the model matches experiment. This should be a cyclical process; the experimental results temper the modelling assumptions, the resultant models in turn suggest avenues for further experimentation.

A multi-disciplinary approach is essential. Theoretical physics and mathematics play a fundamental role in biology (Humphrey 2002) as do clinicians and anatomists.

Fung (1993) and Humphrey (2002) outline approaches, essential to developing constitutive models or equations necessitating inter-disciplinary collaboration. From Fung (1993):

1) Understand the morphology, geometric configuration and histology of the organ considered.
2) Determine the mechanical properties of the constituent parts.
3) Considering fundamental laws of physics and the constitutive equations for the tissues, derive the tissue equations.
4) Understand the environment in which the tissue works to estimate boundary effects.
5) Solve the boundary problems, analytically, numerically or via experiment.
6) Perform experiments to test the model and reformulate if the predictive power fails.

All theoretical approaches to tonometry must be viewed within this framework. To build on past achievements without being bound by them, as Humphrey (2002) recommends, necessitates a review of the evolution of tonometry from inception.

1.3 The Imbert-Fick Biomechanical Model

1.3.1 The Imbert-Fick Construct: A simple biomechanical model, not a law

Schottenstein (1996) reports the Imbert-Fick model as stating 'the pressure inside a sphere is roughly equal to the external force needed to flatten a portion of the sphere divided by the area of the sphere which is flattened', formulaically:

$$P \approx f/A. \qquad \textbf{(1.3.1)}$$ Imbert-Fick Construct (Schottenstein 1996)

The term 'roughly' suggesting errors in the fundamental principle.

The Law of Hydrostatic Pressure dictates internal forces, in the absence of constraints, push toward a sphere, having the largest volume for a set surface area (Markiewitz 1960, Mark 2012); when a sphere is compressed internal pressure is raised. The act of applanating the sphere increases the pressure inside; the larger the applanation zone the larger the artificial change in internal pressure (Schmidt 1959). Practical application of the 'Imbert-Fick' construct is further compromised as it reportedly only applies to surfaces perfectly spherical, dry, flexible, elastic and infinitely thin (Schottenstein 1996). Surface dryness appears a modelling parameter incorporated by Goldmann and Schmidt (1957). The other caveats seem to reflect the physical properties described by the equation of Young-Laplace (detailed in section1.2.2.3) although no reference to this law, or the law of hydrostatic pressure, are included in any description of the Imbert-Fick construct. In reality, the surfaces are described as an elastic envelope (Imbert 1885) and a flexible membrane (Fick 1888); apart from a spherical shape the other attributes, now considered integral to the model, would appear to be later additions.

It seems likely few authors have critically appraised the original papers, inevitably allowing interpretative vagaries to creep into the literature. The origins of the construct are certainly difficult to access directly and the 'law' is quoted *a priori*. Śródka (2010) questions this stance suggesting the premise warrants re-testing.

1.3.2 The Imbert-Fick Law

Both Imbert (1885) and Fick (1888) felt replacing a depression (Indentation) with a plane surface (Applanation) cancelled out all extraneous forces and, they suggest, tonometer pressure equals intraocular pressure (Imbert 1885, Fick 1888). Indeed Imbert and Fick, believed applanation, rather than indentation, allowed the relationship to be written simply as:

P (Tonometry Pressure) = T (Intracameral IOP) **(1.3.2)** The Imbert-Fick Law. (Imbert 1885, Fick 1888)

If a law attributable to Imbert and Fick is to be presented it should be written as 1.3.2, with the proviso this is the case only when the surface is a plane. P=F/A, recognised as representing the Imbert-Fick construct, appear in neither the Imbert nor Fick papers.

1.3.3 Rationalisation of P=T by Imbert and Fick

1.3.3.1 Armand Imbert (1885)

Imbert (1885) felt the eye, for the purpose of measuring intraocular pressure, must be considered a liquid contained in an elastic envelope. Rather than considering internal hydrostatic pressure pushing outward, Imbert, who had done previous work on the elasticity of rubber (Imbert 1885, Mark 2012), considered the elastic pressure (F) pushing inward (Fig 1.7).

Newton's Third Law states: 'to every action there is always an equal and contrary reaction'. Accordingly, at equilibrium the elastic force pushing inward will equal the hydrostatic force pushing back. Further, at a single point on the surface, the force 'N' described by Imbert as the 'Normal' component of force, directed, the author states, 'toward the concavity of the surface', can be taken, at equilibrium, as a measure of intraocular pressure (Fig 1.7).

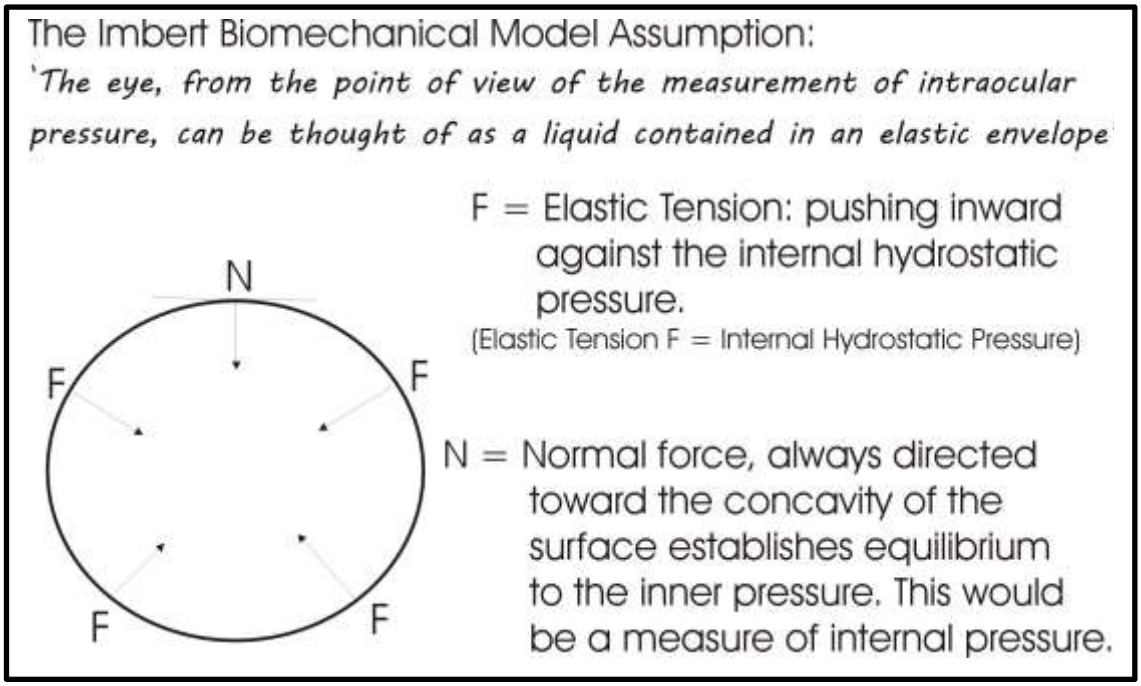


Figure 1.7. The Imbert Biomechanical Model Assumption

To elucidate, Imbert considered the forces involved with indentation tonometry versus applanation. At indentation equilibrium the tonometer force 'P' is counteracted by Intraocular Pressure 'T' plus the Normal Force 'N' pushing toward the concavity, in this case outward from the corneal indentation (Fig 1.8).

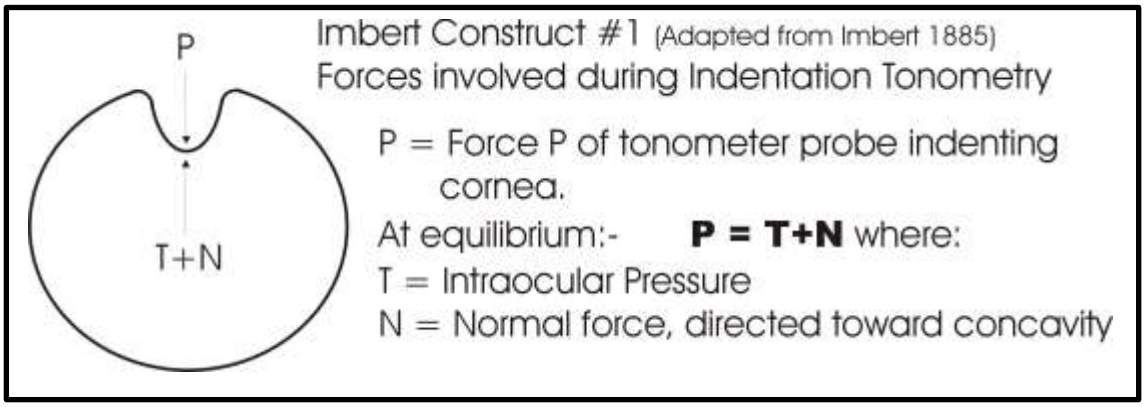


Figure 1.8. Imbert Construct #1

Imbert's reasoning then determined substituting a concave depression with a plane depression eradicated any concavity and with it force N. Interestingly both processes are described by Imbert as inducing depressions. Schiőtz (1905) certainly suggests there is no distinction between the processes, an applanation tonometer becomes an indentation tonometer with increasing pressure. Despite this observation Imbert argued

at stable applanation the normal component 'N' is totally eliminated and the equilibrium equation is reduced to: P=T (Fig 1.9).

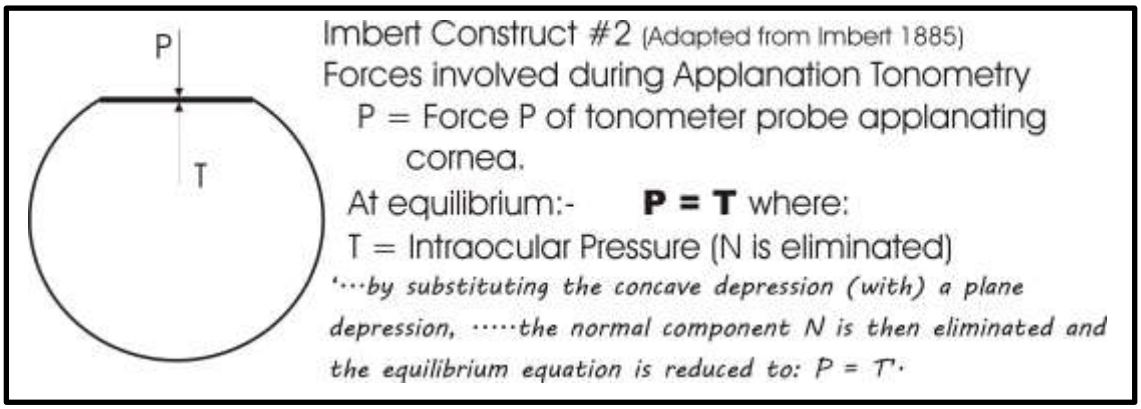


Figure 1.9 Imbert Construct #2

1.3.3.2 Adolf Fick (1888)

Working independently of Imbert, Fick (1888) used geometric diagrams to rationalise his model. Fick (1888) suggested we consider a thread (not a thin shell under stress) held taut by force P (Fig 1.10).

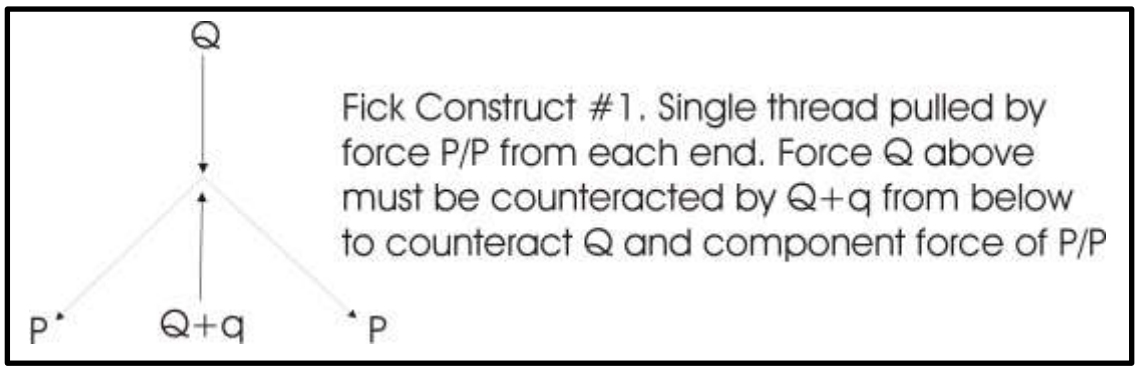


Figure 1.10. Fick Construct #1

An immediate impossibility since the force pulling the thread would pull it flat and taut; a point emphasized by Mark (2012) who ponders by what means, (or force), the thread was held up in the first place. Continuing, Fick explains, to maintain equilibrium, to press down on the thread apex with force Q would require a force Q+q from below to counterbalance the supposed tension of P.

The model is then simplified to consider the thread held taut and flat as in Fig 1.11.

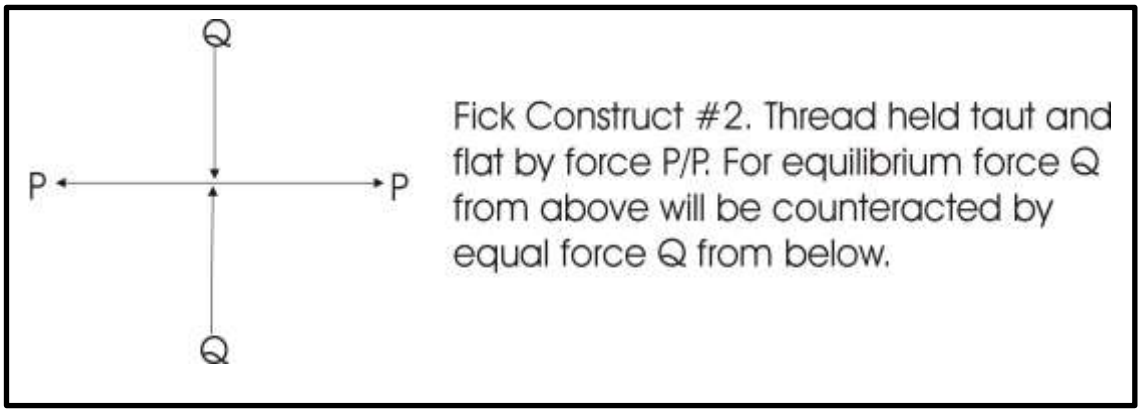


Figure 1.11. Fick Construct #2.

To maintain equilibrium in this case force Q from above must be counter balanced by an equal force Q from below since no other forces are involved. This is certainly true and reflects Newton's Third Law.

Fick went on to extend the metaphor to a balloon with a finite internal hydrostatic pressure (Fig 1.12).

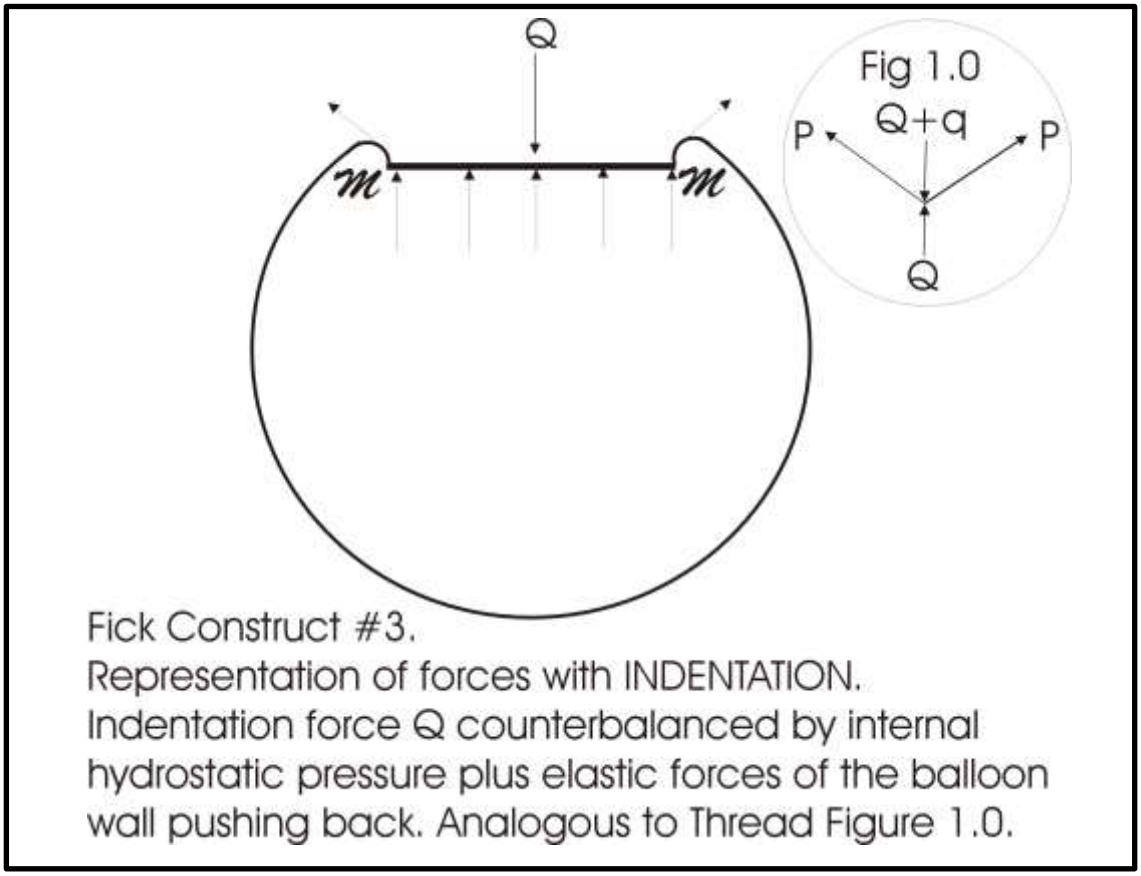


Figure 1.12. Fick Construct #3.

Fick proposed if a plate indents the balloon membrane, at equilibrium the plate pressure would be counterbalanced by internal hydrostatic pressure plus a pressure representing components of the balloon wall tension pushing back, analogous to the bent string model in Figure 1.10 as well as Imbert's indented elastic envelope (Fig 1.8).

Like Imbert in 1885, Fick proposed if the flat plate simply forms a plane (Fig 1.13), rather than an indented, surface on the balloon membrane the wall tension is eliminated and hydrostatic pressure within is exactly equal to the plate pressure, as in Fig 1.11.

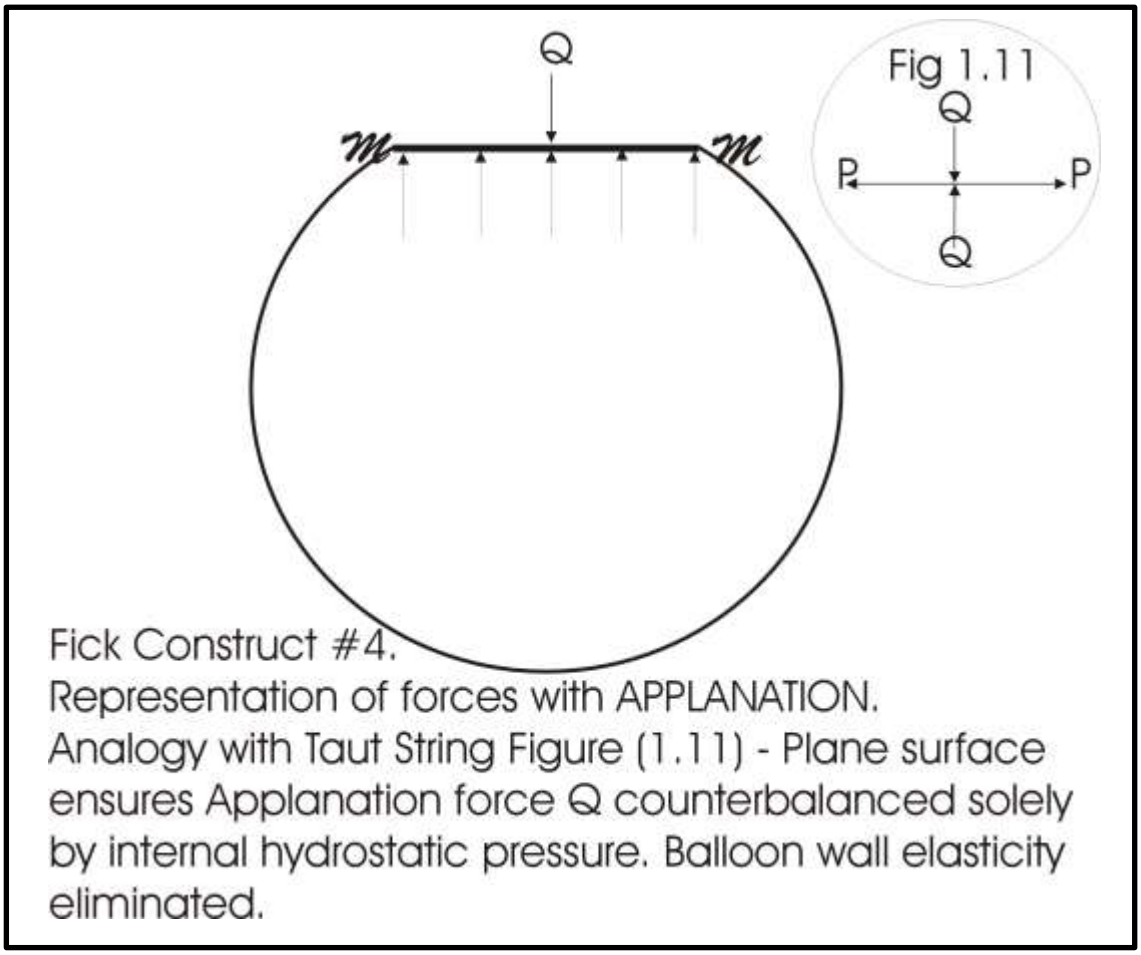


Figure 1.13. Fick Construct #4.

So affirming Imbert's conclusions, Fick believed true IOP could be measured if the tension of the cornea could be eliminated with all forces neutralizing each other. Achieved, Fick (1888) believed, when the tonometer produced a plane surface and not an indentation.

1.3.4 The Imbert-Fick Legacy

If accepted, this gives applanation tonometry a theoretical as well as a practical superiority over indentation. Certainly, applanation makes the math simpler, as well as reducing the impact on internal pressure.

However, in reality the laws of physics remain true for both procedures. Schiőtz (1905), while advocating his own invention, suggests applanation and indentation simply represent different points on the continuum of increasing tonometer loading. Friedenwald (1937) based his formula of tonometry on the Schiőtz instrument and, what was still termed at the time, the Maklakoff-Fick formula (F=PA). Apart from having a greater impact on altering internal IOP, the difficulty with indentation tonometry lies in calculating the force exerted on the cornea per unit area applied in the direction perpendicular to the surface (Law of Pressure - Bird and Ross 2012) when the indentation is a truncated cone (Schiőtz 1905, Friedenwald 1937). A plane surface is easier (Fig 1.14).

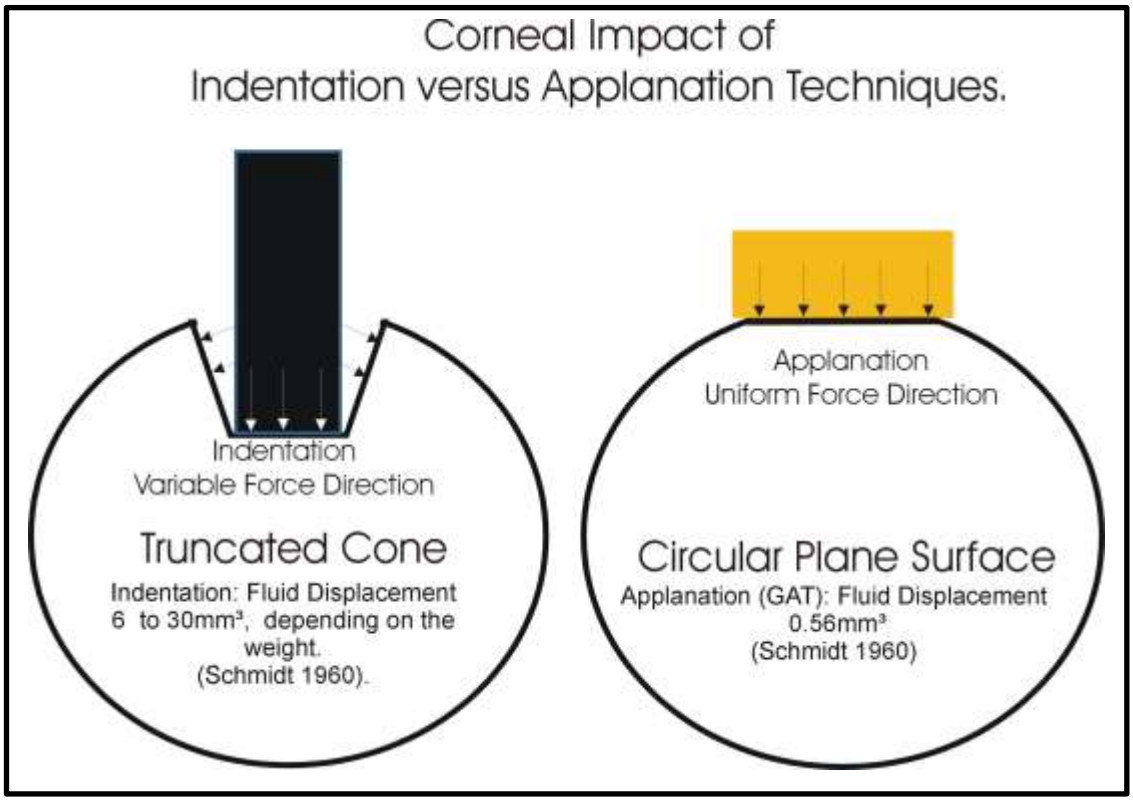


Figure 1.14. Corneal Impact of Indentation versus Applanation Techniques

However the assumption made by Imbert and Fick that during applanation tonometry all forces apart from IOP are cancelled out is false. Certainly equilibrium is achieved and, in

keeping with Newton's Third Law, the pressure applied by the tonometer is equal to the pressure pushing back. It does not however mean this is the IOP but rather represents a combination of all forces pushing toward the tonometer. Traditional reasoning suggests the primary additional force considered reflects the elastic properties of the cornea, acknowledged by Friedenwald (1937), Goldmann and Schmidt (1957) and Schmidt (1959, 1960), and indeed by Imbert himself with his initial elastic shell model. While Imbert and Fick considered corneal elasticity (Imbert 1885, Fick 1888) both authors felt the problem was completely eliminated when a concave depression was replaced by a plane surface.

Presumably in this scenario the only force pushing the cornea back to its habitual shape is the internal hydrostatic force, only possible with infinitely thin membranes possessing no biomechanical properties. While complying with Young-Laplace's equation, the infinitely thin membrane representing surface tension is in total variance with Imbert's original elastic shell model. This represents a modification to the model design assumptions. If the membrane is ascribed no biomechanical properties at applanation then it cannot be assumed to have any impact at indentation either.

The Imbert-Fick legacy then, is not the oft repeated formula P=F/A, a re-labelling of the formula for pressure, but equation P=T with its erroneous assumption all forces apart from IOP and tonometer load are eliminated when an indented surface is replaced by a plane.

The behaviour of complex biological structures is often studied by considering simplified models to target a specific biological tissue action (Śródka 2009). A model is assigned material characteristics to mimic the real tissue behaviour (Śródka 2011), while ignoring parameters with negligible effects (Elsheikh *et al.* 2006). However, the modelling assumptions of Imbert and Fick do not comply with physical laws.

Imbert (1885), while honoring Maklakoff as the real pioneer of the applanation technique, questions this inventor's insistence on considering the principles of physics when establishing the theory of his instrument. Maklakoff also considered necessary the need to test his theoretical model against experimental evidence; a totally superfluous process according to Imbert. When considering the biomechanics of soft tissue, Humphrey (2002) stresses the need to combine theoretical ideas and experimental findings to understand the complexities of physiology; a process Fick did endorse.

Laws reflect evidence based axiomatic fact. The simple biomechanical model, modelling the cornea as a homogenous elastic envelope, evolved from the papers of Imbert and

Fick, but also Maklakoff, would not appear to be affirmatively cited in anything but ophthalmic texts and Patents for ophthalmic equipment (Mark 2012). The Oxford Dictionary of Physics (2009) does not contain an entry for the 'Imbert-Fick Law'. Friedenwald (1937) while referring to what he calls the Maklakoff-Fick formula does not consider it a law.

Critics were certainly present. Mark (2012) quotes an eminent researcher Koster who, in 1895, showed the Imbert and Fick assumptions to be untenable. Markiewitz (1960) also re-challenged, as he called, 'the so-called Imbert-Fick Law' after the introduction of GAT, while White (1990) and Kalenak (1991) demonstrated a lack of scientific accuracy with the principle (Appendix 1). Mark (2012) suggests the moniker of 'Law' or 'Principle' was first formalized in 1904 by Langenhan in an ophthalmic textbook. Mark quotes the author as stating 'Imbert and Fick have both independently of one another proven that the tension of the wall of the eye can be eliminated in a simple manner'.

However, this did not stop Schiőtz, the following year, introducing his indentation tonometer, having reasoned the laws of physics remain the same whether applanating or indenting the cornea. Contrary to everything Imbert believed he had proven beyond doubt or need for experimental supporting evidence, the Schiőtz instrument became the reference standard for the next 50 years.

1.4 The Goldmann-Imbert-Fick Biomechanical Model and Technology

1.4.1 GAT Theory: Extending the Imbert-Fick biomechanical model

Goldmann and Schmidt (1957), in the introduction to their paper presenting their new tonometer report the 'Imbert-Fick Law' as stating the pressure in a liquid sphere surrounded by an infinitely thin, flexible membrane is given precisely by the counter pressure which flattens the membrane to a plane surface. Formulaically:

$$P=f/A$$

(1.4.1) Imbert-Fick construct (Goldmann and Schmidt 1957)

rather than P≈f/A (Schottenstein 1996). A statement, while reflecting the conclusion reached by Imbert (1885) and Fick (1888), is not true.

So were Goldmann and Schmidt able to construct a 'Gold Standard' tonometer based on a spurious theoretical biomechanical model? In his correspondence Markiewitz (1960) suggested the entire doctrine with its' instruments, formulas and curves remains a medical method devoid of any scientific foundation.

Fick (1888) acknowledged his model for the theory of tonometry would not demonstrate precision in the order of direct manometric examination. He felt deviations from true IOP would be in the order of several mmHg but would fulfil practical need. Even if wildly optimistic Fick's contemporary comparison was to the subjective 9 scale grading for digital palpation recommended by Bowman (Kniestedt *et al.* 2008).

Regardless, Śródka (2009) suggests the trust placed on models by their creators can appear boundless even when unverified or untested and can lead to acceptance and propagation of models based on flawed assumptions (Śródka 2010). Imbert (1885), so convinced of his model, expressly stated tonometer calibration to a manometric reference was superfluous.

Goldmann and Schmidt (1957) did describe the Imbert-Fick construct as an abstraction but re-emphasised its status as a 'law' and reaffirmed it as the basis of all tonometry.

Montés-Micó and Charman (2001) describe the Imbert-Fick Law as stating: ‘a container in the form of a perfect sphere has its internal pressure equally distributed, and the force per unit area required to applanate the sphere is equal to this pressure’. This statement accurately states the universally accepted ‘Law of Hydrostatic Pressure’ (Kanngiesser *et al.* 2005) and the equation for pressure P=f/A (Bird and Ross 2012); only the final statement on applanation reflects the conclusions of Imbert and Fick.

Regardless, rather than giving their much refined tonometer a realistically robust premise of physical laws, Goldmann and Schmidt (1957) simply manipulated and complicated the Imbert-Fick abstraction.

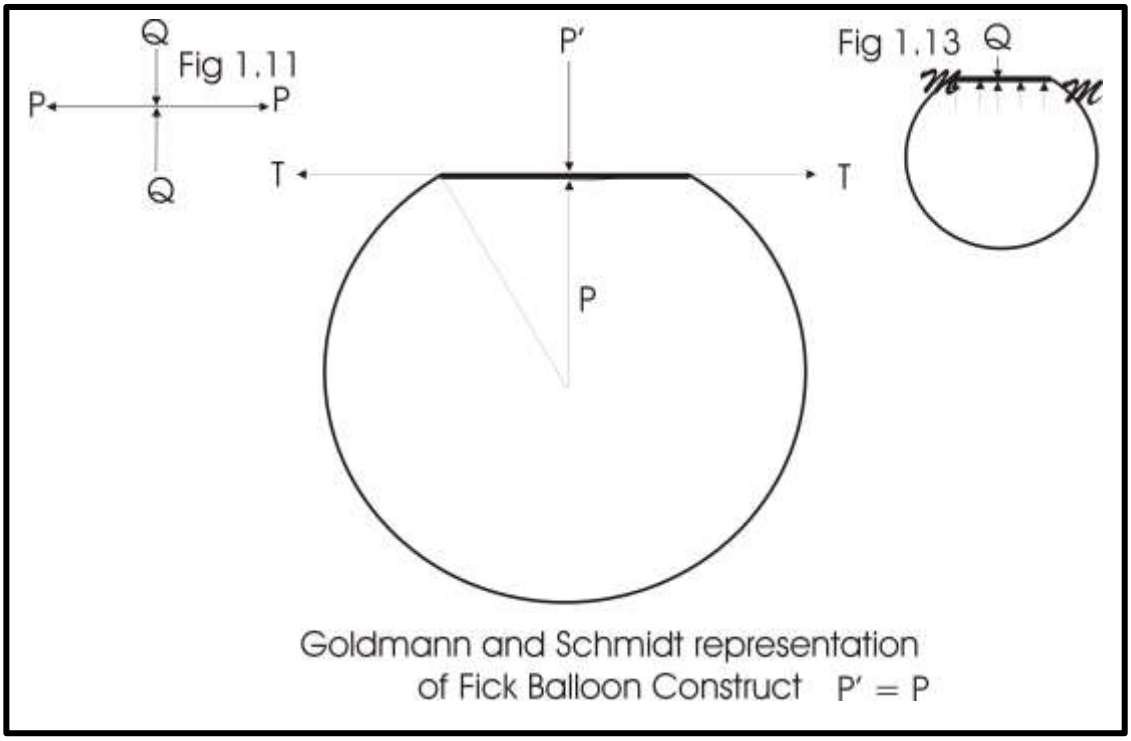


Figure 1.15. Goldmann and Schmidt representation of Fick Balloon Construct.

Figure 1.15 shows the Goldmann and Schmidt (1957) graphic representation of the Imbert-Fick construct; a single balloon membrane compressed by pressure P'.

While not explicitly explained this would appear to combine Imbert’s Figure 1.9 as well as Fick’s Figures 1.11 and 1.13 incorporating the ‘forces’ of PP (Fig 1.11) as TT.

As a vector function, a force (TT) acting tangentially to the applied forces perpendicular to the surface in question is inconsequential to the additive forces acting on the applanated surface.

The authors acknowledged the 0.5mm thick cornea (Goldmann and Schmidt's figure for CCT) is not an infinitely thin membrane. Rather than considering alternative models for the Corneal/Scleral shell, Goldmann and Schmidt proposed we should consider two concentric, and importantly non-extendable, Imbert-Fick style membranes; a balloon within a balloon (Fig 1.16).

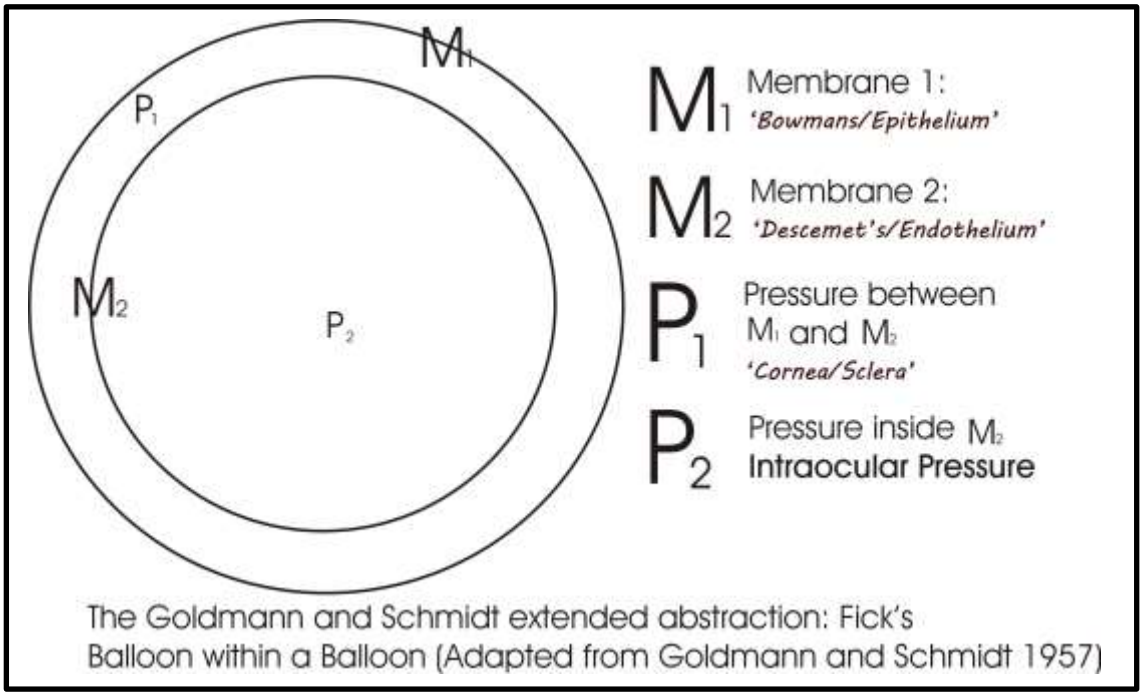


Figure 1.16. The Goldmann and Schmidt extended abstraction.

The stroma is represented as a gel bordered by Membrane 1 (M_1 – Bowans/Epithelium) and Membrane 2 (M_2 – Descemet's/Endothelium). The stroma is considered a liquid, rather than a biological shell, and is assumed to exert fluid pressure P_1. Goldmann and Schmidt (1961) suggest it will behave as a 'heavy, mobile water'. Within M_2 is the intraocular fluid exerting pressure P_2 (IOP).

The authors then make assumptions for their model complying with the Imbert (1885) and Fick (1888) biomechanical models. Reasserting the Imbert-Fick concepts, Goldmann and Schmidt believe Pressure P_2 (IOP) can be measured by applanating M_1 only if pressure is removed from M_2, achieved when M_2 becomes a plane surface. Goldmann and Schmidt (1957, 1961) suggest when M_1 is applanated enough to also applanate M_2 all pressure is removed from the inner surface (as with Imbert's Fig 1.9 & Fick's Fig 1.13), pressure on both sides of M_2 is equal and applanating pressure equals P2 (IOP). While the authors acknowledge corneal elastic properties exist they suggest this state eliminates them.

An explanation of how M_2 is applanated is given. If water exists between M_1 and M_2 applanation pressure on M_1 will not be transmitted to M_2 as water will move freely; a physical impossibility for an incompressible liquid inside an inextensible membrane. Extending the analogy it is suggested instead of water a gelatinous tissue is sandwiched between M_1 and M_2 which prevents free movement of the water content.

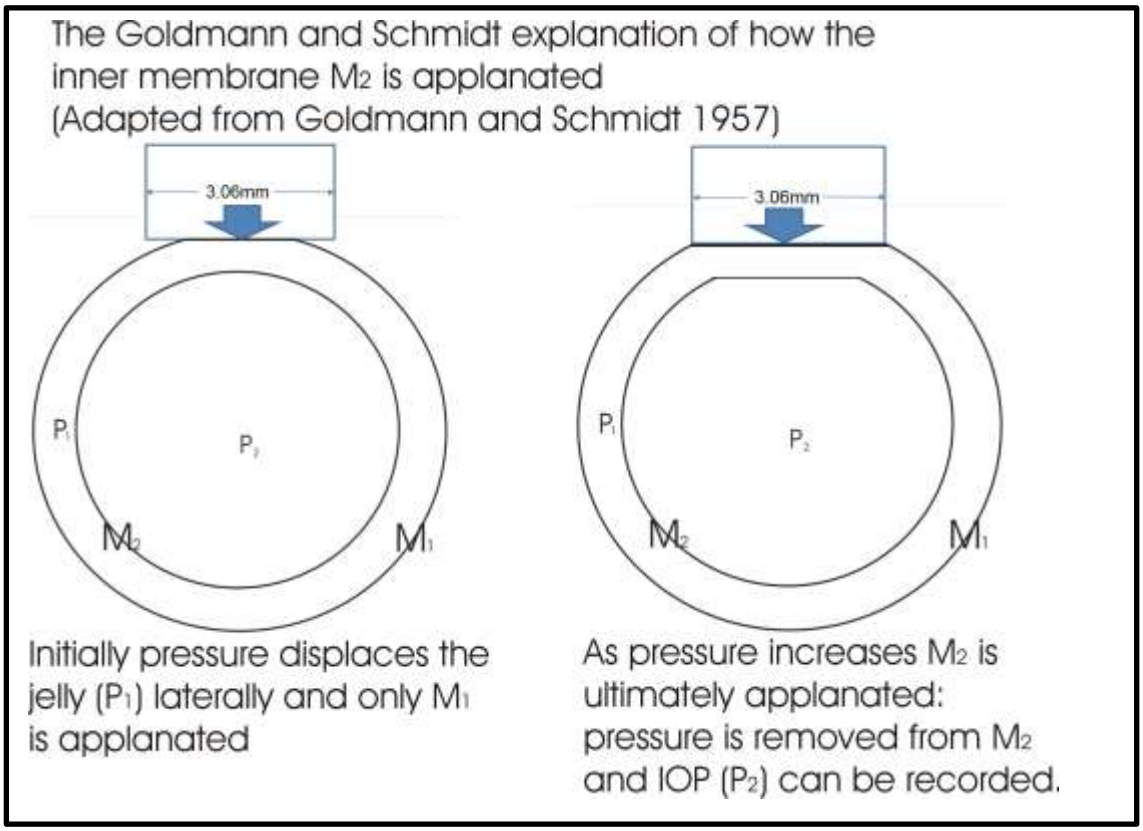


Figure 1.17. Applanation of Inner Membrane M_2

Under these conditions, the authors suggest, the jelly, behaving as a 'heavy mobile water' (Goldmann and Schmidt 1961) is displaced laterally and M_2 is ultimately applanated; pressure is removed from M_2 and IOP can be recorded (Fig 1.17). Only at external applanation diameters greater than 2.5mm would, the authors argued, the inner curve become applanated.

A purely geometric construct (Fig 1.18) led them to believe the inner corneal applanation zone would be proportional to the external when the diameter of this external flattening was 3mm. Why proportionality was essential was not explained. Certainly Schwartz *et al.* (1966) could not rationalise this apparent modelling imperative, their biomechanical calculations indicated this level of applanation would ensure structural resistance to be much higher than tear forces. Goldmann and Schmidt never considered or calculated

the bending resistance of the shell not exposed to load (Sródka 2009). Further, the calculation was based on only 5 enucleated eyes.

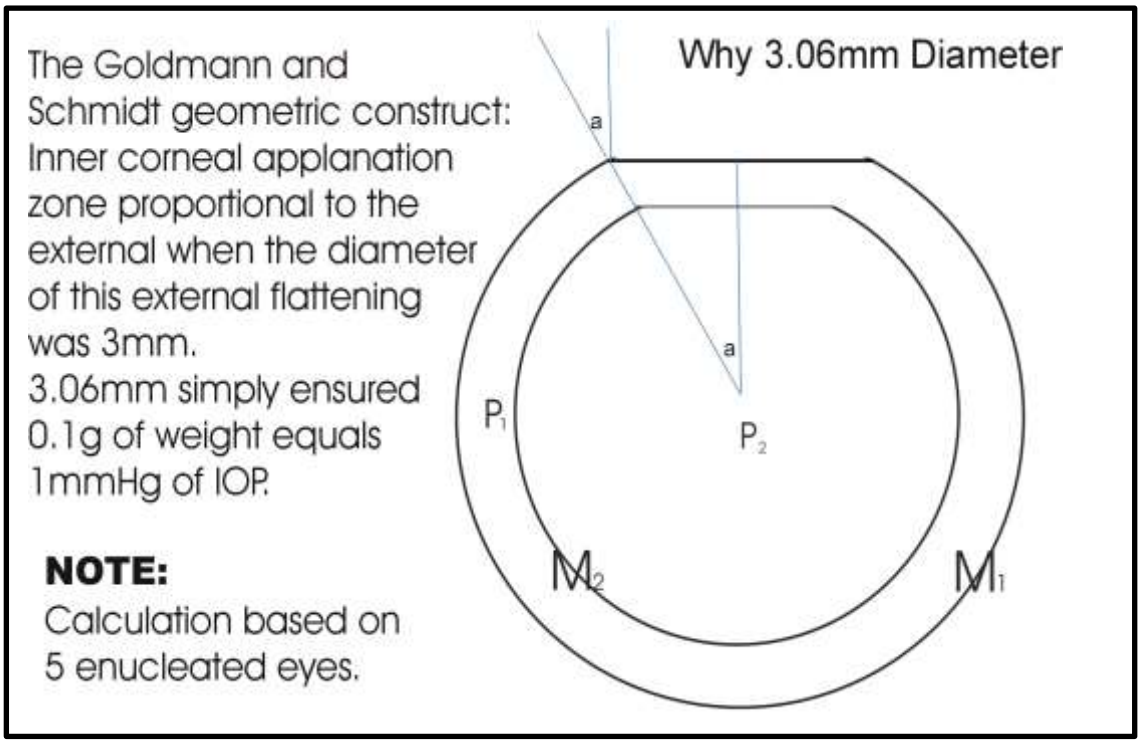


Figure 1.18. Proportionality of inner and outer applanation zones

Goldmann and Schmidt's further adjustment to an applanation diameter of 3.06mm was simply to ensure 0.1g of weight equalled 1mmHg of IOP.

Regardless, the modelling arguments assume impossible physical properties of the corneal stroma and imaginary membranes M_1 and M_2. The cornea is primarily water (Buzard 1992). Water is incompressible. As Elsheikh *et al*. (2011) and Liu and Roberts (2005) point out, whether pure water or a gel, corneal tissue is incompressible. Additionally the membranes are assumed non-extendable (Goldmann and Schmidt 1957) making the example described physically impossible. Markiewitz (1960) echoed this view, displacement of any incompressible fluid inside an inextensible membrane is a definite impossibility even if internal pressure is zero and exerted pressure infinite.

All models are approximations (Śródka 2009) and Goldmann and Schmidt (1957) admit the use of coarse methods to model the eye and suggest their conclusions may represent first approximations; a self-critique warranting more regular re-affirmation. Further, biomechanics was in its infancy in the 1960s (Dorfmann 2013, Humphrey 2002) and Śródka (2009) suggests, models can be reliable even when based on flawed

assumptions. Should Goldmann and Schmidt be criticized for their model's approximations? Contemporaries of Goldmann and Schmidt, Schwartz *et al.* (1966) did invoke constitutive biomechanical principles when highlighting potential difficulties with the GAT model.

While corneal elasticity was incorporated, rigidity was not. Schmidt (1959) states ocular rigidity, while profoundly affecting the Schiőtz instrument, is completely eliminated with GAT. In biomechanical terminology a misleading statement. Goldmann and Schmidt (1957) were simply considering Friedenwald's 'Coefficient of Ocular Rigidity', reflecting overall distensibility of the globe (Friedenwald 1937, Liu and He 2009). The assertion ocular rigidity can be ignored with GAT but not with Schiötz (Amdur 1960, Bayoumi *et al.* 2010) reflects, not true rigidity or stiffness, but reduced shell distention induced by the lower volume displacement. Constitutive biomechanical markers of elasticity, rigidity or stiffness cannot be attributed to Friedenwald's empirical measure.

Certainly the 'ocular rigidity' considered insignificant by Goldmann and Schmidt (1957) for the accuracy of their tonometer is not a true marker of biomechanical stiffness of the avascular cornea. Young's Modulus of Elasticity, detailed in section 1.2.2.6, is a measure of the intrinsic stiffness of a material (Hamilton and Pye 2008). White (1990), considers this the most appropriate metric.

The 'Modulus of Rigidity' or 'Shear Modulus' (section 1.2.2.7) represents the elastic modulus in shear (Young and Budynas 2002). Shearing forces are forces applied to a material in opposite directions in different planes of the material. Shearing forces can only be neglected if the surface is designated a 'membrane' demonstrating negligible resistance to bending (Humphreys 2002). The cornea is modelled as a thin shell. The applanation process clearly creates shearing forces around the probe circumference. It would seem counterintuitive, in the GAT model, to necessitate compensation for elastic forces of the cornea while ignoring rigidity.

Other corneal parameters were either normalised or considered insignificant to the model's predictive power.

Goldmann and Schmidt (1957) assumed a normalised CCT of 500µm; no other data was available at the time (Ehlers *et al.* 1975). With more advanced pachymetry, Ehlers and colleagues (1975) indicate the GAT calibration CCT is 520µm. Śródka (2013) suggests a CCT of 555µm is currently considered 'average', a figure reported by Tomlinson and Leighton (1972). Shimmyo *et al.* (2003) and Kohlhaas *et al.* (2006) suggest 550µm should constitute the CCT baseline for GAT adjustment. Further Hamilton *et al.* (2007a)

suggest an average circadian variation in individual CCT of 20.1±10.9 µm, while Price *et al.* (1999) reported a range of CCT for 450 myopic patients awaiting refractive surgery from 470µm to 650µm. These variations from the Goldmann and Schmidt standard are significant considering Whitacre and Stein (1993) suggest the physiological range of CCT can, in reality, induce a 9.9mmHg span in GAT readings for the same intracameral IOP and Palmberg (2002) noted up to 27% of Caucasian participants in the Ocular Hypertensive Treatment Trial had CCTs greater than 600µm. Certainly NICE (2009b) represent a CCT range from 555 to 590µm as a median while Medeiros and Weinreb (2012) indicate eyes with CCT of 555µm or less have a three-fold greater risk of developing glaucoma compared to eyes with CCT greater than 588µm.

Regardless, Elsheikh *et al.* (2006) also considered the subjective nature of GAT measurement and felt the effect of CCT on GAT, while statistically significant, is small compared to other sources of error. Errors, not solely related to GAT. Shildkrot *et al.* (2005), asserting standard practice is to take a single pachymetry reading, found repeat CCT measurements to vary by 20µm in 20% of cases and 40µm in 5%. Elsheikh *et al.* (2006) consider the measurement imprecision as 'noise' masking true effects, a sentiment echoed by Zadok *et al*. (1999) and Faucher *et al.* (1997).

A normalised radius of curvature of 7.5mm was stipulated by Goldmann and Schmidt (1957), although Śródka (2011) suggests 7.8mm. While Goldmann and Schmidt present a precise technique to compensate for variations in corneal curvature the authors suggest even extreme variations in corneal curvature and rigidity are not significant with GAT (Schmidt 1959).

Regardless, Grabner *et al.* (2005) describe a plethora of modern corneal interventions, ablation and incisional techniques, wedge resections, thermal effects on collagen lamellae as well as riboflavin cross linking. Elsheikh *et al*. (2011) mention degenerative conditions such as ectasia and age affecting corneal properties, while Damji *et al.* (2003) additionally lists corneal oedema, corneal scars and acromegaly affecting GAT measurements. Iester *et al.* (2009) stress extreme variations in CCT, not envisaged by Goldmann and Schmidt, are common with refractive surgery; this effect is well documented (Chatterjee *et al*. 1997, Emara *et al.* 1998, Gunvant *et al.* 2005, Cervino 2006).

The geometric characteristics of the cornea stipulated and normalised, Goldmann and Schmidt (1957) considered the only additional forces acting on the process were the elastic properties of the cornea M' pushing toward the tonometer (equalling the tonometer pressure required to flatten the cornea in the absence of any IOP) and N', the

surface tension of the tear fluid pulling the tonometer probe toward the cornea. Since Goldmann and Schmidt (1957) did not use the term 'rigidity' in a *bona fide* biomechanical sense, it remains conjecture the authors employed the descriptor 'elasticity' to represent the biomechanical law of 'Young's Modulus'.

Liu and Roberts (2005) and Glass *et al.* (2008) cite Damji *et al*. (2003) to support their assumption the tear film attraction equates to a pressure of 4.15mmHg; Damji and co-workers, in turn, cite Sørensen *et al*. (1978) for this figure. In actuality Sørensen and co-workers (1978) made no claims on the magnitude of the force of attraction of the tear film. The figure of 4.15mmHg for the magnitude of the tear attraction force appears to originate from Schwartz *et al.* (1966) who cautioned on the difficulty in estimating this figure accurately.

Kwon *et al.* (2008) also suggest a figure of 4 to 5mmHg but it must be noted Kwon and colleagues mirrored the theoretical calculations of Schwartz and co-workers so the papers do not lend independent support for this tear film force. The estimate presented by Schwartz and colleagues (1966) would appear to represent the foundation of the currently accepted value for tear forces.

However, Schwartz *et al.* (1966) emphasise the difficulty in estimating the magnitude of the tear film forces attracting the GAT probe, as the exact radius of the tear-cornea-tonometer interface is required, not simply the diameter of the applanation body. The authors indicate this is a major limitation of GAT, the surface tension is dependent, not only on its chemical constituents but the surface quality of the tonometer probe and the amount of fluid on the cornea prior to applanation. Indeed, Kralchevsky and Nagayama (2001), Neeson *et al*. (2014) and Goldmann and Schmidt (1957) indicate under specific conditions bridge forces can be attractive, neutral or repulsive. Goldmann and Schmidt (1957) were very conscious unless the tonometer probe is meticulously maintained a repulsive force could be created.

Another variable is the radii of curvatures of the surfaces in contact with the liquid (Schwartz *et al.* 1966). Tear forces are dependent on the geometry of the liquid bridge (Skσæveland 2012). Changes in the tear film dimensions, due to variations in corneal curvature, are not considered and may compensate or compound potential errors.

The calculations of Elsheikh *et al*. (2006), Elsheikh and Wang (2007) and Elsheikh *et al.* (2011) are tenfold lower. The authors calculated the force contribution induced by surface tension to be 0.0455 N/m, equivalent to only 0.45mmHg overestimation of IOP

(Śródka 2013). Śródka (2010) supports this estimate, indicates this level is well below measurement accuracy and operator variability, so wonders why correct for it at all.

Certainly the assumption of a global value for tear forces is not supported by Chihara (2008) who reports ranges quoted in the literature of between 1 and 4.67mmHg; the precise effects of tear film attraction is not well understood.

Can tear film forces be normalised, as Goldmann and Schmidt (1957) presumed? Tear film forces are complex and dependent on surface tension, itself conditional on the constituents of the tears (Nagyová and Tiffany 1999). Further the addition of anaesthetic and fluorescein to perform GAT significantly alters the surface tension (Schwartz *et al.* 1966); in theory controlled via the recommended standard GAT protocol. The surface tension constant for pure water is approximately 0.0728N/m (Elsheikh *et al.* 2006). Puinhas *et al.* (2013) indicate, while tears comprise 98.2% water the remaining 1.8% solids represent over 500 different proteins. These solids reduce the surface tension to approximately 42-46mN/m (≈0.045N/m) (Nagyová and Tiffany 1999). Changes in individual tear constituents will affect this figure. Zeng et al (2008) demonstrated an effect on GAT reading when adding Dextran or Viscoat to the tears prior to applanation. Puinhas *et al.* (2013) found a natural diurnal variation in tear surface tension and also reported changes in patients with dry eye.

Variation in any of these could cause significant variation in readings. Tear forces, constituting 50% of the GAT model pre-requisites, are investigated in Chapter 6.

Mardelli *et al.* (1997) suggest Goldmann assumed the human cornea offered approximately 0.5gms of resistance to indentation, equating to 5mmHg using Goldmann's scale. Schwartz *et al.* (1966) could not corroborate this. They calculated, using Young's Modulus and shell thickness, the corneal resistance to indentation equating to only 0.8mmHg. The authors also question Goldmann and Schmidt's assumption corneal resistance is independent of IOP. As IOP rises the corneal shell will experience an increased state of tension making it unlikely the surface tension could be guaranteed to balance the structural resistance and indeed often overcomes this force. These authors feel corneal elasticity will vary with IOP and the volume and chemical constituents of tears cannot be adequately controlled, potentially adding an extra layer of doubt over the utility of the GAT model.

In actuality, Goldmann and Schmidt (1957) made no claims on the magnitude of tear or corneal elastic forces. Goldmann and Schmidt (1957, 1961) validated their technique via empirical comparison to manometric measures. Rather than striving to quantify the two

additional forces of M' and N', Goldmann and Schmidt (1957) effectively reverse engineered the design process. Presupposing the model assumptions to be true, the designers found the probe dimensions ensuring the GAT measurements equalled manometric readings. The authors found experimentally on 10 living eyes manometric readings equalling GAT when the applanation zone diameter was less than 4mm, concluding N'=M' at and below this applanation diameter. The model predicts the corneal elastic forces are only neutralised by the surface tension of the tears at the specific 'calibration' dimensions of the cornea which include an applanation zone diameter of 3.06mm. Only in this very special case does, according to the GAT model, GAT = IOP. The inventors certainly considered IOP itself independent of GAT measurements (Goldmann and Schmidt 1957, Schwartz *et al.* 1966). The concept IOP could directly affect the measurement by modification of the biomechanical responses of the thin shelled cornea were not considered.

Regardless, these additional forces were incorporated into a modified version of the Imbert-Fick model giving:

$$P+M'=F/A + N'$$ **(1.4.2)** Goldmann-Imbert-Fick Model

(Adapted from Goldmann and Schmidt 1957, 1961).
Where:
F: Force (GAT) acting on the cornea.
A: Area of the plunger acting on the cornea.
P: Intraocular Pressure (albeit slightly raised by subtle ocular volume displacement).
M': Elasticity of the cornea pushing toward the tonometer.
N': Surface tension of the tear fluid pulling the tonometer probe toward the cornea.

However, a major criticism of the model, and by association GAT itself, is the very meagre sample size, and questionable experimental procedures, used to validate the GAT dimensions (Stodtmeister 2012). Pachymetry was not utilised by Goldmann and Schmidt, the CCT was assumed. The insubstantial number of eyes utilised, some enucleated without specification of time post-mortem (Stodtmeister 2012), may not have sampled a normal range of physiological corneal parameters, putting in doubt the GAT calibration dimensions.

It seems unlikely a normalised value for tear forces or corneal elasticity can be quantified. Goldmann and Schmidt (1957, 1961) confess it is unknown whether N'=M' is optimally fulfilled in living patients but, without supporting arguments did not expect errors to exceed 1mmHg.

If normalised values for both forces cannot be ascertained the GAT model fails. As with any modelled system, the model parameters and associated rationales are set initially. Deviations from these parameters, virtually by design definition, eliminate the model's predictive value.

1.4.2 Goldmann Applanation Tonometer: A significantly more precise instrument

Figure 1.19. The Schiőtz Indentation Tonometer

Figure 1.20. The Goldmann Applanation Tonometer

The equation (P=F/A) is accepted to represent the Imbert-Fick law. In reality, neither Imbert (1885) nor Fick (1888) presented this as representative of their conclusions, rather they simply concluded a plane, rather than an indented surface, neutralised all forces. Regardless of Schiőtz' (1905) correct claim the laws of physics apply equally to indentation and applanation, the latter has far less impact on the eye. Schmidt (1960) indicates the volume displacement of intraocular fluid with the Schiőtz can range from 6 to 30mm^3, depending on the weight. Fluid displacement with the Goldmann instrument, Schmidt suggests, is in the order of 0.56mm^3. This less invasive strategy produces significantly less artificial elevation in intraocular pressure; evidenced by the fact Schiőtz

remains essential for tonography (Moses 1971, Dueker 1996) with marked pressure elevations during tonography reported, and expected (Dueker 1996).

While advocating the inherent superiority of applanation theory over indentation, Schmidt (1959, 1960) explains applanation tonometer types are not necessarily superior to indentation. The Maklakoff applanation tonometer, available for a considerable time prior to GAT, did not supplant the Schiőtz as the instrument of choice; the applanation principle needed to be coupled with improved manufacturing standards and techniques.

A significant problem prior to GAT was the variability between machine types, between individual machines of the same make and indeed with the fundamental instrument design. Schiőtz (1920) presented corrections to the conversion curves as well as refinements to the instrument and yet, despite using an official Schiőtz tonometer supplied by the Norwegian company and certified by Professor Schiőtz, Friedenwald (1937) found it varied significantly from the 'Schiőtz Standard Tonometer'. Kronfeld (1945) checked 27 official standard Schiőtz instruments and none were compliant to specifications. Further, Kronfeld (1945) Jackson (1955) and Schottenstein (1996) indicate imitation Schiőtz instruments demonstrating poorer accuracy were widespread. These observations resulted in a committee appointed specifically to standardise the manufacture of Schiőtz instruments (Moses 1971, Schottenstein 1996). When describing GAT, Schmidt (1959, 1960) did suggest improving manufacturing standards was a very important adjunct to developing a theoretically more accurate instrument.

Manufacturing variability was a significant issue to be overcome. Schmidt (1960) reported the 'Committee on Standardisation of Tonometers' found the Schiőtz instrument depended on 20 different dimensions and characteristics. The potential cumulative effects of within-tolerance variations could be significant. Machine variables were reduced from 20 with the Schiőtz to 3 in GAT (Schmidt 1959, 1960). Schmidt (1959, 1960) goes on to explain, apart from friction between moving parts, the only 2 points where the instrument itself may affect the result are the manufacturing precision of the prism and the balance measuring the force. Schmidt (1959) claims error with the former is virtually zero. The latter however does require regular calibration, not necessarily performed (Kass 1996, Sandhu *et al.* 2005, Kumar and Jivan 2007).

As well as superior quality assurance at manufacture, the inventors also incorporated latest technologies. Mounting the system on a Haag-Streit slit lamp allowed the necessary light intensity and magnification to accurately measure the small area involved. The slit lamp viewing system also eliminated the potential error of parallax; significant when viewing a scale reading with other instruments.

GAT was the result of an obviously methodical and analytical assessment of the variables involved in intraocular pressure measurement in the 1950s. Regardless of the biomechanical model used to justify applanation theory, the meticulous design of the new machine and use of superior technologies allowed measurement precision of unquestioning superiority and unequivocally qualified GAT as a worthy 'Gold Standard' for its time.

However, while frictional interactions within the instrument were minimised they could not be eradicated; the need to regularly calibrate the instrument is documented (Sandhu *et al.* 2005). Likewise, operator variability, a significant problem (Kass 1996, Thorburn 1978, Grolman *et al.* 1990, Whitacre and Stein 1993) could only be minimised, as with all contemporary machines, by correct and accurate application of technique. Indeed Thorburn (1978) and Kass (1996) report inter-observer variability with GAT as high as 5mmHg, although Berry *et al*. (1966) found a much lower discrepancy. Elsheikh *et al.* (2006), while considering the statistically significant effect of CCT on GAT measurements, feel the effect is small compared to other sources of error such as inter and intra observer variability. In a paper supporting the new instrument, Moses (1958) lists twelve potential pitfalls when using GAT, of which nine reflect operator errors. Leydecker (1976) suggested, when auxiliary staff are considered, inter-observer variability was less using Schiőtz, confirming the need for much higher technical skills with GAT.

Physiological variability of individual corneas, an area of immense current interest, could be normalised but not eliminated. For all the refinements incorporated in GAT, Schmidt (1960) still acknowledged the ideal tonometer would be a compensated membrane manometer.

Maklakoff stressed tonometry does not measure absolute IOP but rather should be used to assess relative pressure changes in individual eyes (Kniestedt *et al.* 2008). Cridland (1917), reviewing 11 years of Schiőtz use, stressed the importance of considering the relative reading of the instrument and not the supposed pressure equivalent. It could be argued, as Cridland did, an absolute measure of IOP may not be essential as long as the measures used are standardised and repeatable. Zeitgeist must support Schmidt's (1959, 1960) convincing argument of the superiority of GAT; just as Fick's comparison was to digital palpation, Goldmann and Schmidt's was to Schiőtz.

However, our far more precise and ever growing understanding of corneal biomechanics, coupled with the increasing number of surgical procedures causing profound deviations from the normalised, calibration, parameters considered by Goldmann and Schmidt

demands a more radical reappraisal of techniques. Brandt and colleagues (2012) further suggest even if it were possible to correct GAT readings for individual corneal vagaries, the adjusted IOP measures would still suffer from the inherent variability and inaccuracies of the technique. Draeger *et al*. (1989) and Elsheikh *et al*. (2013) indicate observer independent tonometers would be a great advantage; surely an argument for non-contact tonometers? Schwartz *et al.* (1966) certainly considers the skill of the ophthalmologist critical to the accuracy of GAT. While non-contact tonometers are as susceptible to physiological variability as GAT, solid-state electronics allow virtually frictionless operation and automation removes operator variability. The supplementary justification for GAT of incorporating latest technologies (Schmidt 1959, 1960) is no longer valid in the 21st century.

1.5 The Ocular Shell: Corrections for Corneal Biomechanics

1.5.1 Introduction: Clarification of biomechanical terminology

Purslow and Karwatowski (1996) indicates 'Ocular Rigidity' is one of the most confused areas of ophthalmology, propagated by misappropriation of the empirical measure of globe distensibility introduced by Friedenwald (1937) and coined 'Coefficient of Ocular Rigidity'. Considered in detail in sections 1.2.2 and 1.2.5 the term rigidity is not always applied in a *bona fide* mechanical sense. Within this section, authors' descriptive terms will be used for citation accuracy. However, if, in the opinion of this author, an alternative descriptor is more biomechanically accurate, this term will be placed in parentheses and italics.

1.5.2 Central Corneal Thickness: An index of corneal biomechanics

A correlation between CCT and IOP was established well before refractive surgery was introduced (Ehlers and Kruse Hansen 1974, Ehlers *et al.* 1975, Johnson *et al.* 1978, Whitacre and Stein 1993, Whitacre et al. 1993, Argus 1995, Stodtmeister 1998, Bron *et al.* 1999). Ehlers and Kruse Hansen (1974), Copt *et al*. (1999), Singh *et al.* (2001), Ehrlich *et al*. (2012) and Kaushik *et al.* (2012) found normal tension glaucoma subjects to have thinner corneas than controls and ocular hypertensives the reverse. Ehlers *et al*. (1975) adjusted the calibration CCT suggested by Goldmann and Schmidt (1957) of 500µm to 520µm. Despite Goldmann and Schmidt acknowledging variations in CCT would elicit errors in GAT readings, Ehlers and colleagues admitted surprise at the ±5mmHg magnitude of those variations. Johnson *et al.* (1978) presented a single case report of an 'ocular hypertensive' patient with measured pressures persistently between 30 and 40mmHg. With no response to medication, cannulation revealed a true intracameral pressure of only 11mmHg; CCT was found to be 900µm. The authors recommended

measuring CCT in all cases where IOP readings do not correspond to other clinical findings.

The paper by Gordon and co-workers (2002) was pivotal to the acceptance of CCT as vital to the management of glaucoma (Brandt 2004). However, these authors reported CCT was not an initial consideration but was included later when it was observed thick corneas caused over-estimation of true IOP. A cautionary note stating CCT may be inter-related with other factors was included, however the correlation between CCT and IOP measurement was established. Factors such as corneal biomechanics and corneal curvature were not considered and CCT has become an accepted global index of corneal biomechanics. Indeed, Harada *et al.* (2008) explicitly state, in healthy corneas, corneal rigidity *(stiffness)* can be inferred via the measurement of CCT.

Further reinforcement of the concept of CCT as a unique global metric, is its regular description as an independent variable. Whitacre *et al.* (1993), Whitacre and Stein (1993), Herndon *et al.* (1997), Damji *et al.* (2003), Rask and Behndig (2006) and Harada *et al.* (2008) describe CCT as independent. However their comparisons were to a discrete number of measureable parameters, anterior chamber depth, lens thickness, vitreous body length, applanation and indentation readings, axial length and age. The authors did not consider other corneal biomechanical properties, not necessarily independent of CCT.

Mardelli *et al*. (1997), Rao *et al.* (1999) and Zadok *et al.* (1999), while confirming GAT underestimates IOP post PRK, could not correlate this with post-operative corneal pachymetry. Refractive surgery outcome, Roberts (2000) speculates, is as dependent on healing processes and corneal biomechanical response to alterations in structure as ablation profile. Mardelli *et al*. (1997) speculated the reduced readings were due to decreased resistance of the cornea suggesting CCT is a reflection of corneal biomechanics rather than an independent metric. This view is supported by Broman *et al.* (2007) who note, while there is a similar distribution of CCTs between European and Chinese, IOP is statistically lower in the latter group. The authors suggest this may reflect differences in the physiological make-up of the corneal tissues.

Argus (1995), Wilensky (1999) and Damji *et al.* (2003) argue CCT is related to corneal rigidity *(stiffness)* and corneal resistance to indentation. Brandt (2004) suggests individual variations in mix of collagen types, corneal hydration, collagen density and extracellular matrix may dwarf the effect of CCT on the accuracy of GAT. Touboul *et al.* (2008) and Broman *et al.* (2007) mention corneal hydration, properties of the corneal layers and biomechanics of the stroma as important in determining the viscoelastic

responses of individual corneas. Krueger and Ramos-Esteban (2007), considering patients with diabetes, indicate hyperglycaemic induced corneal collagen cross linking may lead to stiffening of these corneas and associated overestimation of IOP with GAT. Liu and He (2009) also demonstrated the expected outcome IOP elevations were significantly higher in artificially stiffened corneas even when volume changes were small.

Hamilton *et al.* (2007b) and Kotecha *et al*. (2009) also suggest circadian variations in corneal hydration can elicit significant errors and variability in GAT readings. Elsheikh *et al.* (2006) remark on the complexity of microscopic ocular structures as well as the macroscopic; models, they suggest, must incorporate all significant parameters.

Familiarity and ease of measurement may impart CCT with a disproportionate level of significance. Hamilton and Pye (2008) report IOP may be paradoxically underestimated in thick but oedematous corneas; only an apparent paradox if CCT is designated an independent global index rather than a single, measurable reflection of corneal biomechanics. Liu and Roberts (2005) give a simple metaphor for this concept: a steel rod, regardless of having the same thickness as a wood rod will be more resistant to deformation. Hamilton and Pye (2008) indicate Young's Modulus is at least as important as CCT to the accuracy of GAT. Saleh *et al.* (2014) are unambiguous in their declaration Young's Modulus defines the rigidity *(stiffness)* of a material.

Ehlers and co-workers (1975) did suggest the likelihood oedematous corneas, while thickened, would register falsely low GAT measurements, necessitating the need to distinguish between physiologically thick corneas with dense collagen fibrils and those thickened by interfibrillar fluid. Simon *et al.* (1993) confirmed experimentally a reduction in GAT readings with thicker, but oedematous, corneas. Further, Moses (1971), considering non-primate corneas, and Tang *et al.* (2011) discussing canine eyes, note the lack of Bowman's Layer engenders a far more plastic behaviour; an observation unconnected to corneal thickness. Tang *et al.* (2011) further found canine corneas, although thicker than human, gave lower GAT measurements reflecting varying biomechanics rather than CCT or corneal curvature. The biomechanical support afforded by Bowman's Layer was also highlighted by Kohlhaas and co-workers (1995), the destruction of this layer in Radial Keratotomy and Excimer Ablation leads to altered corneal bending. Pepose *et al.* (2007), while acknowledging, on average, GAT readings decrease post LASIK, stresses this is not universally the case. A GAT rise in a significant number of patients may, the authors suggest, reflect complex biomechanical changes of regional flap variations, alterations in hydration, viscoelasticity, ablation zones and

curvature. Finally, while corneal thickness is not found to increase with age (Wolfs *et al.* 1997, Shildkrot *et al.* 2005), Tonnu *et al.* (2005) demonstrated corneal rigidity *(stiffness)* does. Whitford *et al.* (2015) suggest this increased rigidity *(stiffness)*, with stable thickness, is due to changes in fibril behaviour rather than orientation.

Suggesting simple correction factors, often assuming linearity (Ehlers *et al.* 1975, Stodtmeister 1998), are consequently over-simplistic.

Damji *et al.* (2003) comment published correction factors for CCT range from insignificant to highly significant. Summarised in Table 1.1, correction factors considering CCT in isolation range from 2mmHg to 7.1mmHg per 100µm of corneal thickness (Ehlers et al. 1975, Whitacre *et al.* 1993, Doughty and Zaman 2000, Kohlhaas *et al.* 2006, Özcura *et al.* 2008).

Author/Year	GAT IOP Correction per 100µm CCT	Number of Eyes Sampled
Ehlers *et al.* 1975	**7.1**	29
Whitacre *et al*. 1993	**2.0**	15
Doughty and Zaman 2000	**6.7**	Meta-analysis of 300 data sets
Kohlhaas *et al*. 2006	**4.0**	125
Özcura *et al*. 2008	**2.9**	98

Table 1.1 Proposed GAT corrections for variations in CCT

However experimental procedures and participant numbers varied considerably. Doughty and Zaman (2000) conducted a meta-analysis of 300 data sets. While incorporating large numbers of individual measurements meta-analysis understandably averages results. Conversely, Ehlers *et al.* (1975) and Whitacre *et al.* (1993), presented data from only 29 and 15 individuals respectively. While both groups calibrated against manometric pressures, Ehlers and colleagues found 7.1mmHg per 100µm while Whitacre and co-workers found the lowest correction of only 2mmHg per 100µm. Both

groups suggested a strong linear relation. Kohlhaas *et al.* (2006) sampled 125 eyes and estimated the correction to be 4.0mmHg per 100µm.

The *in vivo* mechanical properties of the eye have not been well described (Śródka and Iskander 2008). While it is understood these properties affect GAT measurements the application of this knowledge is limited by our current inability to measure these properties *in vivo* (Elsheikh *et al.* 2011). CCT remains the only measurable parameter to correlate GAT measures to corneal biomechanics (Touboul *et al.* 2008). As a result CCT correction tables are readily accepted and intuitively plausible.

Ehlers *et al.* (1975) considered both CCT and corneal radius when preparing one of the earliest correction nomograms for GAT. No correlation with corneal radius was identified and the authors concluded it was sufficient to consider GAT measurement as a function of CCT in isolation. This influential paper, supported by Whitacre *et al*. (1993), helped set the accepted GAT calibration dimensions of the cornea. The authors conclude for normal corneal thickness of approximately 520µm GAT gives the correct value for IOP; thicker corneas lead to overestimation and thinner underestimation of true IOP. For corneas thicker or thinner than 520µm the GAT reading must be modified accordingly. A table was included (reproduced in Table 1.2) giving the required GAT correction to attain true intracameral measures.

The table gives the correction to be added to the tonometer reading in order to obtain intraocular hydrostatic pressure in mmHg. The table can be applied to normal corneas.

CCT (mm)	10mmHg	15mmHg	20mmHg	25mmHg	30mmHg
0.450	+4.2	+4.7	+5.2	+5.7	+6.2
0.460	+3.5	+4.0	+4.4	+4.8	+5.3
0.470	+2.9	+3.3	+3.7	+4.1	+4.5
0.480	+2.2	+2.6	+2.9	+3.3	+3.6
0.490	+1.5	+1.8	+2.2	+2.5	+2.8
0.500	+0.9	+1.2	+1.4	+1.7	+1.9
0.510	+0.3	+0.5	+0.7	+0.9	+1.1
0.520	-0.4	-0.2	0.0	+0.1	+0.3
0.530	-1.0	-0.8	-0.7	-0.6	-0.5
0.540	-1.6	-1.5	-1.4	-1.3	-1.2
0.550	-2.2	-2.1	-2.1	-2.0	-2.0
0.560	-2.8	-2.8	-2.8	-2.8	-2.7
0.570	-3.4	-3.4	-3.4	-3.4	-3.4
0.580	-3.9	-4.0	-4.1	-4.1	-4.2
0.590	-4.5	-4.6	-4.7	-4.8	-4.9

Table 1.2 Additive correction (ΔP) for Goldmann applanation tonometer readings. Adapted from Table III Ehlers *et al*. (1975)

Kohlhaas *et al.* (2006) also considered corneal radius, axial length and ranges of intracameral IOP as well as CCT. Like Ehlers and colleagues they found no correlation with corneal radius or axial length and also produced a correction table for adjusting GAT readings for CCT induced errors. Unlike the earlier researchers Kohlhaas and co-workers found GAT equaled intracameral pressure when CCT was 550µm. The range of correction did not tally with the Ehlers and colleagues table either; Kohlhaas *et al.* recommended an adjustment of 4.0mmHg per 100µm change in CCT while Ehlers and co-workers found 7.1.

Francis *et al.* (2007), Hager *et al.* (2008), Boehm *et al.* (2008) and Śródka (2010) emphasise the number of nomograms proposed to adjust GAT readings for CCT and indicate none are satisfactory. The mechanical behaviour of the cornea, as predicted by biomechanical laws (Whitford *et al.* 2015) reflects not simply CCT but corneal microstructure and topography (Ariza-Gracia *et al*. 2015).

Shah *et al.* (1999) and Feltgen *et al*. (2001) state it is impossible to determine the level of inaccuracy induced by a specific CCT. Tranchina *et al.* (2013) support his view; they suggest CCT can be used in a global sense but specific correction for tonometer readings is ill-advised. Certainly Cao *et al*. (2012) could not correlate thin CCT with more rapid progression of visual field loss in glaucoma patients. Park and colleagues (2012) are critical of CCT based correction formulae; clinicians should necessarily amalgamate all the evidence before formulating a clinical management plan, irrespective of CCT. The authors suggest while CCT may be valid for population based analysis they must not be relied upon for the diagnosis and management of individual patients. Medeiros and Weinreb (2012) are quite explicit CCT correction formulae do not improve the accuracy of predictive models for development of glaucoma.

Brandt (2004) also questions the simplistic CCT correction, stating no correction algorithm has been validated, an opinion echoed by Iester *et al*. (2009) and Medeiros and Weinreb (2012). Without validation clinicians cannot use the data. Brandt *et al.* (2001) and Myers (2006) further indicate a linear correction for CCT is an oversimplification. Linear nomograms, Brandt and colleagues suggest, could lead to a negative value of IOP in specific cases. Gunvant *et al.* (2005) demonstrated the Ehlers *et al*. (1975) correction predicts erroneously low IOP in thicker corneas and erroneously high pressure when corneas are thinner, supporting the view correction for CCT cannot be linear.

Brandt (2004) suggests a failure to question tonometry techniques has led to the proposal of a variety of hypotheses, including CCT corrections, to explain variations. He

argues the incorporation of CCT into our IOP estimations represents the beginning, not the culmination, of tonometry refinement. Brandt *et al.* (2001) consider the question on correcting for CCT as open and Young (2014) warns the desire to characterise the cornea with a single number is simplistic and unrealistic. Certainly, Doughty and Zaman (2000) argued at the time, CCT had yet to be established as the most useful parameter and suggested it has been adopted as a standard much by repeated usage.

1.5.3 Further Biomechanical Considerations

The recognised difficulties in a CCT specific correction for GAT, tempered by historical precedent and inclusion as reference tonometer, potentially drives momentum to improve, rather than replace, GAT. A range of additional measureable parameters and estimates have been presented.

Orssengo and Pye (1999) were amongst the earliest to consider additional variables, including *bona fide* biomechanical concepts, to strive to improve the GAT model. The authors state the study aim was to prepare a nomogram to determine true intracameral IOP from GAT measurements. To achieve this, both theoretical model predictions and experimental results were essential. The experimental data, from Goldmann and Schmidt (1961), Ehlers and colleagues (1975) and Whitacre and co-workers (1993), gave the CCT anchor assumption at the GAT calibration dimensions: IOP_G (GAT Pressure) = IOP_T (True intracameral IOP).

Unlike Goldmann and Schmidt, however, the authors modelled the cornea as a thin shell, (Young and Budynas 2002). As opposed to the double Fick-style membranes, with fluid properties between, suggested by Goldmann and Schmidt (1957), loading stresses are essentially uniform throughout the thickness of a thin shell. The mechanical properties of the shell, considered to best model the system's response to load, had to be designated. Importantly, recognised biomechanical parameters of Poisson's Ratio and Young's Modulus were incorporated into the model.

Using best approximations gleaned from the literature, the authors assumed an average radius of curvature, thickness and Poisson's ratio of the cornea as 7.8mm, 520µm and 0.49 respectively. Totally incompressible materials will have a Poisson's ratio of 0.5 (Liu and Roberts 2005), the authors further indicate most biological soft tissues are virtually incompressible and convention tends to apply the value of 0.49.

A correction factor K adjusting IOP (GAT) to IOP (True), was calculated and can be read from a table and IOP (True) calculated thus:

$$\text{IOP (True)} = \text{IOP (GAT)}/K$$

(1.5.1) Orssengo-Pye GAT Correction

Chihara (2008) suggests the model includes unfeasible assumptions. The cornea was presumed fixed to an immovable sclera, ensuring the tonometer loading impacted on the cornea in isolation creating exaggerated boundary conditions. Further, forces of the tear layer were ignored. The model also assumes a uniform CCT of 520µm across the entire cornea, a simplification complying with strict shell theory but not reality. The actual value of the calibration CCT, whether uniform or not, has also been questioned (Kohlhaas *et al.* 2006, Shimmyo *et al.* 2003, Śródka 2013).

In the absence of manometric comparison, Gunvant and colleagues (2005) used statistical analysis of variance to demonstrate the Orssengo and Pye model underestimates IOP in thick corneas and overestimates IOP in eyes with thin corneas. The authors indicate had the model perfectly annulled all extraneous variables, CCT should be found to be independent of IOP. This was not the case. There is, according to Gunvant and co-workers, a residual effect of CCT, or perhaps as Elsheikh *et al.* (2011) indicated there are other unmeasured corneal biomechanical features at play.

Elsheikh *et al*. (2011) strived to produce a method of improving GAT accuracy using metrics easily measured with current practice technology. CCT, Corneal Radius and Age were incorporated. Corneal rigidity *(stiffness)*, the authors suggest, increases with age (Elsheikh *et al.* 2008a, Elsheikh *et al.* 2011). Like CCT, within this study, age was essentially another measureable surrogate for biomechanics. A non-linear finite element analysis incorporated the corneas non-uniform thickness, asphericity of anterior and posterior surfaces, low stiffness of the epithelium and endothelium compared to the stroma and weak stromal interlamellar adhesions. While the authors found CCT to have the greatest impact on GAT, Corneal Curvature and Age did affect the readings.

The authors themselves stress their correction equation may not be accurate for individual patients as it assumes a consistent age related change in corneal stiffness. While Tonnu *et al*. (2005) also demonstrated increased corneal rigidity *(stiffness)* with age, due, it was suggested, to changes in the collagen fibrils of the stroma, Shimmyo and colleagues (2003) found no such correlation.

Kwon *et a*l. (2008) used a non-linear, transversely isotropic material model, utilising 'finite elements' to estimate the impact of CCT and corneal biomechanics on GAT; radius was

not considered. Due to the isotropic nature of the cross-sectional profile, the model is characterised by a single material parameter of Young's Modulus (E). Setting CCT at 536µm and Intracameral IOP at 16mmHg, the effects of Young's Modulus on IOP was in the order of ±5mmHg. Simulated GAT underestimated IOP when Young's Modulus was lower and overestimated with stiffer material properties. The authors suggest the underestimation with lower Young's Modulus is due to the tear layer attraction which they calculated as equivalent to 4.7mmHg. Conversely, Śródka (2010), considering tear forces to be only 0.45mmHg, suggesting it is implausible GAT could record lower than IOP. However, examination of both sets of authors' calculations (Chapter 6) casts doubt on these values leaving both claims unsupported.

Assessment of the CCT effect was modelled with Young's Modulus set at 0.23MPa and maintaining Intracameral IOP at 16mmHg. The CCT effect was not found to be the overriding contributor to GAT variation; Young's Modulus was equally dominant. As with much research, corneal biomechanics and CCT were dealt with as independent variables. The supposition CCT is a reflection of biomechanics was not considered.

This group also assessed the impact of Intracameral IOP on GAT. The authors suggest there is a real effect in which IOP affects the corneal stiffness. Higher IOP results in stiffer corneal responses to GAT. A proposed correction algorithm for GAT readings was presented.

All models cited are applicable to physiologically normal corneas. Regardless of which set of assigned material characteristics mimic the real tissue behaviour, all are ineffectual when considering pathologically or surgically modified corneas.

Damji *et al.* (2003), presented a comprehensive, but complicated, tonometry strategy, striving to encompass normal corneas as well as those physiologically, pathologically and iatrogenically modified. Importantly these authors did not accept the GAT/CCT mandate. Damji and colleagues did not assume GAT to be the reference standard; the assumption of GAT pre-eminence is restrictive. The unconventional approach to tonometry hierarchy is important; the suitability of different tonometers for various corneal biomechanical states was the imperative. A flow diagram indicates when CCT compensation is required, which type of tonometer best suits specific pathological conditions such as oedema and scarring, while for post refractive surgery a patient specific individualised correction factor based on pre and post-surgery GAT measurements can be calculated.

Kohlhaas and co-workers (1995), concerning themselves with early refractive surgery procedures of Radial Keratotomy and Excimer Ablation, recognised the need for a specific correction table for these procedures because, as they suggest, destruction of Bowman's Layer leads to destabilisation of the entire globe and consequential altered corneal bending.

While Shih *et al.* (2004) reported a change in management of half their patients using the Orssengo-Pye (1999) correction algorithm, none of these nomograms supply a solution to the tonometry conundrum. Chihara (2008) warns a correction algorithm for GAT may not be accurate for individual subjects. Brandt *et al.* (2012), Śródka (2010) and Özcura *et al.* (2008) indicate no formula or correction nomogram adequately corrects IOP measurements; the available formulae are incapable of incorporating biomechanical properties of which CCT is simply a component. Śródka (2010) also suggests specific algorithms for corneal radius correction lacking. Further the potential cumulative effects of normal variations in factors such as age, Poisson's ratio, corneal asphericity and non-uniform corneal thickness could be significant. Elsheikh *et al*. (2011) also stress no algorithms can correct the inherent technical and clinical imprecision of the technique itself.

All these factors are significant, however the adjustment for thinner corneas creates a challenge as it would seem irreconcilable with the GAT model.

1.5.4 Assumption of the Legitimacy of the GAT Calibration Dimensions: Intracameral pressure and GAT

Many authors question Goldmann and Schmidt's assumption corneal resistance is independent of IOP (Schwartz *et al.* 1966, Purslow and Karwatowski 1996, Kohlhaas *et al.* 1995, Francis et al. 2007, Kwon *et al*. 2008, Śródka 2009, 2013, Leung *et al.* 2013).

Ariza-Gracia *et al*. (2015) modelling the biomechanical response of the cornea to air-puff tonometry, not specifically ORA, conclude the corneal response is influenced, not only by corneal biomechanics, but also IOP and topology, incorporating CCT and curvature.

The modified Young-Laplace equation as applied to thin shells (Purslow and Karwatowski 1996), described in detail in section 1.2 and equation 1.2.7, also predicts the interdependency of radius of curvature, internal pressure and shell thickness.

Purslow and Karwatowski (1996), derive a more complex equation demonstrating an incremental change in wall stress induced by an incremental change in volume (ΔP/ΔV) is related to changes in pressure (P), radius (R) and thickness (t):

$$\frac{\Delta P}{\Delta V} = \frac{1}{4\pi R^3}\left(\frac{4E_p t}{R} - 3P\right) \qquad \textbf{(1.5.2)}$$

Where:
E_p: Incremental value of Young's Modulus
R: Radius of the membrane.
P: Internal pressure at radius R.
t: Membrane thickness.

The authors show E_p (incremental change in Young's Modulus) cannot be a constant but must vary with radius or pressure.

While inaccuracies in GAT due to corneal material properties are well accepted, the traditional GAT model does not consider the possibility the actual intraocular pressure may affect accuracy (Śródka 2009). Modelled (Kwon *et al.* 2008, Śródka 2009, 2013) and experimental (Francis *et al.* 2007) results suggest increased IOP induces a stiffer corneal response to applanation. This would be consistent with general biomechanics. As the tensile stress on the cornea, induced by increasing IOP, rises the Hookean nature of the corneal proteoglycan is overwhelmed and the cornea becomes stiffer, as well as thinner. Roberts (2014) reiterates this concept, never envisaged by Imbert, Fick or Goldmann, IOP is not independent but directly affects wall tension ensuring the cornea stiffens with increasing IOP; IOP confounds tonometry.

Like the automatic acceptance of the original Imbert-Fick precept, should the veracity of GAT readings at the calibration dimensions be unquestioned?

The GAT model is assumed accurate when M' (elasticity of the cornea pushing toward the tonometer) equals N' (surface tension of the tear fluid pulling the tonometer probe toward the cornea). At the calibration dimensions M' cancels N' ensuring the GAT reading equals the true IOP.

CCT adjustment nomograms indicate, for corneas thinner than 520µm, GAT underestimates true IOP. If all extraneous forces are neutralised at 520µm, the only force

pushing back toward the tonometer is IOP. Śródka (2013) pondered how, in thinner corneas, the external tonometer pressure can be lower than the internal ocular pressure? The GAT model only allows one possibility, under thinner corneal dimensions, force N', pulling the tonometer toward the cornea, must be greater than the corneal elastic forces pushing back.

It seems impossible to accurately quantify either force.

A tear film force equating to a pressure of 4.15mmHg is often quoted (Liu and Roberts 2005, Glass *et al.* 2008, Damji *et al.* 2003). This estimate originates from Schwartz *et al.* (1966) who cautioned on the difficulty in estimating this figure accurately. Chihara (2008) does not support the acceptance of a global figure for this force; the author indicates tear film attraction reported in the literature ranges between 1 and 4.67mmHg. Elsheikh *et al.* (2006) calculated the force to be as low as 0.45mmHg.

The precise effects of tear film attraction is not well understood (Chihara 2008). An absolute magnitude for this attraction force was not stipulated by Goldmann and Schmidt (1957), nor did they quantify corneal elastic forces. Rather, they found, via experimentation on living and enucleated eyes, the dimensions of the probe ensuring GAT readings equated to manometry values. At this point, if the model was correct, surface tension of the tears (N') would neutralise the elastic force of the cornea (M'); M' = N'. Under these specific design arrangements, logic implies, GAT is equal to true IOP; the GAT probe dimensions were dictated by the model assumptions.

Mardelli *et al.* (1997) assume corneal resistance equivalent to 5mmHg. Schwartz *et al.* (1966), using Young's Modulus and shell thickness, published an estimation of only 0.8mmHg while Śródka (2010, 2011) suggested a figure of 1mmHg.

Śródka (2010) suggests the complete inability to find a universal correction for CCT and corneal radius reflects the actuality there is no theoretical justification for the calibration values. The simulation of Kwon *et al.* (2008), fixing IOP at 16mmHg, found GAT underestimates IOP not only in thinner corneas but also those with lower Young's Modulus; the reverse is predicted in thicker and stiffer corneas. These authors calculated a tear force of 4.7mmHg and accept underestimation of IOP in thinner corneas due to tear film effects. However, examination of the author's derivation in Chapter 6 casts doubt on this figure, the conclusion is consequently unsupported.

Conversely, Śródka (2010), recognising tear forces to be only 0.45mmHg, suggest it is implausible GAT could record lower than IOP. Intuitively, the thinner the cornea

becomes, the closer it approximates the infinitely thin, flexible membrane stipulated as fundamental to the Equation of Young-Laplace and purportedly the 'Imbert-Fick' construct. The negligible effect of tear surface tension aside, an irrelevant inclusion according to Śródka (2010), GAT should, in compliance with the 'Imbert-Fick' construct, more closely approximate intracameral IOP in the thinnest corneas.

The proposition made by Goldmann and Schmidt (1957) that the properties of the cornea are independent of intraocular pressure is at variance with biomechanical laws.

The specific dependence of GAT readings on IOP was investigated by Śródka (2009, 2013) via the development of a biomechanical eyeball model. The basic eyeball dimensions conform to the Gullstrand-Le Grand standard with anterior corneal radius 7.8mm, posterior corneal radius 6.49mm, CCT of 520µm and peripheral corneal thickness 720µm. The finite element model incorporates stress, strain and Young's modulus of the corneal and scleral material. Importantly, the author also controlled for IOP with a calibration level set at 16mmHg; the calibration standard was an IOP level rather than a CCT level. A range 5 CCTs, 3 radii of curvature, 4 corneal material characteristics, were considered.

Śródka (2013), considering CCT, for the standard CCT of 520µm, GAT = IOP (True) solely at 16mmHg, a figure also supported by Kwon *et al.* (2008). At IOP levels below 16mmHg, GAT records pressure higher than IOP. As IOP increases GAT increasingly underestimates IOP. Under this modelled system it cannot be assumed at the calibration CCT, GAT will equal IOP, except specifically when IOP equals 16mmHg. CCTs other than 520µm also demonstrate specific single equilibrium points; the larger the CCT the higher the IOP equilibrium point. For a CCT of 800µm, for instance, the point at which GAT equals IOP is 37mmHg but for a thin CCT of 400µm GAT will accurately reflect intracameral pressure at a meagre 6mmHg.

Śródka (2013) illustrates the fundamental flaw in a CCT specific nomogram: GAT of 35mmHg measured on a cornea with CCT 440µm and radius of 8.6mm. The Orssengo-Pye (1999) correction factor, based on the standard calibration parameters, indicates GAT will underestimate IOP by 10.5mmHg, of which 10mmHg are due to CCT and 0.5mmHg due to the flat radius. The numerical calculations of Śródka however indicate GAT will underestimate IOP by 13mmHg, but crucially, 9.9mmHg is due to the impact of the true IOP, the remainder (3.1mmHg), is due to the combination of CCT and radius.

At high IOPs, independent of a CCT effect, the GAT model cannot be satisfied by the real eyeball either (Śródka 2010). Corrections for CCT and radius are inter-related and

depend on the IOP level; these corrections are not constants, but change with IOP. As the internal pressure load increases, above 16mmHg, relatively less applanation pressure is required to flatten the corneal apex (Śródka 2010).

Goldmann and Schmidt (1957) suggested the corneal constant (M_0, M' in the equation P+M'=W/A + N') represents the elastic force of the cornea, registering a pressure, in the absence of IOP. Śródka (2010, 2011), estimated this corneal force, for a very wide range of realistic corneal material parameters, to be only 1mmHg. Śródka (2011) suggests at an IOP of 48mmHg, GAT would register only 37mmHg; a finding not accountable by the meagre impact of shell elasticity.

As Śródka (2010) explains, it is counterintuitive for GAT to be lower than IOP. The correction factors incorporated into the GAT model (M': elasticity of the cornea, N': surface tension of the tear fluid) are potentially too slight to impact on the variations noted. The experimental and modelled results imply the flexural forces of the bent cornea are pulling the GAT probe toward the cornea rather than repelling it (Śródka 2010).

These model predictions are supported by the experimental findings of Francis *et al.* (2007). Like Damji and colleagues (2003) the supremacy of GAT was not assumed and IOP was recorded with both GAT and Dynamic Contour Tonometry (DCT). The DCT, reviewed in section 1.7.4.2, is not a GAT mimic, does not consider the Imbert-Fick principle but rather the physical Law of Hydrostatic Pressure by Pascal (Kanngiesser *et al.* 2005). Referenced against the DCT, GAT was found to overestimate IOP at low pressure and underestimate high pressure, mirroring the predicted results from the Śródka model.

Forces other than those included in the GAT equation must be implicated. Bending forces induced by the tonometer loading, coupled to the relatively fixed state of the cornea to its supporting sclera, will create shear forces not considered in the GAT model.

Śródka (2010) explains the concept via an example; a cornea loaded with internal pressure of 40mmHg. At applanation equilibrium the peripheral corneal shell has to contain 40mmHg of pressure while the applanated zone of the shell, still at equilibrium, exhibits a different pressure profile. Representing a boundary stress condition (Young and Budynas 2002), a shear force at the circumference of the applanation disc is necessary to balance the equilibrium; a shear pressure acting toward the inside of the eye. Under this modelled scenario GAT would record only 32.8mmHg.

If this is accepted it means the entire tonometry doctrine cannot be satisfied in the real eyeball, regardless of calibration dimensions, since, as Sródka (2009) explains, the law is based on false assumptions.

None of these theoretical and practical attempts to improve clinical routine have entered mainstream practice. Does that make them worthless? Whether speculative or not each step has challenged current clinical knowledge; a challenge suggesting avenues for further research (Fung 1973, Humphreys 2002).

1.6 *The Corneal Radius of Curvature*

1.6.1 Corneal Radius of Curvature: A potentially under-estimated variable

While an historical review does implicate CCT as a confounder of IOP measurement (Ehlers and Hansen 1974, Ehlers *et al.* 1975, Johnson *et al.* 1978, Whitacre and Stein 1993, Whitacre *et al.* 1993), the advent of refractive surgery dramatically increased the observed inaccuracies with GAT (Schipper *et al*. 1995, Emara *et al.* 1998, Kaufmann *et al.* 2003, Gunvant *et al.* 2005, Ko *et al.* 2005, Cervino 2006, Koshimizu *et al.* 2010). Certainly refractive procedures significantly modify CCT, but the magnitude of the reduction in measured IOP post refractive surgery is not easily reconcilable to reduced CCT in isolation. Regardless, many authors emphasise the primacy of CCT when discussing IOP measurement inaccuracies post refractive surgery (Ko *et al.* 2005, Gunvant *et al.* 2005, Emara *et al.* 1998, Hamed-Azzam *et al.* 2013).

This could reflect historical bias. Goldmann and Schmidt (1957) themselves suggested even extreme variations in corneal curvature to be insignificant with GAT; no data was presented. Prior to the advent of refractive surgery Ehlers *et al.* (1975) and Whitacre *et al.* (1993) also indicated a lack of correlation between IOP and corneal curvature (CC) although the sample sizes were extremely small. Absence of correlation was also reported by Faucher *et al.* (1997), Gunvant *et al.* (2005) and Kohlhaas *et al.* (2006). However, despite sampling 125 eyes, Kohlhaas and colleagues include the cautionary note their data set is too narrow to allow interpretation of the impact of corneal radius while Faucher and co-workers stress the mean astigmatism of their patients was low. Bland and Altman (1996) and Grolman *et al.* (1990) explain narrow sample distributions severely limit the accurate plotting of regression lines. A regression line of slope 1 and y intercept 0 indicates equality, less accurately plotted with a narrow sample range. Ehlers *et al.* (1975) and Whitacre *et al.* (1993) did not include ranges of corneal radii so their conclusion of non-significance may simply reflect a lack of statistical power.

While CCT has gained credence as a confounder to accurate IOP measurement since the 1970s, shape was recognised as a potential source of error from the earliest introduction of GAT (Goldmann and Schmidt 1957, Whitacre and Stein 1993), and is incorporated into recommended procedures when measuring IOP on astigmatic

corneas. Since the GAT applanation end point is a circular disc, area 7.354mm², (Holladay *et al.* 1983, Mark and Mark 2003) it would be intuitive to expect a greater force required to flatten a structure with steeper curvature (Whitacre and Stein 1993, Kohlhaas *et al*. 1995). Ang *et al.* (2008) and Tomlinson and Leighton (1972), in variance with some studies (Ehlers and Kruse Hansen 1974, Copt *et al.* 1999, Kaushik *et al.* 2012) did not find a significant difference in CCT between NTG, POAG and Normal Controls. Tomlinson and Leighton did, however, find NTG eyes to have significantly flatter corneas than both POAG eyes and Normal Controls.

Regardless there is contradictory evidence corneal curvature affects the accuracy of GAT. Conflicting conclusions are summarised in Table 1.3. Experimental protocols vary.

Author/Year	GAT IOP Correction per 1mm of corneal curvature change	Statistical Significance
Mark 1973	**1.96**	Significant
Ehlers *et al*. 1975	**0.89**	Not Significant
Holladay *et al*. 1983	**1.47**	Significant
Whitacre *et al*. 1993	**Not quantified**	Not Significant
Kohlhaas 1995	**1.50**	Not Significant
Mark and Mark 2003	**3.12**	Significant
Gunvant *et al.* 2005	**1.14**	Not Significant
Broman *et al*. 2007	**Not quantified**	Weak Significance
Rask and Behndig 2006	**3.5**	Significant
Saleh *et al*. 2006	**1.91**	Weak Significance
Özcura *et al.* 2008	**0.0**	Not Significant
Hagishima *et al*. 2010	**1.06**	Weak Significance
Elsheikh *et al*. 2013	**0.89**	Significant

Table 1.3 Proposed impact of corneal curvature alterations on GAT measurements

Gunvant *et al.* (2005) considering mean curvature (range 6.64mm to 8.73mm from 334 subjects) reported a change of 1.14mmHg per 1mm change in mean corneal curvature; this was not statistically significant. Saleh *et al.* (2006) also averaged corneal astigmatism and sampled a range of corneal radii from 7.3 to 9.0mm. Impact of corneal curvature on GAT was estimated at 1.91mmHg per 1mm of curvature change. Considered in isolation this represented a weak statistical significance, however significance was lost when multiple regression tests were applied. The authors noted a moderate correlation between curvature and CCT. Like Saleh and colleagues, Özcura *et al.* (2008), while finding a significant inverse relationship between CCT and corneal curvature, found only a statistically insignificant correlation between IOP and corneal curvature. The inter-relationship of CCT and corneal curvature could be significant, Shimmyo *et al*. (2003) suggested thicker corneas were flatter and thinner corneas steeper. While this observation was not corroborated by Sánchez-Tocino *et al.* (2007) or Wirbelauer *et al.* (2009), the inter-dependence of corneal properties would dilute a real effect. While their results did not suggest a link, Wirbelauer and colleagues (2009) do suggest theoretically corneal curvature could influence thickness by 25%. Conversely AlMahmoud *et al.* (2011) found, for the entire sample of 3395 eyes a weak statistical correlation between corneal curvature and CCT, thicker corneas were also flatter. If confirmed this could help explain the lack of consensus on the impact of corneal curvature in isolation.

Broman *et al.* (2007), also found a small effect of corneal curvature on GAT. The group also averaged corneal astigmatism but found an increased impact on GAT the larger the difference between the principal meridians. Like other authors, various corneal parameters were investigated simultaneously and the authors did stress the varying results between tonometer types co-investigated could reflect complex relationships between ocular characteristics and tonometers.

Hagishima *et al.* (2010) found a weak but statistically significant correlation between GAT and corneal astigmatism of 1.06mmHg per 1mm change in corneal curvature. The authors also averaged the corneal astigmatism, had no cylindrical power higher than 2.25D and had a range from 0 to 2.25DC. Kohlhaas *et al.* (1995), Rask and Behndig (2006) and Elsheikh *et al.* (2013) also reported corneal curvature effects of 1.5mmHg per 1mm change in corneal curvature, 0.58 to 0.67mmHg/Dioptre (≈ 3.5mmHg per 1mm change in corneal curvature) and 0.89mmHg per 1mm change in corneal curvature respectively.

All these studies incorporated corneal curvature amongst parameters measured suggesting the possibility effects could be attributed disproportionately. Zadok *et al.* (1999), considering exaggerated CCT and corneal curvature changes after LASIK, could not correlate the reduced IOP measurement post procedure to either CCT or corneal curvature. Zadok *et al.* (1999) and Faucher and colleagues (1997) suggested any effect could be obscured by the clinical noise of natural GAT variability.

Unlike most investigators, Holladay *et al*. (1983), Mark (1973) and Mark and Mark (2003), considered corneal shape in isolation.

Mark (1973) sampled 400 eyes with a range of corneal curvature from 40 to 49.5 dioptres. Over the 9.5D range of curvatures a 3mmHg variation in IOP could be expected; equating to 1mmHg per 3D of differential curvature (1.96mmHg per 1mm change in corneal curvature). Mark suggests 3% of GAT values could be explained by curvature variation; a small but, according to Mark, significant effect. This result is close to the 2% effect of corneal curvature predicted by the non-linear finite element model of Elsheikh *et al.* (2006), equating to 1.35mmHg per1mm change in corneal curvature.

Mark and Mark (2003) measured GAT along the two principal meridians of eyes with ≥1.75D of regular astigmatism. The sample, while including only 30 eyes, was accepted when a strong and very significant correlation of the data was identified. For corneal astigmats the data suggested as much as 37% of the disparity in GAT data was determined solely by the difference in corneal curvature. The experimental design effectively controlled for CCT and corneal biomechanics making the significance of curvature more apparent.

Holladay *et al.* (1983) also considered regular astigmats and calculated the shape effect to be 1mmHg per 4D of astigmatism, equating to 1.47mmHg per 1mm change in corneal curvature.

Liu and Roberts (2005), modelling physiologically normal corneas, estimated the range of IOP variation attributable to the variables of corneal curvature, CCT and Corneal Biomechanics were 1.76mmHg, 2.87mmHg and 17.26mmHg respectively. This mathematically modelled system used Young's Modulus as the measure of corneal biomechanics. The authors estimated shape to be least significant. However they did not find the CCT effect appreciably more substantial yet CCT profoundly affects current clinical practice. Regardless of possible errors in the model, recognised by the authors, these results highlight the need to pursue other avenues of research. Corneal shape,

particularly surgically manipulated shape, needs to be convincingly discredited as a possible confounder or incorporated into future developments**.**

1.6.2 Exaggerated Corneal Shape Change via Refractive Surgery

Can Schmidt's (1959, 1960) statement suggesting cases where variations in corneal radius capable of inducing large errors are rare remain acceptable, especially with the increasing number of corneal modifications routinely undertaken? Ablation must influence the reading of any machine using the applanating technique. Since the end point of applanation is a plane surface (Imbert 1885, Fick 1888, Shottenstein 1996, Whitacre and Stein 1993), the clinically observed reduction in IOP post laser refractive surgery must be due to exaggerated corneal flattening as well as corneal thinning or changes in biomechanical properties. An imaginary corneal surface, perfectly flat, post ablation, must represent the end point of applanation; neither GAT nor a non-contact equivalent would need to apply any force at all to supply a reading. Indeed, Shaikh *et al.* (2002) report a single case where IOP with GAT was recorded as 0 (zero) post LASIK; IOP checked via ballottment (palpation) was estimated between 40 and 50mmHg.

Lack of reported evidence of an effect of ablation induced changes in corneal curvature on GAT could reflect research bias. Corneal thickness is well recognised as an essential metric to help predict refractive surgical success by avoiding complications (Fakhry et al. 2002, Kymionis *et al.* 2007), potentially leading to pre-dominance in the literature. Indeed, the Munnerlyn/Koons/Marshall equation to calculate the ablation depth prior to PRK incorporates ablation depth and diameter as well as myopic correction required and corneal refractive index, corneal curvature is not a consideration (Swarbrick 2006).

Ko *et al*. (2005), Gunvant *et al.* (2005) and Hamed-Azzam *et al.* (2013) acknowledge CCT and Corneal Curvature affect GAT measurements yet all preferentially stipulate the effect of modified CCT on GAT readings with laser refractive surgery. Likewise Duch *et al.* (2001) mention changes in both corneal shape and thickness will, in theory, affect GAT readings. The authors confirm a drop in GAT readings post LASIK, showed a significant correlation with both keratometry and pachymetry, yet stipulate only a correction of 2.9mmHg per 70µm of CCT reduction.

Emara *et al.* (1998), explicitly assessed CCT and IOP post laser surgery and so did not record pre or post-surgical keratometry. Nonetheless, the authors do suggest the possibility a decrease in corneal curvature could account for some of the observed reduction in IOP measurements. Yao and Crosson (2014) acknowledge the potential impact of corneal curvature on tonometry discrepancies post refractive surgery in their introduction. Regardless, the authors indicate their results suggest undetermined factors, apart from CCT and biomechanics, must contribute to altered IOP readings post refractive surgery; changes in corneal curvature is not considered a possible co-contributor.

Rosa *et al.* (1998) question the acceptance of the pre-eminence of CCT when considering pre and post PRK IOP measurements. The authors re-emphasise both corneal power and thickness are altered by PRK and as such correction algorithms based on altered CCT are inadequate.

Arimoto *et al.* (2002), Montés-Micó and Charman (2001) and Tamburrelli *et al.* (2005) found a statistically significant decline in IOP post refractive procedures, due, the groups speculate, to a combination of reduced CCT and corneal curvature. Kohlhaas *et al.* (1995) also reported a correlation between reduction in IOP measurements and corneal flattening but observe corneal stiffness and CCT, as well as corneal curvature, are modified with refractive surgery. Chatterjee *et al.* (1997) suggest the observed reduction in measured IOP post PRK is due to both reduction in CCT and corneal flattening. The authors comment the relative contributions of these two variables to the decrease in measured IOP in eyes having undergone PRK, cannot be determined.

Mardelli *et al.* (1997) and Zadok *et al.* (1999), while unable to find a correlation between corneal flattening and GAT underestimation post PRK, could not identify an association with post-operative corneal pachymetry either. Mardelli and colleagues speculate the reduced readings were due to decreased resistance of the corneal stroma as well as alteration in Bowman's layer, a view echoed by Holladay *et al.* (1983). Both the Mardelli and Holladay groups suggest biomechanical alteration is most significant. A sentiment reflecting the theoretically generated results of Liu and Roberts (2005).

1.6.3 Modification of Corneal Parameters via Orthokeratology

Like refractive surgery, a statistically significant reduction in measured IOP post orthokeratology has been reported. Ishida and colleagues (2011) noted a drop from 13.5mmHg to 12.3mmHg at twelve weeks lens wear.

Defined as the temporary reduction in myopia by the programmed application of rigid contact lenses (Nichols *et al.* 2000), a traditional view of orthokeratology would suggest the cornea is bent.

If corneal bending were the primary mechanism, shape could be isolated as a potential confounder of accurate IOP measurement. A corneal bending effect would imply, unlike refractive surgery, both anterior and posterior corneal surfaces would flatten (Swarbrick *et al.* 1998). While some flattening of the posterior curve has been reported this returns promptly to baseline (González-Méijome *et al*. 2008). Chen *et al.* (2010) found a statistically significant steepening of the posterior corneal curvature on immediate removal of lenses after the initial overnight wear, rather than flattening as would be predicted if simple corneal bending were the primary mechanism. However, the magnitude of the change was only 0.06D and the effect dissipated within 2 hours. Read and Collins (2009) found habitual variations in posterior corneal curvature to follow a similar pattern and magnitude with a steepest posterior curve on waking followed by reduction over several hours. A coincidental flattening of the anterior corneal curvature was also reported. Considering the habitual results reported by Read and Collins (2009), Chen and co-workers (2010) concluded the magnitude and duration of the effect cannot represent a contributor to the orthokeratology effect. Swarbrick (2006) concludes corneal bending is insignificant, making this simplistic concept no longer accepted.

The biomechanical behaviour of the corneal stroma, made primarily of water (Buzard 1992) and virtually incompressible (Liu and Roberts 2005), having a Poisson's ratio 0.49, does not allow for corneal compression. Unlike refractive surgery, stromal tissue is not removed during orthokeratology. If corneal bending is not the mechanism how does orthokeratology alter corneal power?

The current view suggests orthokeratology effect represents, primarily at least, central epithelial thinning (Alharbi and Swarbrick 2003, Choo *et al.* 2008) involving redistribution of epithelium from the central to mid-peripheral cornea (Nichols *et al*. 2000). Swarbrick *et al.* (1998) affirm the epithelial thinning is of a magnitude to explain the myopia

reduction and is more predictive of refractive change than either apical corneal power or keratometric changes. Swarbrick (2006) indicates the power change elicited in orthokeratology can be predicted using Munnerlyn's formula for estimating ablation depth for PRK; a formula which assumes refractive change based on corneal thickness alone.

Biomechanically, Schipper *et al.* (1995) state epithelium is flexible but incompressible, as would be expected of a membranous container of non-gaseous fluid. Hence the redistribution of epithelium during orthokeratology rather than simple compression. Elsheikh *et al.* (2008b) indicate a lack of consensus on the contribution of the epithelial to overall corneal biomechanics. Patel *et al.* (1995) estimated the epithelium to have a refractive index of 1.401, anterior stroma 1.380 and posterior stroma 1.373, suggesting perhaps the epithelium is biomechanically denser. However, epithelial thickness of 50µm, compared to 450µm for the stroma (Pipe and Rapley 1999), would moderate any impact to overall corneal biomechanics created by the epithelium. While Schipper *et al.* (1995) propose significant errors in GAT can be elicited by changes in the epithelium in isolation, Elsheikh *et al.* (2008b) suggest epithelial stiffness to be appreciably lower than the stroma and can, for modelling purposes, be ignored.

Significant alterations to epithelial morphology are evident. Initial compressive force induces cell deformation, followed by elongation of adjacent cells in the mid-periphery suggesting transfer of intracellular contents. With increased wearing time alterations in cell mitosis, apoptosis, cell sloughing and proliferative changes occur (Choo *et al.* 2008). Zhong *et al.* (2009) also suggests the density of central epithelial basal cells decreases with long term orthokeratology. Primary roles of the epithelium include a protective barrier function, controlling stromal swelling and absorption of oxygen and nutrition for the avascular cornea (Elsheikh *et al.* 2008b). Yeh *et al.* (2013) did not report reduced epithelial barrier function; an observation of potential significance to the apparent lack of stromal and endothelial biomechanical alteration.

Certainly, Swarbrick (2006) states the evidence of biomechanical alterations to the stroma and endothelium is not compelling. Carkeet *et al.* (1995) reported no change in corneal biomechanics post orthokeratology but the authors did not use a biomechanical measure of 'Modulus of Rigidity' or 'Stiffness' but rather Friedenwald's 'Coefficient of Ocular Rigidity'. Friedenwald's metric is actually a measure of the entire globe's expansion with the introduction of intraocular fluid into the globe; modification of the central 6mm zone (Chen *et al.* 2010) during orthokeratology would not impact on this measure. The biomechanical markers of Corneal Hysteresis and Corneal Resistance

Factor, as measured by the Ocular Response Analyser (ORA), were found to change very little by Chen and associates (2009) and González-Méijome *et al. (*2008), at least in the short term. A cautionary note: the Ocular Response Analyser metrics are self-proclaimed measures of biomechanics and must be viewed within this context. However, the current theory of epithelial re-distribution (Swarbrick 2006) would suggest limited impact on overall corneal biomechanics. Corneal biomechanical changes, while intuitively possible, should not be in the order of those induced by refractive surgery.

Mountford (1997) and Sridharan and Swarbrick (2003) indicate a normal corneal profile is a prolate ellipse. Read *et al.* (2006), while relating reports of oblate corneas in a minority of cases, confirm, within the central 6mm, the average cornea is prolate. The end point of myopia reduction with orthokeratology is not a suitably flattened cornea but a sphericalised one with eccentricity zero. The evidence suggests the orthokeratology process cannot push a cornea into an oblate elliptical configuration (Mountford 1997). The cornea then, while relatively moulded, is still spherical.

Swarbrick (2006) indicates there is little change in corneal shape over the central 3mm, the diameter of the GAT probe. Swarbrick suggests the cornea remains approximately spherical or prolate up to chord lengths of 5mm. Regardless, the mechanism of epithelial re-distribution, now well documented, ensures the net result remains statistically flatter corneas (Chen *et al.* 2009, Swarbrick *et al.* 1998, Sridharan and Swarbrick 2003, Swarbrick 2006).

Evidence would suggest orthokeratology will modify, primarily corneal topography with virtually no change to stromal structure but a subtle change to epithelial thickness.

1.7 Alternative Tonometer Approaches

Benefits could be gained approaching tonometry *de novo*. All tonometers are prone to error with corneal biomechanics a significant contributor to overall variability. Understanding the biomechanical modelling assumptions of various tonometers, rather than accepting ISO 8612 comparison to GAT, is more likely to engender fundamental progress in tonometry development.

1.7.1 ISO 8612:2009 and 'Gold Standards'

As a member of the standards committee the United Kingdom should comply and implement European Standard ISO 8612. If an instrument reaches the UK market, it should be assumed to have passed stringent, controlled processes (European Committee for Standardisation 2009). In actuality ISO set the standards but do not regulate them (Customerservice iso.org personal communication: Appendix 2). BSI Standards Group is the British regulatory body ensuring compliance with standards. Ultimately, this responsibility lies with the manufacturer and a Notified Body, a private organization accredited to assess whether a product meets standards, pre and post market introduction (Bos and Vollebregt 2015).

Defining the scope of International Standard ISO 8612:2009, the European Committee for Standardisation (2009) state true IOP cannot be measured without recourse to manometry. The standard specifies the minimum requirements and the design compliance procedures for tonometers intended for routine clinical use.

ISO 8612 states the manufacturer must demonstrate the test tonometer, when compared to the reference tonometer, meet the standards outlined in Table 1.4. No more than 5% of the paired differences between the two tonometer readings for each pressure range must be greater than the tolerance for that range. The tolerances given in Table 1.4 account for allowable error of both test and reference tonometers. Further, manufacturers must analyse the data using regression analysis, specifying the slope, offset and the standard deviation of the regression line.

IOP Range (mmHg)	Tolerance (mmHg)	Minimum Number of Eyes
7 to 16	**±5**	40
>16 to <23	**±5**	40
≥23	**±5**	40

Table 1.4: Requirements for Tonometers (ISO 8612)

It would seem beneficial for tonometer manufacturers to publish their pre-release data, data complying with strict protocols and arguably making redundant further comparison. Unless ISO 8612 itself is being questioned, which never appears the case, there seems little benefit in further comparing instruments to GAT. Roukonen *et al.* (2007) is the only paper cited which specifically emulated ISO 8612 test protocols. The conclusions reached by other comparative papers, not procedurally compliant with the standard, could be questioned. Sandner *et al.* (2005), for instance, recommend, for clinically interchangeable use, a limit of agreement of ±2mmHg with GAT is the minimum for acceptance. Since Intra-observer variation with GAT is reported as high as -3.8 to +2.4 mmHg (Thorburn 1978), the expectations of Sandner and colleagues assume unrealistic repeatability of GAT and does not reflect ISO 8612 recommendations.

While ISO 8612 may be acceptable to expedite commercial release of new tonometers, designers fundamentally questioning the GAT biomechanical model need to calibrate their machines against a more robust standard. McLean (1919) indicates even digital palpation had been quantified against manometry as were the Schiőtz (Schiőtz 1905) and GAT machines (Goldmann and Schmidt 1957, 1961). Like Schiőtz (1905) and Goldmann and Schmidt (1957, 1961), the fundamentally different theoretical premise of the Dynamic Contour Tonometer (DCT), described in detail in section 1.7.4.2, necessitated calibration against a global standard.

Regardless of the technological refinements incorporated in GAT, Schmidt (1960) still acknowledged the ideal tonometer would be a compensated membrane manometer. Even this standard is not without criticism. The law of hydrostatic pressure presumes free movement of particles ensuring uniform distribution of pressure within the pressure vessel (Young 2007). Manometry in a complex, compartmented, organ such as the eye is not as straight forward as Schmidt's statement would suggest. It has been suggested

vitreous cavity manometry may be more indicative of pre-retinal or pre-optic nerve IOP (Young 2007, Yang *et al.* 2013) but the viscosity of the vitreous body appears to interfere with measurements (Hernández-Verdejo *et al.* 2010). However, while Yang *et al.* (2013) suggest the best way to validate non-invasive tonometers remains undetermined, Hernández-Verdejo *et al.* (2010) indicate the accepted 'Gold Standard' is cannulation of the anterior chamber.

1.7.2 The Tonopen: The Mackay-Marg tonometry principle

Figure 1.21. The Tonopen

The Tonopen operates on the Mackay-Marg principle, albeit with significant micro-processing refinements (Hines *et al.* 1988).

Mackay and Marg (1960) state previous tonometers, whether indentation or applanation, require a level of skill and are tedious. However, most notably the authors contend these tonometers are based on questionable assumptions. Schwartz *et al.* (1966) demonstrate the difficulty in quantifying tear forces and also dispute the corneal model of Goldmann and Schmidt (1957, 1961). The authors question the assumption corneal biomechanical response is independent of the IOP level. Regardless of the tensile stresses imparted by varying IOP, Schwartz and colleagues (1966) could not balance the extremely variable nature of tear forces to corneal resistance.

Essential to developing constitutive models is inter-disciplinary collaboration (Fung 1993, Humphrey 2002). R Stuart Mackay, coming from a background of biomedical

engineering and mathematics, approached the measurement of IOP from an alternative perspective.

At the time transducers converting mechanical displacement into electrical signals were becoming available. When attached to electrodes, the change in electrical resistance with pressure registers a drop in resistance which gives an estimate of IOP (Mackay and Marg 1960).

The tonometer design (Fig 1.22) included a non-sensitive base plate extending beyond the zone of the electrically conductive plate. Bending and boundary forces of the cornea are supported by this base plate, which also removes tear forces from the electrically sensitive zone. Further, circumferential stress within the tissue will be tangential (Marg *et al.* 1962) and can neither push nor pull on the transducer.

The only force acting on the transducer, through the thin corneal shell, is the IOP, albeit artificially raised by the volume of fluid displaced by corneal compression. A total diameter of 3mm ensures the fluid displacement is the same order of magnitude induced by GAT, approximately 0.56mm^3 (Schmidt 1960). This regular displacement equates, Marg *et al.* (1962) suggest, to a 0.4mmHg artificial rise in IOP which is subtracted from the calibrated measure of IOP. The force transducer in the final marketed tonometer consisted of a plunger held in place by elastic elements, originally by silicone rubber, but ultimately of steel web springs (Moses and Grodzki 1971).

Figure 1.22. Mackay-Marg Tonometer (Mackay 1964)

As the tonometer is advanced toward the cornea (Fig 1.23) an initial small trough reflects tear forces attracting the plunger, prior to full probe/cornea contact.

Stepanik (1970) indicates the first crest appears when only the sensitive zone is in contact with the cornea. This crest reflects IOP and the bending forces of the cornea and, Stepanik (1970) explains, represents the classic applanation measurement obtained by GAT. As corneal compression continues, a second trough appears as the bending and tear forces are transferred to the supporting annulus (Marg *et al.* 1962).

Paranhos *et al.* (2000) suggest the smaller applanation zone of the Tonopen, compared to GAT, could explain why Tonopen may be more accurate in irregular corneas. Actually, while the pressure sensitive zone is only 1.02mm diameter, the total applanation diameter remains 3mm. A more likely explanation would be the removal of tear, bending and boundary forces.

Jain and Marion (1976) suggested corneal anomalies such as ectasia and keratoplasty do not affect Mackay-Marg accuracy. Since, by definition, the law of Hydrostatic pressure, represents a 'static state' in equilibrium, and if the corneal shell is 'thin', then corneal anomalies should not influence Tonopen readings. While expounding a personal opinion, Shah (2000) suggests CCT affects, in descending order, non-contact tonometers, GAT and finally Tonopen; the biomechanical theory of Mackay-Marg would support this supposition.

As theoretically robust as the Tonopen principle appears, experimental comparisons of this instrument to manometry vary.

In 79 living eyes, Yang *et al.* (2013) found very good agreement between Tonopen (16.1±3.8) and Anterior Chamber Manometry (16.1±4.4); comparison with vitreous cavity manometry demonstrated poorer agreement. While described as weak, the authors did, however, find a correlation of Tonopen measurements to CCT. Hessemer *et al.* (1988), comparing Tonopen to manometry on human cadaver eyes within six hours of death and without irrigating the eyes during Tonopen measurements, also found excellent correlation and agreement between Tonopen and intracameral IOP.

Boothe *et al.* (1988), using two enucleated eyes, found the Tonopen to be reproducible and accurate when compared to manometry. Assessed clinically on living human eyes the authors also found the instrument to demonstrate excellent agreement with GAT. It must be noted the manometry study arm did not assess GAT, while the clinical study

used GAT as the control. If the modelling principle of Tonopen is accepted, agreement with GAT would not necessarily be anticipated.

Eisenberg *et al.* (1998) found Tonopen to be the most accurate instrument when tested on enucleated eyes but was not adequately accurate on living eyes. The authors admit to not understanding this dichotomy. Yang and colleagues (2013) suggest the very low number of eyes (11 eyes of 9 patients) and the age distribution may have contributed to the poor performance on living eyes although only 10 enucleated eyes, of five patients, were utilised. The underestimation of IOP in living eyes suggests the possibility tear attraction may have affected the Tonopen measurements on living eyes. Reitsamer *et al.* (2004) and Moore *et al.* (1993) report falsely low readings when the Tonopen touches the tear layer without expelling tears from beneath the probe. Another explanation could be the fact transient fluctuations in ocular pulse are eliminated in manometic studies of enucleated eyes (Boothe *et al.* 1988). The refined Tonopen AVIA averages 10 instantaneous readings (Bhartiya *et al.* 2011) rather than 4 (Boothe *et al.* 1988) and this effect, if genuine, should be reduced.

Reitsamer *et al.* (2004), using live mice with vitreous cannulation, and Moore *et al*. (1993) using anterior chamber cannulated manometry of live rat eyes indicate Tonopen underestimates manometric IOP below 20mmHg and overestimated above. This result is similar to GAT (Francis *et al.* 2007), a finding which supports the boundary condition postulate of Śródka (2010) for GAT. The rat cornea is significantly thinner than humans, averaging only 159.08(±14.09) µm (Schulz *et al.* 2003). While expected to affect GAT, the theoretical premise of Tonopen would not predict a CCT impact. These results do suggest Tonopen, regardless of the design, does not totally neutralise biomechanics. The results of Yu *et al.* (2012), as well as demonstrating poor agreement and significant variability compared to manometry, found a significant correlation with CCT. Tang *et al.* (2011), using canine eyes with manometry as reference, found Tonopen to underestimate intracameral pressure; the instrument was, however, more accurate than GAT. While the authors also indicated the Tonopen to be less dependent on corneal biomechanics than GAT, they did not suggest the problem was eliminated.

Analogous to the technical improvements of GAT over Schiótz, the Mackay-Marg, compared to GAT, reduces operating variables to the stiffness and protrusion of the plunger (Schwartz *et al*. 1966). Further, Mackay and Marg (1960) suggest the instrument is also objective, itself an improvement on GAT. Bhartiya *et al.* (2013) certainly found the Tonopen AVIA to be repeatable however there are potential sources of operator error which could explain some of the conflicting experimental results.

Firm contact with the cornea is required, if the tip breaks contact an 'off' reading may be recorded (Moore *et al.* 1993). If the contact is not firm enough, ensuring tear bridging is eliminated, a falsely low reading may be recorded (Reitsamer *et al.* 2004). Hines *et al.* (1988) describe re-applying the probe to the ocular surface until the accepted, average, figure is recorded. Re-application, the recommended routine in the Tonopen AVIA User's Guide (2014) is possibly more likely to introduce tear forces under the probe tip. Once the probe is in light, but uniform, corneal contact, the instrument automatically takes the required 10 (Bhartiya *et al.* 2011) instantaneous readings to find the average within the cardiac cycle. Holding contact until the final recording was advocated by Moore *et al.* (1993). The total probe tip should also be flush with the corneal surface (Moore *et al.* 1993). As a hand held instrument it is difficult to ensure this is the case. This scenario would not register an acceptable reading, however a level of proficiency is required to ensure rapid measurements. Finally, the necessity of using the Ocufilm cover must introduce another layer of mechanics and the operating instructions do emphasis the necessity to ensure correct application to avoid false readings (Tonopen AVIA User's Guide 2014).

1.7.3 The Ocular Response Analyser

Mackay (1964) suggests a severe shortcoming of air pulsed tonometers is their dependence on elastic and viscoelastic properties of the cornea. Interestingly these biomechanical properties of the cornea are characteristics purportedly exploited by the ORA.

The first marketed non-contact tonometer was patented by Grolman (Grolman 1971). The method describes deforming the cornea from convex, through applanation to concave with subsequent relaxation to the convex configuration. Rather than pressure, time to applanation was measured and converted to an IOP equivalent calibrated against GAT. The technique was refined with the Reichert Xpert NCT but the purpose remained an instrument calibrated to provide a GAT equivalent IOP measure (Taylor *et al.* 2013).

Luce (2004) adapted Grolman's original concept with its described corneal relaxation and patented the ORA.

Figure 1.24. Ocular Response Analyser

Time remains the measured variable. The fluid pulse increases linearly with time until corneal applanation is detected when the drive current is cut off. This equates to a non-linear pressure ramp to applanation and cut off. The time to cut off is converted to IOP.

Imperative to the interpretive relevance of the ORA signal is the equal but opposite linear gradation of pressure application during the bi-directional applanation process. The inward, traditional, measure is taken as the air pressure increases and the convex cornea is flattened to a plane surface (Pressure 1, P1 in Fig 1.25). The ORA shuts off the plenum shortly after P1 is reached, however inertia in the piston ensures the pressure continues to increase before reaching a peak (Glass *et al.* 2008). The pressure then decreases linearly with time, purportedly at the same rate as it increased, through a second applanation point (Luce 2004) (Fig 1.25).

Figure 1.25. ORA Waveform

Significantly, the inward acquisition reading does not correspond to the outward acquisition. Time is the controlled variable and Fig 1.25 shows a longer lag period before the second applanation pressure (P2), reflecting a lower instantaneous pressure level at the specific time point. Radcliffe (2014) indicates the difference between P1 and P2 quantities the new metric introduced by Luce (2005): Corneal Hysteresis.

In biomechanical terms Hysteresis is the observation the stress-strain relationship during loading is somewhat different to unloading (Fung 1993) (Fig 1.26).

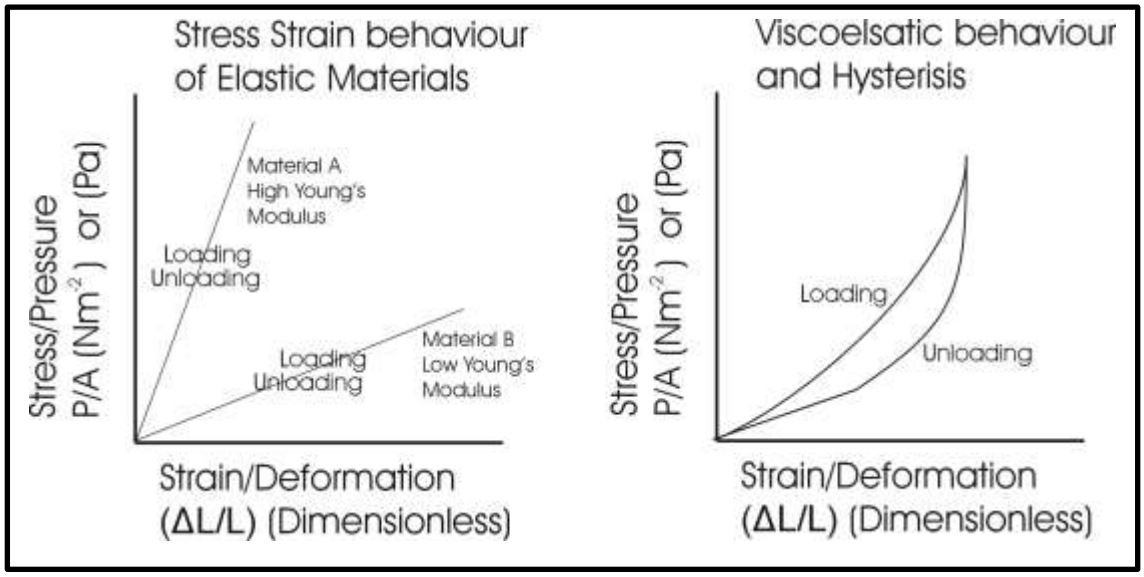


Figure 1.26. Ideal Elastic behaviour versus Viscoelastic behaviour

Hysteresis specifically represents the stress/strain curve to cyclical loading and unloading (Fung 1983). A more concise definition, rationalising the phenomena, indicates hysteresis represents the dissipation of energy as heat during a stress cycle (Young and Budynas 2002, Kotecha 2007). Taylor *et al.* (2013) do suggest hysteresis has numerous definitions and present it as the lag between making a change and response to that change. In this sense the introduction of the term 'Corneal Hysteresis' by Luce (2005) reflects accurately the phenomenological observation of the corneal response to loading and then unloading created by the air pressure plenum.

However, Dupps (2007) reports Luce as defining 'Corneal Hysteresis', conservatively as the output of the Reichert ORA under the specific measurement conditions imposed by the ORA. The cautionary interpretation of the new metric, Luce and Taylor (2006) suggest, reflects the limited understanding of what the waveforms actually represent, although the authors are unequivocal they contain clinically valuable information.

Regardless of Luce's initial caution (Dupps 2007), Luce (2005) and Luce and Taylor (2006) suggest Corneal Hysteresis is created by the viscous damping of the cornea and, the authors continue, quantifies biomechanical properties of the cornea.

There appears a growing acceptance ORA-CH represents a new global index of corneal biomechanics. Terai *et al.* (2012) indicate the ORA is a new diagnostic tool enabling *in vivo* assessment of corneal biomechanical properties. The authors suggest the considerable number of papers on ORA have helped solve the mystery of corneal biomechanics. Further, Franco and Lira (2009) and Kotecha (2007) suggest ORA-CH is a direct measure of corneal biomechanics. Luce and Taylor (2006) propose ORA-CH is not an artefact of any other variable, yet it has been correlated to CCT (Luce and Taylor 2006) and Luce (2005) further indicates ORA-CH represents aggregate effects of CCT, rigidity, hydration and other factors yet to be identified.

Luce and Taylor (2006) indicated ORA-CH is independent of IOP, tested by inducing IOP fluctuations via ophthalmodynamometry. This was confirmed by Laiquzzaman *et al.* (2006) and Kida *et al*. (2006) who reported, while IOP varied throughout the day, ORA-CH did not; a finding not consistent with thin shell theory. Ariza-Gracia *et al.* (2015) modelling the biomechanical response of the cornea to air-puff tonometry, not specifically ORA, conclude the corneal response is influenced, not only by corneal biomechanics, but also IOP, CCT and curvature. The authors concluded the relative contribution of each factor cannot be established. The claim ORA-CH is independent of IOP is also questioned by Sergienko and Shargorodska (2009). This needs to be confirmed. General biomechanical principles dictate corneal elasticity and stiffness, as defined by Young's Modulus, must vary with pressure. Increased IOP induces a stiffer corneal response (Anderson *et al.* 2004). If, as Franco and Lira (2009) and Kotecha (2007) suggest, ORA-CH is a direct measure of corneal biomechanics, then it should vary with IOP. It may transpire IOP fluctuations within normal ranges are not of an order to cause measureable changes in ORA-CH. ORA-CH has to be accepted a gross measure and Luce's cautionary note it is independent of IOP only to the first order reflects this qualification. Conversely ORA-CRF is reported to increase with IOP (Luce and Taylor 2006).

The interpretation of the ORA waveforms must be accompanied with an index of caution. Luce and Taylor (2006), striving, as Dupps (2007) suggests, to express the output of the ORA in standard parlance can lead to misinterpretation.

First, the authors, for simplicity, suggest low ORA-CH values reflect 'soft' corneas, potentially prone to ocular diseases and complications. Roberts (2014) emphasise the flaws in this interpretation. Hysteresis has little relation to how stiff or soft a material may

be, it reflects how much energy is dissipated during loading and unloading. As Dupps (2007) and Roberts (2014) explain, elasticity and stiffness reflect components of Young's Modulus of Elasticity. An elastic material is one which obeys Hooke's Law: stress is proportional to strain (Fung 1993). Young and Budynas (2002) indicate elasticity reflects a material's capacity to sustain stress without permanent deformation. A high elastic modulus indicates a steep stress/strain relationship characteristic of stiff materials (Material A - Fig 1.26). A low modulus has a smaller slope and represents a more extensible material (Material B Fig 1.26) (Dupps 2007). Neither demonstrate hysteresis within the range of stress tested. Material A in Figure 1.26, steel perhaps, while very stiff and demonstrating a steep stress/strain curve, still complies with Hookean principles. The mechanical stress energy is stored reversibly as strain energy (Roylance 2001), allowing it to revert immediately to its original dimensions on removal of the stress load. While stiff it will demonstrate no hysteretic behaviour, Elastic Modulus is a more appropriate measure (Lau and Pye 2011). Secondly, Luce and Taylor (2006) indicate low ORA-CH reflects corneas less capable of absorbing (damping) the air pulse energy; a statement seemingly at odds with the idea 'soft' corneas have lower Corneal Hysteresis.

Dupps (2007) query how the ORA measurements are obtained, how the measurement may or may not relate to classical biomechanical constitutive functions, such as elasticity, and what variables may affect the measurement. If ORA-CH represents aggregate effects of corneal thickness, corneal rigidity, hydration and other unidentified factors (Luce 2005, Lau and Pye 2011, McMonnies 2012), can it be claimed a new ocular parameter as Luce and Taylor (2006) suggest? It appears to reflect an amalgam of ocular responses suggesting as unlikely the unloading response accurately reflects true hysteresis. Lau and Pye (2011) certainly question how a complex time dependent hysteretic process can be defined by two instantaneous non-contact tonometer readings; readings simply inferring a pressure by the time to applanation (Grolman1971). The tonometer algorithm converts the time to accelerate a stationary convex cornea to applanation into a pressure equivalent. The return cycle, progressing under forces not equivalent to the inward process, but still measured in units of time and converted to an assumed IOP equivalent, is unlikely to reflect a true hysteretic cycle. Ishii and colleagues (2013) explain different hysteretic loops could pass through the same two measurement points. Further, since hysteresis represents the dissipation of energy as heat, a unit of pressure is meaningless as a biomechanical measure of hysteresis.

The term 'Corneal Hysteresis' also insinuates a corneal specific response. The cornea is not in isolation but is attached to the sclera via the limbus. Metzler *et al.* (2014)

demonstrate an isolated cornea responds more stiffly to an air pulse than when part of the entire globe. Ishii and colleagues (2013) indicate the nature of the loop and phase delay of recovery cannot be assumed a corneal response. The authors suggest ORA-CH may be derived from internal structures. Chang *et al.* (2010) found a correlation between ORA-CH and anterior chamber depth and described ORA-CH as a determinant of ocular biometry in the anterior and posterior segments, further emphasising the inexact nature of this metric.

The circumferential annulus of corneal flexure around the applanated/indented zone also creates a boundary condition with the introduction of shear forces between the region under plenum air pressure and the peripheral cornea not withstanding additional loads (Śródka 2010). Ariza-Garcia *et al.* (2015) indicate non-contact techniques assess mechanical response to bending while internal corneal biomechanics reflect membrane stress due to inflation loading. The authors conclude *in vivo* corneal mechanical characterisation necessitates multiple testing strategies.

These additional stresses suggest the interpretation of ORA-CH, as described by Luce (2005), is potentially over-simplistic. Ishii *et al*. (2013) does not consider 'Corneal Hysteresis' as measured by the ORA, to represent viscoelastic hysteresis of the corneal tissue. Without constitutive microstructural equations, ORA-CH records a phenomenological feature, its potential biomechanical significance is implied.

Further, Dupps (2007), Lau and Pye (2011) and Radcliffe (2014) indicate ORA-CH, as defined by Luce and Taylor (2006), can only be measured by the ORA. Bayoumi *et al.* (2010) indicate ORA readings vary depending on the distance between eye and tonometer; the closer the cornea the earlier the first applanation resulting in a lower CH reading for the same eye.

Interpretation of the ORA metrics as constitutive biomechanical functions rather than phenomenological reflections of the ORA instrument is precarious. Piñero and Alcón (2014, 2015) emphasise ORA-CH does not relate to any biomechanical model. The authors further stress there is no direct relationship between ORA-CH and Modulus of Elasticity.

In total the ORA produces four parameters (Franco and Lira 2009, Roberts 2014). Roberts (2014) presents the following formulae for the proposed metrics.

1. Corneal Hysteresis:

$$CH = a[P1 - P2] \quad \textbf{(1.7.1)}$$

2. Corneal Resistance Factor (CRF):

$$CRF = a[P1 - 0.7P2] + d \quad \textbf{(1.7.2)}$$

3. GAT correlated IOP (IOPg):

$$IOPg = a[(P1 + P2)/2] + c \quad \textbf{(1.7.3)}$$

4. Corneal Compensated IOP (IOPcc):

$$IOPcc = b[P2 - 0.43P1] + e \quad \textbf{(1.7.4)}$$

These are expansions of the more generally presented equations (Franco and Lira 2009, Lau and Pye 2011) incorporating, outside the bracketed expressions, what Roberts (2014) describes as calibration and regression constants. The calibration/regression constants (a to e) are not defined by Young (2014), support for their inclusion is personal communication with Reichert. Pepose (2007) indicates ORA-CRF is a linear property of P1 and P2. Luce and Taylor (2006) state the constant k, which Roberts (2014) quantifies as 0.7 in the CRF equation, is the result of large-scale clinical data analysis derived from specific combinations of inward and outward applanation values using proprietary algorithms. ORA-CRF is, in the opinion of Luce and Taylor (2006), a measure of the cumulative effects of both viscous and elastic resistance encountered by the air jet while deforming the cornea. Ortiz *et al.* (2007) acknowledging the undisclosed algorithm accept ORA-CRF is a measure of the overall resistance of the cornea. Lau and Pye (2011), realistically question how, defined as it is by P1 and P2 and highly correlated to CCT (Taylor *et al.* 2013), ORA-CRF can define corneal stiffness without any reference to constitutive biomechanical properties such as Young's Modulus. Yu *et al.* (2012) suggested the ORA metrics of CH and CRF reflect more than CCT in isolation, as does Luce (2005).

Another proprietary algorithm, utilising P1 and P2, with an ORA-CH adjustment for biomechanical responses (Taylor *et al.* 2013), allows the calculation of Corneal Compensated IOP (ORA-IOPcc). ORA-IOPcc is a measure of IOP, the authors believe, less affected by corneal properties. While Luce and Taylor (2006) admit they cannot

claim to be measuring ‘true’ IOP, they indicate early investigations, not cited by the authors, demonstrate ORA-IOPcc is a better indicator of real IOP than GAT. Since the instrument was specifically calibrated against GAT (Reichert 2012, Taylor- personal communication Appendix 3) with the corrections P1, P2 and ORA-CH generated without consideration of Young’s Modulus (Lau and Pye 2011), this claim is unsubstantiated. These investigators presented data suggesting ORA-IOPcc is only minimally lower in patients having undergone LASIK, apparently confirming a new measure independent of CCT. However, the calculation of ORA-IOPcc was based purely on pre and post LASIK clinical data (Terai *et al.* 2012), a procedure affecting far more than CCT in isolation. While Taylor *et al*. (2013) indicates this measure is adjusted for corneal biomechanics, corneal shape was not a consideration. The ORA waveform must be affected by corneal curvature. An ablated cornea will reach both inward and outward applanations earlier; lower pressure equivalents will be inferred from the reduced time to applanation events.

Regardless of the sophisticated nature of the ORA, Luce (2004) and Taylor (personal communication – Appendix 3) stress, as with all state-of-the-art NCTs, the applanation signal is processed using a regression equation based on clinical calibration to GAT. A primary index of a NCT’s reliability, Luce suggests, is the standard deviation of differences of matched pairs of NCT and GAT readings.

While ostensibly an improved GAT replicate, the ORA actually involves both applanation and indentation effects. The entire premise of applanation tonometry rests on the imperative, asserted by Imbert (1885) and Fick (1888), accurate IOP depends on applanating rather than indenting the corneal surface. Schiőtz (1905), quite rightly, indicated there is actually no distinction between the processes, an applanation tonometer becomes an indentation tonometer with increasing pressure. The ORA does exactly this and the dynamics involved as the cornea reverts from indentation to convexity, and impacting on the second pressure reading, cannot be simplified to a single measure of hysteresis. The dynamics of a cornea at maximum indentation (zero velocity and maximum acceleration) and about to return toward convexity, introduces combined forces not possibly equivalent to the initial force necessary to accelerate a stationary, convex cornea toward applanation.

Further the ORA does not appear to compensate for ocular pulse. While the user manual (Reichert 2012) recommends 4 measurements, these are not averaged but rather the reading with the highest wave form score is accepted (Reichert 2012, Goebels *et al.* 2012). A major criticism of non-contact tonometers is the instantaneous nature of

individual readings within the cardiac cycle (Shields 1980, Vernon *et al.* 1991, Vernon 1993). Kotecha *et al*. (2010) explain non-contact devices record a reading within 5ms, only 1/500th of the cardiac cycle and reports intra-pulse cycle variation of up to 4mmHg, while Vernon (1993) reported a range of 5.5mmHg. The ORA deduces GAT equivalent IOP by averaging the single P1 and P2 readings, albeit with the addition of proprietary calibration constants (Roberts 2014). Terai *et al.* (2012) acknowledge this snap shot measurement but suggest since the biomechanical measures of ORA-CH and ORA-CRF are also deduced from P1, measures which then allow the estimation of ORA-IOPcc, the influence of ocular pulse is eliminated. However, the instantaneous measure of P1 could, presumably, vary by up to 5.5mmHg depending on the cardiac cycle moment. The authors indicate the entire data acquisition of the ORA is within 20ms, equating, according to the estimate of Kotecha *et al.* (2010), to 1/125th of the cardiac cycle, suggesting P1 and P2 will not reflect the total cycle range. This must impact on the calculated GAT equivalent. Xu *et al.* (2011) certainly rated ORA repeatability as merely moderate. These authors report a difference between diastolic and systolic IOP potentially as high as 7.2mmHg ensuring a 20ms sample window prone to physiological variability. The magnitude of the inward applanation acquisition P1, a measure of instantaneous IOP within the cardiac cycle, will necessarily govern all four ORA metrics. The latest ORA, the Ocular Response Analyser® G3 (Reichert 2016) does allow averaging of results. This updated instrument may help compensate for ocular pulse but was not available for this research.

Since the machine has been designed to mimic GAT, an instrument with well documented variability (Thorburn 1978, Whitacre and Stein 1993, Dielemans *et al.* 1994), regardless how accurate the ORA may be, agreement with the reference is unlikely (Bland and Altman 1886). Regardless, since the design priority was a machine correlating with GAT (D Taylor – personal communication Appendix 3) direct comparison is defensible.

Bayoumi *et al.* (2010) and Rennier *et al*. (2010) reported both ORA-IOPg and ORA-IOPcc to be significantly higher than GAT, although if ORA-IOPcc is an improved measure then it should vary. Lam *et al.* (2007) and Kaushik *et al*. (2012) did suggest good correlation between GAT and ORA-IOPg reporting a mean difference of only +0.33mmHg and -0.3mmHg respectively. However, while Lam *et al.* (2007) reported limits of agreement acceptable for ISO 8612 (European Committee for Standardisation 2009), Kaushik *et al.* (2012) published a range, at 95% confidence, of +6.8 to -6.6mmHg. Attributing this variability to either machine is inapplicable but the results do suggest, regardless of design claims, there is variability in the system.

Both Ehrlich *et al.* (2010) and Bayoumi *et al.* (2010) conclude bias between GAT and ORA IOP measures could affect clinical management. Bayoumi and colleagues do not feel the machines can be used interchangeably while Ehrlich and co-workers indicate the bias is no more than reported for inter and intra observer variability with GAT in isolation.

Calibration against GAT ensures all ORA and GAT measures are related and cannot, for statistical analysis (Newcombe and Duff 1987), be considered independent.

Since Luce (2005) suggests ORA-CH reflects aggregate effects of CCT, corneal rigidity *(stiffness),* hydration and other undetermined factors, statistical co-dependence must temper interpretation of the ORA metrics. ORA-CH weakly correlates to CCT while ORA-CRF is significantly correlated (Luce and Taylor 2006). ORA-CH is independent of IOP but ORA-CRF is correlated. Since all are derivatives of two measurements P1 and P2 (Roberts 2014) statistical analysis must be interpreted with caution.

1.7.4 The Icare and Dynamic Contour Tonometers

Because of their innovative design principles, two further tonometers, the Icare® and Dynamic Contour Tonometer®, feature in discussion. While not utilised experimentally, brief descriptions of those principles are relevant.

1.7.4.1 The Icare Tonometer

Figure 1.27. The Icare Tonometer

The primary design mandate for the Icare was as a research tool rather than commercial tonometer. The ability to genetically manipulate mice and rats make murine models of glaucomatous optic neuropathy attractive (Danias *et al.* 2002, Goldblum *et al.* 2002, Filippopoulos *et al*. 2006). The rebound tonometer reflects a research imperative to assess IOP non-invasively on very small eyes.

The Icare tonometer records the deceleration and rebound movement of a probe as it contacts the cornea (Cervino 2006). A stainless steel probe, 24mm long, weighing 11mg with a 1mm wide spherical tip to minimise corneal micro-trauma (Martinez-de-la-Casa *et al.* 2005), is launched toward the eye from a distance of between 3 and 10mm (Kontiola 2000). The probe is launched by a voltage-pulse induced by a coil inside which the probe moves (Fig 1.28) (Muttuvelu *et al.* 2012). A frictionless magnet (Ruokonen *et al*. 2007) and Teflon bearings (Kontiola 2000) reduce mechanical variables potentially compromising accuracy and repeatability.

When the probe hits the eye and rebounds, the voltage in the measurement solenoid changes direction (Kontiola 2000). The probe movement is monitored by a sensing coil and deceleration time, which is dependent on IOP, is used to estimate IOP (Muttuvelu *et al.* 2012). The probe bounces faster as the IOP increases (Cervino 2006).

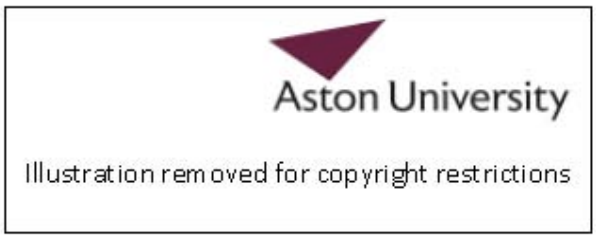


Figure 1.28 Icare Tonometer mode of action (from Ruokonen *et al.* 2007)

Not presumed to challenge GAT, the Icare prototype for human use was considered a niche product for patients unable to sit at a slit lamp, children and uncooperative patients (Kontiola 1997). Further rationale for its introduction was the need for a low cost, accurate and easy to use tonometer (Kontiola 2000). The compliance data for ISO8612

was obtained on 158 patients. The mean paired difference and standard deviation (GAT-Icare) were -0.5mmHg and +3.4mmHg (Icare Finland Oy 2009), thus adhering to ISO 8612 standards.

The small probe size eliminates any potential effect corneal shape may have on measures making it potentially more suitable for scarred or distorted corneas.

Comparing the rebound tonometer to manometry in rats, Goldblum *et al.* (2002) found the Icare measured IOP accurately over the entire pressure range of 9 to 20mmHg. However, the rat cornea is significantly thinner than humans, averaging only 159.08(±14.09) µm (Schulz *et al*. 2003). CCT and by association, corneal biomechanics, will intuitively affect the rebound response. Martinez-de-la-Casa *et al*. (2005) Iliev *et al.* (2006) and van der Jagt and Jansonius (2005) did find the rebound tonometer measured higher IOP and concluded the Icare is affected by CCT.

1.7.4.2 The Dynamic Contour Tonometer (DCT)

The theoretic principles of the Dynamic Contour Tonometer (DCT) appear to represent an extension of the Tonopen (section 1.7.2). Apart from designing a curved, rather than flat, non-sensitised support annulus the theory seems identical and based on constitutive principles.

Figure 1.29 Dynamic Contour Tonometer

DCT does not consider the Imbert-Fick principle but rather the actual physical Law of Hydrostatic Pressure by Pascal (Kanngiesser *et al.* 2005), described in section 1.2.2.11.

To explain the concept, Kanngeisser and colleagues (2005) imagine a hypothetical device encasing the entire eye. In this static state, the Law of Hydrostatic Pressure dictates the force is transmitted equally in all directions throughout the fluid and acts at right angles to the surface. Since this state is in equilibrium, Newton's Third Law holds; the pressure of IOP pushing out is equal and opposite to the force of the casing. A pressure sensor embedded in the casing will read intraocular pressure.

The cornea is gently moulded to the shape of the concave tonometer probe, at which point the pressure on either side of the cornea is equal. The force needed to achieve this is believed to exactly counterbalance the force of IOP (Boehm et al 2008). Essentially, and pivotal to development, these authors compared their results, not to the ISO standard of GAT but to manometric reference pressures.

Kanngeisser *et al.* (2005) evoke the principle of Law of Hydrostatic Pressure. The authors correctly suggest traditional tonometers should be described as force tonometers rather than pressure tonometers.

Kanngiesser *et al*. (2005) do stress the corneal shape on which the probe contour is modelled is idealised but indicate this sufficiently matches the physiological range of human corneas. Surgically modified corneas were considered and the authors do acknowledge theoretically each cornea requires a bespoke contour matched tip. Just as Goldmann had to normalise for CCT, the DCT seems to necessitate normalisation for radius of curvature. Kanngiesser *et al.* (2005) and Boehm *et al.* (2008) only sampled physiologically normal eyes. The effect on readings of anatomically altered corneas, as with refractive surgery could be questioned.

1.8 Key Chapter Points

1. The Imbert-Fick construct must be interpreted a simply biomechanical model rather than a law.
2. The Imbert-Fick legacy simply states: Replacing a depression (Indentation) with a plane surface (Applanation) cancels out all forces. Such that:

   P (Tonometry Pressure) = T (Intracameral IOP).
3. The Young-Laplace equation, defining the relationship between internal pressure, surface tension and the curvature of a liquid surface would seem to underpin the caveats ascribed to the Imbert-Fick Law: Infinitely Thin, Perfectly Elastic and Spherical.
4. These caveats imply the Imbert-Fick construct is most accurate when the membrane is infinitely thin and lacking any biomechanical properties. This is incompatible with the current opinion thinner corneas underestimate IOP.
   a. CCT corrections defy the Imbert-Fick caveats; creating a paradox.
5. Goldmann and Schmidt, accepting the Imbert-Fick logic, modelled the cornea as two infinitely thin, incompressible, membranes (Endothelium and Epithelium) sandwiching a compressible, 'heavy mobile water' like, stroma.
   a. The Goldmann Applanation Tonometry (GAT) model does not comply with physical laws.
6. CCT is an imperfect measure of corneal biomechanics. Corneal biomechanics reflects not simply stromal microstructure dictating material stiffness but also its geometry, incorporating thickness and topography.
7. Young's Modulus, defining a material's stiffness, is the primary measure of a tissue's biomechanical microstructure. The terms ocular or scleral rigidity have no place in physics, mechanics or ophthalmology.
8. In biomechanical terms Hysteresis is the observation the stress-strain relationship during loading is somewhat different to unloading and represents the dissipation of energy as heat during a stress cycle.
9. Corneal Hysteresis, as measured by the Ocular Response Analyser (ORA), reflects aggregate effects of CCT, corneal rigidity (*undefined),* hydration and other undetermined factors *(unspecified).* The ORA metrics appear to simply reflect the engineered output of the ORA.
   a. The utility and acceptance of these markers as unique *in vivo* measures of corneal biomechanics is questionable.
10. Of the tonometers investigated, the theoretical principles of Tonopen and DCT seem the most robust.

1.9 Experimental Goals

Chapter 2 considers corneal biomechanics as a function of geometry, incorporating thickness and topography, and material stiffness reflecting the microstructure of the stroma. CCT may simply represent a measureable reflection of internal microstructure and topography. Further, Decision Tree Analysis may reveal if any tonometer is capable of neutralising complex, inter-related biomechanical dynamics.

Chapter 3 assesses agreement between GAT, the ORA measures and Tonopen. No tonometer is considered a reference standard. Results will be interpreted within a framework of biomechanical principles. The question is raised, should a development goal emphasise GAT agreement or improvement?

Chapter 4 will assess repeatability of the three tonometers and biomechanical measures keratometry, pachymetry, ORA-CH and ORA-CRF on 35 eyes. Coefficients of Repeatability (CoR) will allow interpretation of results presented in Chapter 5.

Chapter 5 isolates corneal shape as the sole modified biomechanical parameter via Orthokeratology. The effect of corneal flattening on applanation tonometer readings as well as the biomechanical markers of ORA-CH and ORA-CRF is investigated.

Chapter 6 considers the potential variability tear forces may have on the accuracy of GAT. Scant research considers this aspect of the GAT model despite tear forces representing 50% of the model patches. Conflicting tear models are critiqued and a refined mathematical model presented and tear magnitudes assessed. What do tear forces represent, can stability be presumed and indeed is the magnitude necessarily significant?

Chapter 2: Global Corneal Biomechanics and the effect on Three Tonometers: Validity of Biomechanical Markers

Abstract

Aim: Biomechanical principles indicate the biomechanics of the thin shelled cornea relies, not only on its microstructure, but also curvature, thickness and internal pressure. Characterising the cornea via a single number such as CCT is simplistic and unrealistic. Further biomechanics suggests alternative tonometers may be more effective in neutralising biomechanically induced artefact. Inter-dependency of corneal biomechanical markers of CCT, ORA-CH, ORA-CRF, Corneal Curvature and IOP is evaluated on 91 normal eyes. Decision Tree Analysis (DTA) is utilised to assess, simultaneously, the global impact of these metrics on Goldmann Applanation Tonometer, Tonopen and Ocular Response Analyser measures.

Results: Corneal Curvature, ORA-CRF and ORA-CH are inter-related to CCT. CCT was the only measured metric to impact GAT measures, assessed via DTA. Tonopen was unaffected by any of the measurable biomechanical markers.

Conclusions: Thicker corneas are also flatter. Interdependency will dilute the global acceptance of CCT, helping to explain the lack of a unified CCT correction. CCT was also inter-related with ORA-CH and ORA-CRF, however these metrics may not be robust measures of *in vivo* biomechanics. Of the measurable biomechanical markers, CCT is confirmed the sole influence on GAT readings. Tonopen was the only tonometer not affected by the measured biomechanical proxies.

2.1 Introduction

The Goldmann Applanation Tonometry (GAT) model assumes the accuracy of GAT is defined by the equation:

$$IOP_T + M' = IOP_{GAT} + N' \qquad \textbf{(2.1)}\ \text{GAT Model}$$

(Adapted from Goldmann and Schmidt 1957, 1961).

Where:

IOP_T: True Intracameral IOP (albeit subtly raised by fluid displacement).

IOP_{GAT}: Pressure recorded by GAT (assumed equivalent to Force/Area) acting on the cornea.

M': Elasticity of the cornea pushing toward the tonometer.

N': Surface tension of the tear fluid pulling the tonometer probe toward the cornea.

2.1.1 Inter-dependency of Ocular Parameters

Whitford *et al.* (2015) indicates the mechanical stiffness of the cornea relies on its geometry, incorporating thickness and topography, and material stiffness reflecting the microstructure of the stroma. This would suggest the magnitude of M', designated 'Elasticity' by Goldmann and Schmidt (1957), dependent on a variety of potentially inter-related variables, both macroscopic and microscopic.

The Young-Laplace Equation, as applied to thin-shelled pressure vessels (Purslow and Karwatowski 1996) (Chapter 1 section 1.2.2.3), also establishes the interdependency of thickness, curvature as well as internal pressure. As contended in Chapter 1 (section 1.2.2.3) the Young-Laplace Equation, originally defining the relationship between internal pressure, surface tension and the curvature of a liquid surface (Fung 1993), underpins the caveats imposed on the GAT model.

An absolute magnitude for M', or N', was not stipulated by Goldmann and Schmidt (1957). Rather, they found, via experimentation on a meagre number of living and enucleated eyes, the corneal and tonometer dimensions ensuring GAT readings equated to manometry values. Only under these specific design arrangements, arrangements potentially too narrow to encompass all physiological and pathological variability, can GAT be assumed equal to true IOP. This well recognised flaw in the GAT model has driven numerous authors (Orssengo and Pye 1999, Kwon *et al.* 2008, Elsheikh *et al.* 2011, Kaushik *et al.* 2012, Khan 2014) to generate corrections with, as Orssengo and Pye (1999) suggest, the aim of preparing nomograms to determine true intracameral IOP from GAT measurements.

Despite these academic ventures, and the well documented inaccuracies implicit in striving to characterise the cornea via a single gross parameter, CCT remains the sole patch for variations in corneal biomechanics when using GAT. The primacy of CCT correction is integral to the treatment guidelines for Ocular Hypertensives (NICE 2009b).

If CCT was an independent variable, correction algorithms should be readily authenticated, yet proposed corrections range from 2mmHg to 7.1mmHg per 100µm of corneal thickness (Ehlers *et al.* 1975, Whitacre *et al.* 1993, Doughty and Zaman 2000, Tonnu *et al.* 2005, Kohlhaas *et al.* 2006). Brandt (2004), Francis *et al*. (2007), Hager *et al*. (2008), Boehm *et al*. (2008) and Śródka (2010) emphasise no nomogram proposed to adjust GAT readings for CCT is satisfactory. Considering specifically corneal

microstructure, Brandt (2004) suggests variations in collagen types, corneal hydration, collagen density and extracellular matrix may dwarf a CCT effect.

The failure of individual GAT corrections to totally explain inaccuracies may reflect the possibility global effects of corneal morphology dilute the impact of individual parameters.

2.1.2 Study aim

CCT, rather than an independent corneal parameter, may simply represent a measureable reflection of internal microstructure and topography. Potential inter-correlation of the measurable biomechanical metrics is assessed. This morphological approach to biomechanics may suggest tonometry readings are dependent on complex, inter-related biomechanical dynamics.

Further, the combined effect of the measured biomechanical markers on the three tonometers, GAT, Tonopen and ORA, is assessed simultaneously via Decision Tree Analysis. No tonometer is considered a reference standard; the results are interpreted within a framework of biomechanical principles.

2.2 Methods

This was a retrospective analysis of data collected from healthy volunteers among patients, NHS employees and students and staff of Aston University, Birmingham, UK.

A full eye examination ensured those enrolled were healthy with no signs of corneal abnormalities or ocular disease. Volunteers with diabetes, glaucoma or symptoms of sub-acute angle closure were excluded, as were subjects with conditions likely to cause unsolicited IOP fluctuations, such as obstructive lung disease or general anxiety. Exclusion criteria also included any corneal or ocular abnormalities, previous therapeutic or refractive surgery and concurrent contact lens wear. Table 2.1 summarises inclusion and exclusion criteria.

If inclusion criteria were attained, the full Consent Form (Appendix 4) was explained. Any subjects unable to give consent were also excluded.

Inclusion Criteria	Exclusion Criteria
Age between 18-85 years old	Any frank ocular disease such as glaucoma
Subjects able to give informed consent	Symptoms or signs of sub-acute angle closure
Ocular anatomy enabling successful measurements with instrumentation	Any corneal abnormalities – scarring, oedema, severe tear deficiency,
Absence of any ocular abnormalities or risk factors.	Concurrent contact lens wear
Ability to give consent	Any previous therapeutic or refractive corneal and ocular procedure – including cross linking
	Any frank systemic disease such as diabetes or COPD
	General anxiety

Table 2.1 Inclusion and Exclusion Criteria

Raw data from 260 eyes of 130 patients was collated. To avoid interdependency of results (Newcombe and Duff 1987, Murdoch *et al.* 1998) right eyes only were utilised for data analysis. After excluding incomplete data, visual examination identified a single extreme outlier which was also excluded. 91 right eyes were suitable for analysis.

This data set included 61 females and 30 males. Mean age was 38±21 years (range 18 to 86). Ethnicity: South Asian 45, Caucasian 35, Afro-Caribbean 5, Oriental 6.

All data were collected by a single experienced ophthalmologist commencing in 2013 after receiving institutional ethics approval via Aston University (Appendix 5). The study complied with the tenets of Helsinki.

2.2.1 Instrumentation

Ocular Response Analyzer®, (ORA) Reichert Ophthalmic Instruments, Buffalo, New York, recorded Corneal Hysteresis (ORA-CH) and Corneal Resistance Factor (ORA-CRF), as well as Ultrasound Pachymetry.

ORA-CH and ORA-CRF were used as proxy reflections of corneal biomechanics. Accepting the well critiqued inadequacies, detailed in Chapter 1 (section 1.7.3), without the ability to measure Young's Modulus *in vivo*, the ORA metrics can be considered quasi-biomechanical measures of corneal biomechanics. It should be re-emphasised ORA-CRF is highly correlated to CCT (Luce and Taylor 2006). While essential to interpret both metrics with caution, it was assumed they reflect, to an unquantified extent, biomechanics of the cornea. As such the ORA metrics were assumed adequate for the experimental goal to assess interdependency of corneal biomechanical parameters.

Four ORA signals were collected and the best waveform selected. The waveform score is presented on a scale of zero to ten with higher scores representing improved reliability (Reichert 2012). Waveform scores less than 9 were discarded. An acceptable score was always attained within the initial 4 measures.

Anterior corneal curvature was recorded with a Nidek OPD-Scan II ARK-10000® Nidek Co Ltd Tokyo Japan.

Without recourse to manometry, it is impossible to directly assess the expectation intracameral IOP will affect the biomechanics and topography of the corneal shell. The chosen surrogate was TonoPen XL®, Bio-Rad, Glendale, California, least affected by the biomechanics measured, and assumed to best approximate true IOP. The choice of instrument was *post hoc*; its independence of corneal biomechanics is supported by this experimental chapter. The machine theory is described in Chapter 1 (section 1.7.2) and is analogous to the Dynamic Contour Tonometer (section 1.7.4.2.), recognised to approximate intracameral IOP extremely well (Kanngiesser *et al.* 2005, Kniestedt *et al.* 2004, Kniestedt *et al*. 2005, Boehm *et al.* 2008, Leung *et al.* 2013). Briefly, corneal biomechanics are neutralised by protecting the 1.02mm diameter pressure sensitive plate from bending and boundary conditions and tear interactions by the 3mm diameter non-sensitive annulus (Schwartz *et al.* 1966). Thus neutralising biomechanics, the only force acting on the pressure sensitive zone, through the thin corneal shell, is IOP.

The global effect of the biomechanical makers on three tonometers are then investigated. Tonometers investigated are the Goldmann Applanation Tonometer (GAT), Haag-Streit, Bern, Switzerland, TonoPen XL® (Tonopen), Bio-Rad, Glendale, California and the non-contact GAT mimic Ocular Response Analyzer® (ORA), Reichert Ophthalmic Instruments, Buffalo, New York. The ORA records a GAT equivalent reading (ORA-IOPg) and a reading purportedly correcting GAT for CCT (ORA-IOPcc). The modelling principles of the three tonometers are presented in Chapter 1: GAT (section 1.3 and 1.4), Tonopen (section 1.7.2) and ORA (section 1.7.3).

CCT was recorded with an ultrasound Pachymeter, Ocular Response Analyzer®, Reichert Ophthalmic Instruments, Buffalo, New York. The instrument records seven readings in rapid succession and records an average.

Instruments were calibrated and cleaned prior to the study and periodically as recommended by the applicable user manuals. A pause of approximately 30 seconds was allowed between each measurement. All subjects were examined by slit lamp at every session conclusion to ensure corneal integrity.

2.2.2 Statistical Analysis

As a retrospective analysis of data pre-collected, the number of eyes available was fixed. Power calculation, via G Power version 3.1.9.2 (Faul *et al.* 2007) using the *a priori*, 2 tailed strategy with $\alpha = 0.05$, power = 0.8 ($1-\beta$) and medium effect yielded a sample size of 90; 91 eyes were available.

All statistical analyses were performed using SPSS 22.0 (IBM 2014).

Kolmogorov-Smirnov test demonstrated the biomechanical markers were distributed normally. However the tonometer measures were not normally distributed making non-parametric multivariate statistical tests necessary.

Employed previously in ophthalmic literature (Twa *et al.* 2005, Pancholi 2016, Rushton *et al.* 2016), Decision Tree Analysis (DTA), incorporating Chi-squared Automatic Interaction Detection (CHAID), was favoured over multiple regression analysis for a number of reasons. Firstly it does not necessitate normality (Pancholi 2016). Further, DTA accounts for all variables simultaneously, advantageous in this protocol as global effects are being assessed. The question being asked is whether biomechanical

confounders of tonometry are inter-related. Modification of a single parameter may impact on others. DTA ensures outcome expectancies cannot confound the process.

The outcomes are displayed as a flow chart in a hierarchical form (Pancholi 2016). This highly visual display makes DTA easy to interpret, a significant advantage of all Decision Trees, not specifically those incorporating CHAID. The researcher must identify the initial dependent variable, in this chapter either CCT or tonometer readings, representing the target parameter other variables may effect (Wilkinson 1992). The stepwise CHAID algorithm questions whether this outcome is altered by the independent variables (CCT arm: Corneal Curvature, ORA-CH and ORA-CRF. Tonometer arm: CCT, Corneal Curvature, ORA-CH and ORA-CRF).

Kass (1980) indicates another strength of CHAID is the built in significance testing ensuring the most significant predictor is chosen. DTA essentially predicts an outcome for consecutive groups given the outcome from preceding divisions (Ritschard 2013). The CHAID algorithm chooses the independent variable having the strongest interaction on the dependent one (Dunstone 2014, Rushton 2015). Twa *et al.* (2015) describe the tree presentation as consisting of nodes specifying a particular attribute of the data while the branches represent a test of each attribute's value. CHAID rejects insignificant cross tabulations ensuring the researcher's attention is drawn to potentially useful subdivisions, very useful for inexperienced researchers (Kass 1980).

Sample size and power calculations are inapplicable with DTA (Pancholi 2016), although its use of multiway splits ensure larger sample sizes are more effective. Simultaneous multiple hypothesis testing, especially if the sample size is small, increases the possibility rare events could be interpreted as significant, potentially leading to a Type I error. A Bonferroni adjustment compensates for this risk by adjusting the alpha level for multiple testing (Ritschard 2013). Further splitting ceases when any branching fails to meet the test (Wilkinson 1992)

2.3 Results

2.3.1 Inter-dependency of Biomechanical Measures

Of the biomechanical markers measured, CCT is correlated to corneal curvature, ORA-CH and ORA-CRF. As ORA-CRF is recognised to demonstrate significant correlation to CCT no significance to this relationship must be implied. No relationship between ORA-CH and corneal curvature or ORA-CRF and corneal curvature was evident (Table 2.2).

	CCT	ORA-CH	ORA-CRF	CCave
CCTus Sig 2 Tailed	1	+0.515** 0.00	+0.633** 0.00	+0.232* 0.027
ORA-CH Sig 2 Tailed		1	+0.801** 0.00	-0.082 0.439
ORA-CRF Sig 2 Tailed			1	0.009 0.934
CCave Sig 2 Tailed				1

**. Correlation is significant at the 0.01 level (2-tailed). N=91

*. Correlation is significant at the 0.05 level (2-tailed).

Abbreviations:
CCTus: Ultrasound Pachymetry.
CCave: Average Spherical Corneal Curvature.
ORA-CH: Corneal Hysteresis: measured by ORA.
ORA-CRF: Corneal Resistance Factor: measured by ORA

Table 2.2 Pearson's Correlation of Biomechanical Markers.

As CCT increases so too does ORA-CH and corneal curvature, thicker corneas are also flatter. An inter-relationship between CCT and corneal curvature is confirmed.

Decision Tree Analysis (DTA) (Figure 2.1) displays more subtle interactions.

Figure 2.1 Classification Tree – Dependency of CCT on CC, ORA-CH and ORA-CRF

Model Summary

Specifications	Growing Method	CHAID
	Dependent Variable	CCTus
	Independent Variables	CC..ave, ORA..CH, ORA..CRF
	Validation	None
	Maximum Tree Depth	3
	Minimum Cases in Parent Node	2
	Minimum Cases in Child Node	1
Results	Independent Variables Included	ORA..CRF, ORA..CH, CC..ave
	Number of Nodes	9
	Number of Terminal Nodes	6
	Depth	2

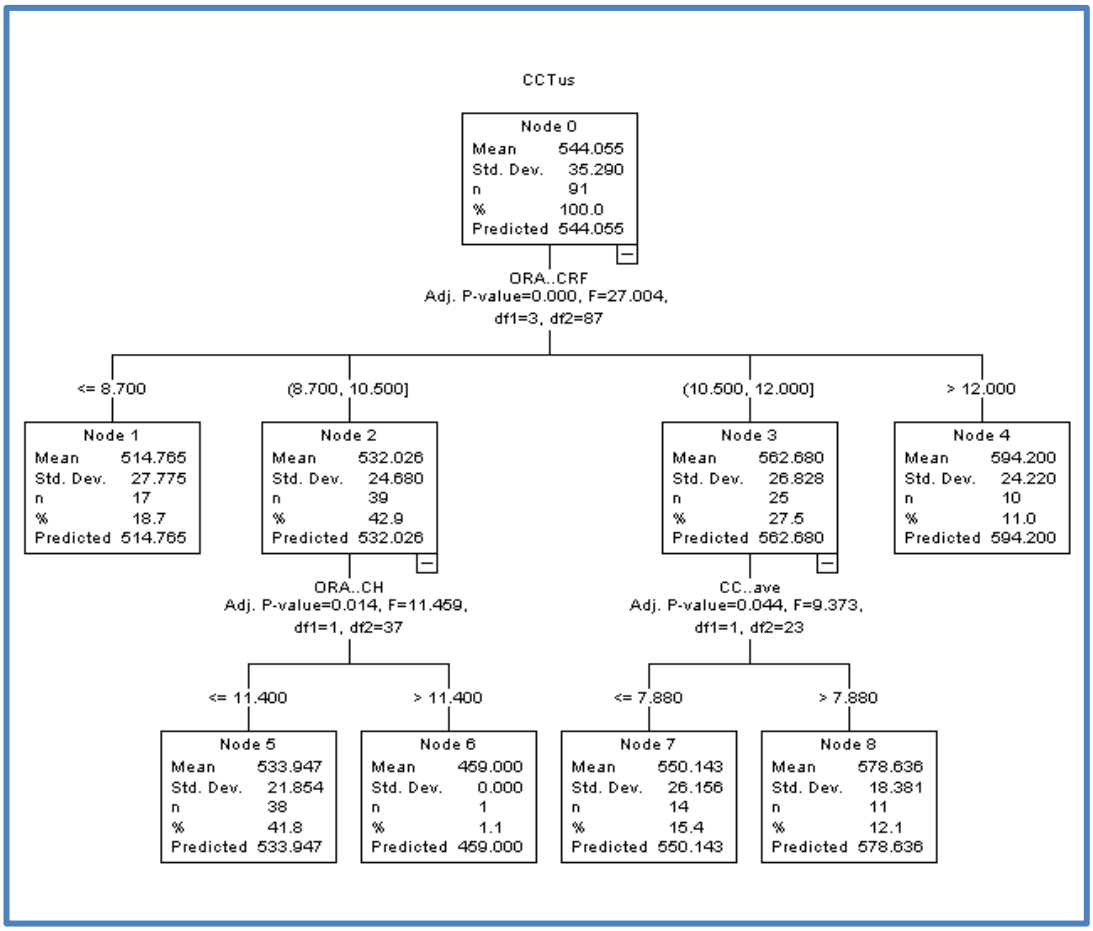
Growing Method: CHAID
Dependent Variable:CCTus

Abbreviations:
CCTus:
Ultrasound Pachymetry

CC..ave:
Average Spherical Corneal Curvature

ORA..CH
Corneal Hysteresis

ORA..CRF:
Corneal Resistance Factor



Corneal curvature impacts on CCT via ORA-CRF (Node 3), demonstrating, regardless of the guarded interpretation of ORA-CH and ORA-CRF, corneal biomechanics cannot be explained by CCT in isolation.

2.3.2 Impact of Intracameral IOP on Biomechanics

The chosen surrogate for manometry was Tonopen, least affected by the biomechanics measured, and assumed to best approximate true IOP. The Tonopen principles are described in Chapter 1 (section 1.7.2).

Table 2.3 Kendall's Non-Parametric Correlation of Tonopen (as best approximation of Intracameral IOP) and Corneal Biomechanical Markers.

	CCTus	ORA-CH	ORA-CRF	CCave
Tonopen Sig 2 Tailed	+0.260* 0.013	-0.083 0.432	+0.254* 0.015	0.006 0.952

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed). N=91

Abbreviations:
CCTus: Ultrasound Pachymetry
CCave: Average Spherical Corneal Curvature
ORA-CH: Corneal Hysteresis: measured by ORA
ORA-CRF: Corneal Resistance Factor: measured by ORA

As IOP, estimated by Tonopen, increased so too does ORA-CRF and CCT. No correlation between IOP and ORA-CH or corneal curvature was demonstrated (Table 2.3).

2.3.3 Impact of Corneal Biomechanics on Tonometers Assessed

Figures 2.2 to 2.5 illustrate the impact of ORA-CH, ORA-CRF, CCT and corneal curvature (CC) on the tonometer measures.

Contrary to expectations and the findings of Holladay *et al.* (1983), Mark (1973) and Mark and Mark (2003), corneal curvature was not found to influence the readings of any instrument (Figure 2.2 to 2.5).

The primacy of CCT on GAT is confirmed, at least on physiologically normal corneas. No other independent variables were included, the quasi-biomechanical markers of ORA-CH, ORA-CRF were of no consequence (Figure 2.2).

The GAT mimic measure of ORA-IOPg (Figure 2.3) displayed complex inter-relationships. Primary impact is ORA-CRF (Nodes 1, 2 and 3). Nodes 2 and 3 both showed dependency on ORA-CH in isolation. CCT becomes implicated solely on ORA-CH at Node 7, while ORA-CRF re-impacts on ORA-CH at Nodes 10 and 11.

A cyclical co-dependency of 'independent' variables on ORA-IOPcc was evidenced in the DTA (Figure 2.4). ORA-IOPcc was primarily affected by ORA-CH, followed by ORA-CRF and then by ORA-CH again. It is noteworthy only ORA generated biomechanical markers registered on the ORA-IOPcc DTA.

Tonopen was not influenced by any biomechanical markers tested (Figure 2.5). This supports the contention the theoretical constitutive modelling of Tonopen is sound and effectively eliminates the biomechanical confounders measurable *in vivo*.

Figure 2.2 Classification Tree – Impact of CCT, CC, ORA-CH and ORA-CRF on GAT

Model Summary

Specifications	Growing Method	CHAID
	Dependent Variable	GAT
	Independent Variables	CCTus, CC..ave, ORA..CH, ORA..CRF
	Validation	None
	Maximum Tree Depth	3
	Minimum Cases in Parent Node	2
	Minimum Cases in Child Node	1
Results	Independent Variables Included	CCTus
	Number of Nodes	4
	Number of Terminal Nodes	3
	Depth	1

Growing Method: CHAID

Dependent Variable: GAT

Abbreviations:
GAT: Goldmann Applanation Tonometry
CCTus: Ultrasound Pachymetry
CC..ave: Average Spherical Corneal Curvature
ORA..CH: Corneal Hysteresis
ORA..CRF: Corneal Resistance Factor

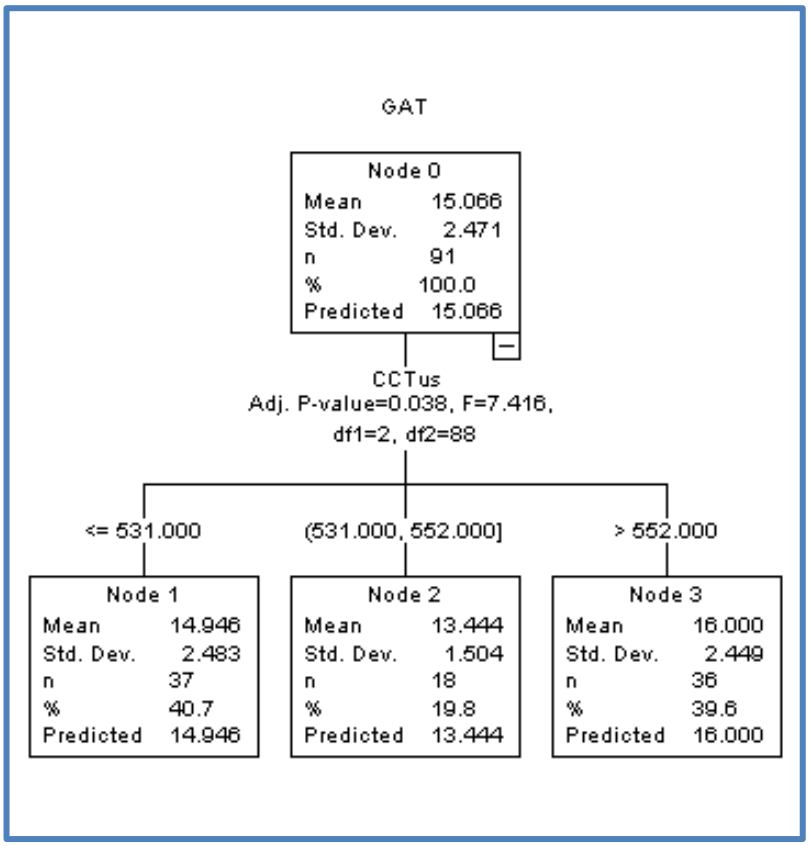


Figure 2.3 Classification Tree – Impact of CCT, CC, ORA-CH and ORA-CRF on ORA-IOPg

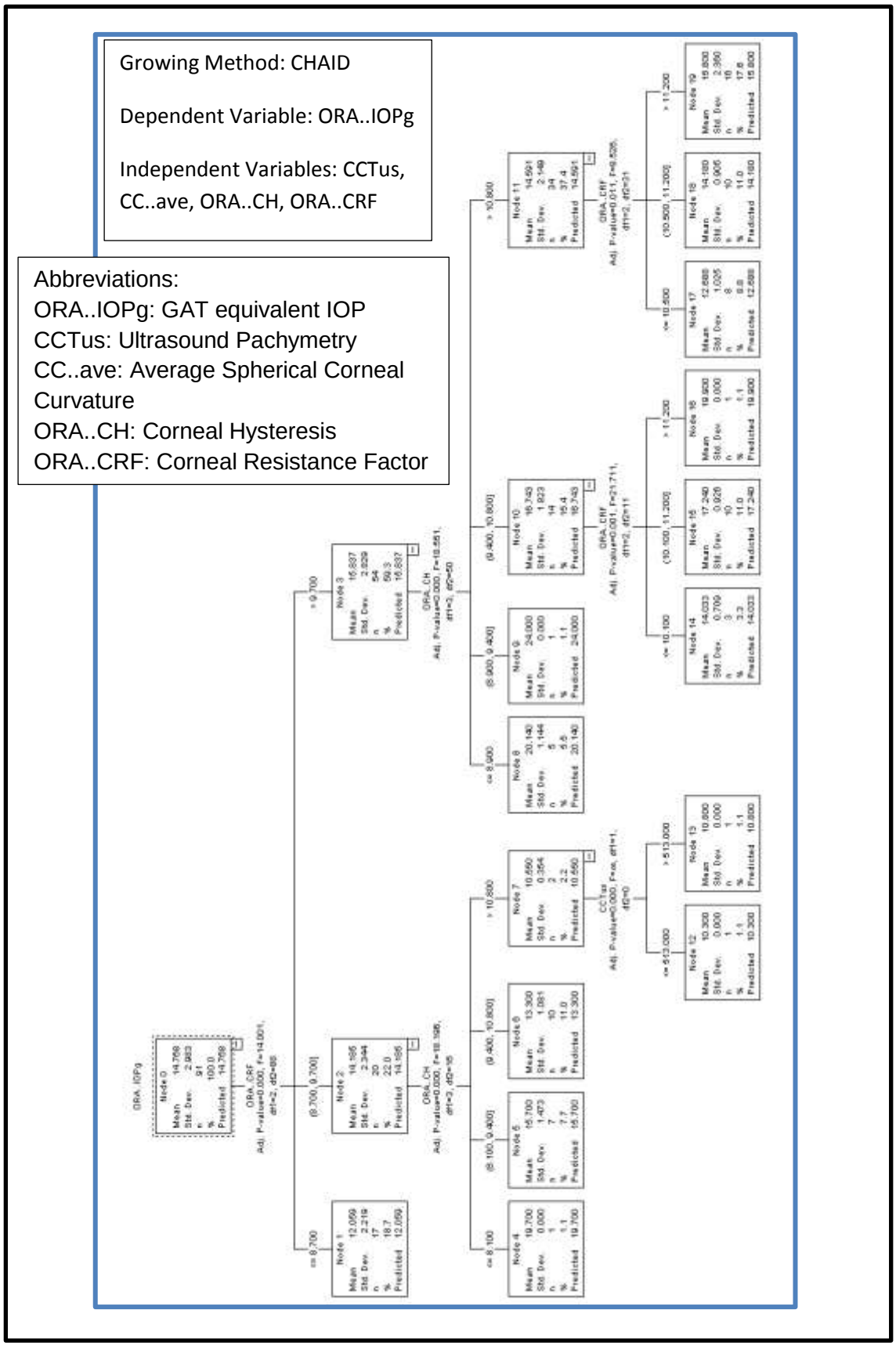


Figure 2.4 Classification Tree – Impact of CCT, CC, ORA-CH and ORA-CRF on ORA-IOPcc

Growing Method: CHAID

Dependent Variable: ORA..IOPcc

Independent Variables: CCTus, CC..ave, ORA..CH, ORA..CRF

Abbreviations:
ORA..IOPcc: Corneal Compensated IOP
CCTus: Ultrasound Pachymetry
CC..ave: Average Spherical Corneal Curvature
ORA..CH: Corneal Hysteresis
ORA..CRF: Corneal Resistance Factor

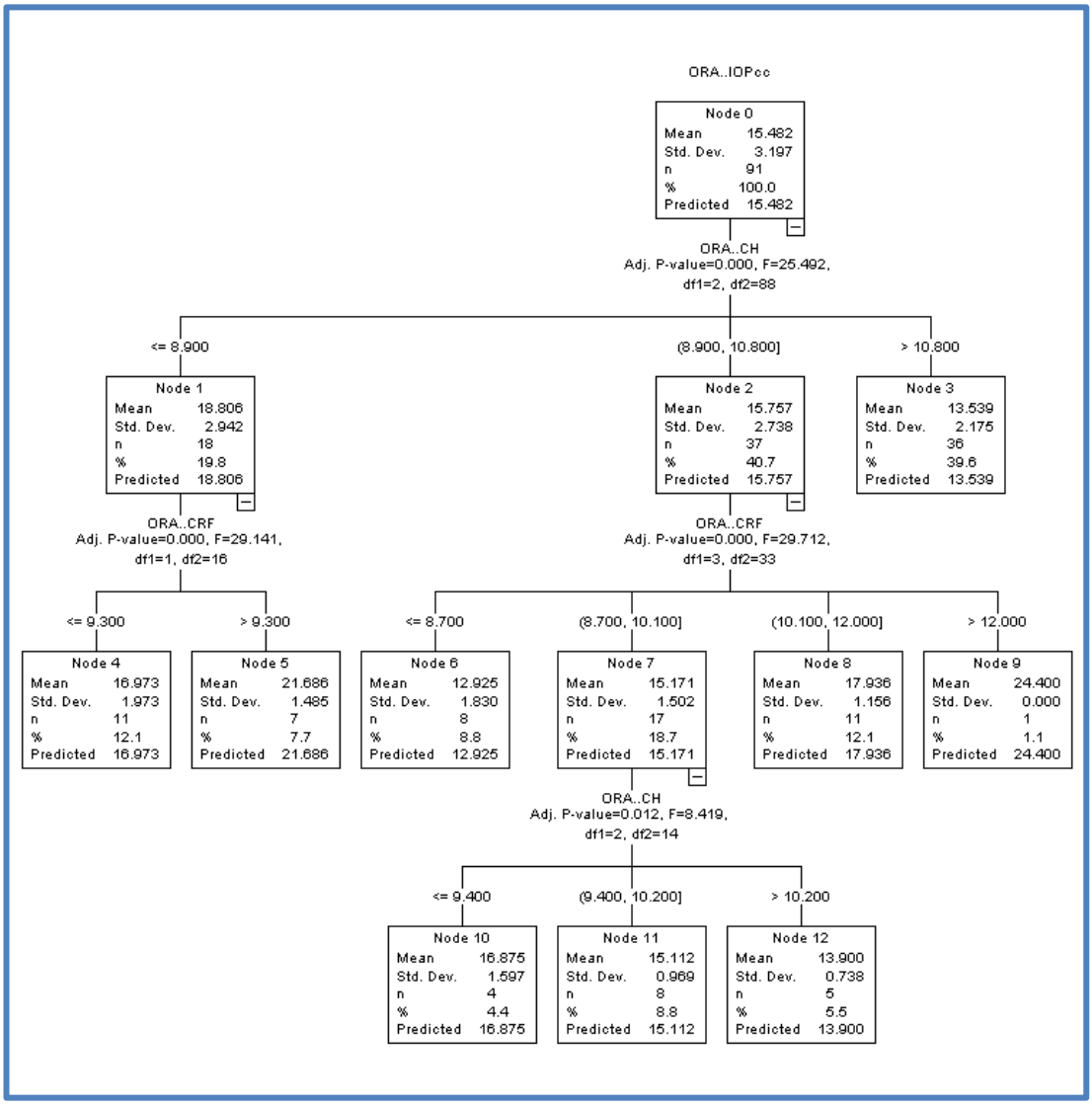


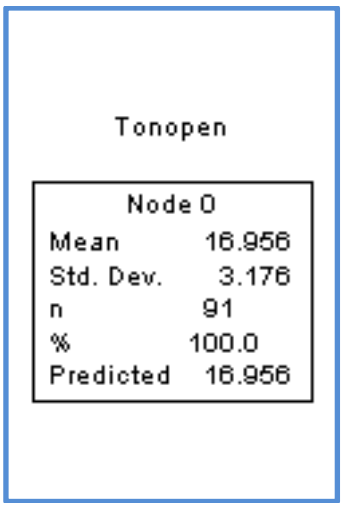
Figure 2.5 Classification Tree – Impact of CCT, CC, ORA-CH and ORA-CRF on Tonopen

Model Summary

Specifications	Growing Method	CHAID
	Dependent Variable	Tonopen
	Independent Variables	CCTus, CC..ave, ORA..CH, ORA..CRF
	Validation	None
	Maximum Tree Depth	3
	Minimum Cases in Parent Node	2
	Minimum Cases in Child Node	1
Results	Independent Variables Included	No Independent Variable Included
	Number of Nodes	1
	Number of Terminal Nodes	1
	Depth	0

Growing Method: CHAID
Dependent Variable: Tonopen

Abbreviations
CCTus: Ultrasound Pachymetry
CC..ave: Average Spherical Corneal Curvature
ORA..CH: Corneal Hysteresis
ORA..CRF: Corneal Resistance Factor



2.4 Discussion

The interdependency of CCT, Corneal Curvature and ORA-CH supports the theoretical contention of Whitford *et al.* (2015), the overall mechanical stiffness of the cornea is dependent on its thickness (CCT), topography (CC) and microstructure (ORA-CH) (Table 2.2, Figure 2.1).

The interdependency of corneal curvature and CCT (Table 2.2) should confound the unqualified use of CCT as a global correction for GAT measurement. Corneal curvature demonstrates a clear inter-relationship with other biomechanical metrics, CCT with direct correlation (Table 2.2) and indirectly via ORA-CRF in the DTA in Figure 2.1. While corneal curvature only impacts on CCT via ORA-CRF (Figure 2.1 at Node 3) this is significant as the ORA-CRF algorithm made no assumptions about corneal curvature (Luce 2005).

These results support the view continuum principles seem more appropriate when modelling tonometry than implying constitutive relevance to single parameters.

Nevertheless, contradicting expectations, CCT was displayed as the sole pre-eminent metric reflecting corneal biomechanics affecting GAT (Figure 2.2). This was despite the demonstrated inter-dependency of measureable biomechanical markers (Figure 2.1), the inter-relationship of CCT and corneal curvature (Table 2.2) and the reasoned claim CCT is an imperfect surrogate for corneal biomechanics (Brandt 2004, Liu and Roberts 2005, Hamilton and Pye 2008, Young 2014). These contradictory results must be reconciled.

It is postulated, apart from CCT, corneal curvature was the only unique biomechanical feature measured in this experiment. Radius of curvature, incorporated in the Young-Laplace Equation (equations 1.2.6 and 1.2.7), is a biomechanical feature and did impact ORA-CRF (Figure 2.1), defined by CCT (Luce and Taylor 2006). Corneal curvature is also interdependent with CCT (Table 2.2). Regardless, the absence of a shape effect on GAT is despite sampling a broad range of corneal curvatures. Mean curvature of 7.85mm ± 0.7mm (range from 8.92 to 6.94mm). Mehravaran *et al.* (2013) publishing data from 400 normal right eyes presented a range of only 8.84 to 7.1mm (mean 7.79mm± 0.31mm) while Mashige (2013) presenting results from 9 studies including Caucasian, Indian, Chinese and African subjects reported ranges from 8.75 to 7.03mm.

These corneal curvature results contradict Holladay *et al*. (1983), Mark (1973) and Mark and Mark (2003), who did find corneal curvature to affect GAT. Mark and Mark (2003) measured GAT along the two principal meridians of eyes with ≥1.75D of regular astigmatism. In so doing the authors effectively controlled for CCT and biomechanics and suggested as much as 37% of the difference in GAT data was determined by the difference in corneal curvature.

The modelled system of Liu and Roberts (2005), estimated, for normal corneas, the impact on GAT by corneal curvature, CCT and Corneal Biomechanics to be 1.76mmHg, 2.87mmHg and 17.26mmHg respectively. If representative of real corneas this would suggest biomechanics could dwarf a pure curvature effect. However the model would also predict a CCT effect to be overwhelmed by biomechanics. The authors used Young's Modulus as a measure of corneal biomechanics. The sole impact of CCT, recognised as flawed, on GAT (Figure 2.2) implies other, unmeasured microstructural parameters, are implicated. Brandt (2004) suggests variations in collagen types, corneal hydration, collagen density and extracellular matrix may dwarf a CCT effect. However, CCT is a reflection of its microstructure. Without definitively sampling Young's Modulus, CCT appears the only measureable reflection of corneal microstructure.

The results support a very conservative interpretation of the ORA metrics.

ORA-CH is described by Luce (2005) as reflecting rigidity, hydration and other factors not yet identified. The undetermined factors have not been clarified, nor was the term 'rigidity' defined by the author. Claims of a definitive interpretation of the ORA metrics are speculative. It was assumed *a priori* ORA-CH and ORA-CRF reflected, at least to an unquantified extent, corneal stiffness as defined by Young's Modulus. A complex, multifactorial nature of the ORA output may suggest any biomechanical component is insignificant to the total waveform. To assess the impact of corneal microstructure on CCT and GAT, a measure of 'Modulus of Elasticity' as well as 'Modulus of Rigidity' would be required. The ORA metrics are gross measures. Any contribution attributable to Young's Modulus of the corneal stroma appears insignificant.

Further validation the ORA biomechanical measures do not reflect Modulus of Elasticity or Modulus of Rigidity is the absence of evidence elevated inflation loading increases corneal stiffness. As IOP increases the anticipation is the corneal shell will stiffen (Metzler *et al*. 2014) as it stretches and thins (Buzard 1992). This was not demonstrated. As IOP increased ORA-CRF did increase but so too did CCT. ORA-CH remained unaltered. If ORA-CRF or ORA–CH reflected corneal stiffness, as IOP increases, CCT should decrease as ORA-CRF or ORA-CH increase. The results cannot be assumed to

represent an increase in corneal stiffness due to alterations in its biomechanical microstructure with raised IOP. Rather the results simply re-confirm the CCT/CRF correlation described by Luce (2005).

The exact extent and significance of ORA-CH and ORA-CRF remains debatable and no conclusions on the effect of internal hydrostatic pressure on corneal shell biomechanics can be drawn.

Corneal biomechanics also predicts alterations in corneal curvature with increased inflation loading. This effect too was not perceptible with this experimental arrangement.

There are several explanations for the deviation from classic shell theory.

All measurements were within normal ranges, the highest Tonopen measure was 22mmHg. The viscoelastic nature of the cornea indicates only beyond normal IOP limits does the tensile stress on the cornea overwhelm the Hookean nature of the corneal proteoglycan at which point the cornea will become significantly stiffer, as well as thinner (Fung 1993, Anderson *et al.* 2004). Prior to a frank alteration in form, function is maintained by the elastic nature of the proteoglycan matrix. Certainly the model presented by Śródka (2010) demonstrating the effect of IOP on CCT and curvature used corneal loading of 40mmHg, well outside physiologically normal IOP ranges.

Secondly the measurement techniques, keratometry and ORA specifically, are simply too coarse to detect the biomechanical changes; changes which must not induce perceptual alterations in visual function. Lam and Douthwaite (1996) certainly could not demonstrate a clinically significant effect of raised IOP, from within normal ranges, on corneal curvature. The authors speculate an auto-regulatory mechanism to maintain corneal performance. Indeed ocular self-adjustment must accommodate rapid fluctuations in IOP of up to 9mmHg due to ocular pulse (Xu *et al*. 2011) as well as circadian variations in normal subjects up to 5mmHg (Clement *et al.* 2014).

Finally, it is proposed, rather than definitive measures of corneal biomechanics, the ORA metrics reflect, as Dupps (2007) indicates, the engineered output of the Reichert ORA under the specific measurement conditions imposed by the ORA. While the corneal response to the air plenum will be influenced by stromal stiffness it seems not the primary response.

In actuality, the biomechanical expectation corneal curvature will vary in response to intracameral IOP is real and has been demonstrated and incorporated in a commercially available device; SENSIMED Triggerfish, Switzerland (Mansouri *et al.* 2012b) is CE

marked (Mansouri and Weinreb 2015). Triggerfish, consisting of a micro fabricated platinum-titanium strain gauge (Laukhin *et al*. 2011) embedded in a soft contact lens (Chen *et al.* 2013) quantifies variation in corneal curvature induced by IOP. Importantly, the changes in corneal curvature are subtle, Chen *et al.* (2014) suggest approximately 3µm change per 1mmHg, well below the accuracy of optical keratometry. Additionally, the alterations are recorded at the corneoscleral junction (Mansouri *et al.* 2012a). Introducing manometry would not have altered the outcome, the effects are too subtle for the instrumentation employed.

2.4.1 Choice of Tonometer

Only Tonopen measures of IOP were unaffected by the corneal biomechanical parameters measured in this study (Figure 2.5).

Comparing Tonopen to GAT, Geyer *et al.* (1992) found Tonopen to over-estimate IOP; their frame of reference, GAT, dictated Tonopen to be judged inaccurate. No conclusion about accuracy measuring intracameral pressure can be inferred by simple comparative papers. A contradictory conclusion may have been reached if elimination of tear forces and neutralisation of corneal biomechanics by Tonopen were prioritised, both profoundly affecting GAT.

The Dynamic Contour Tonometer (DCT – principle outlined in 1.7.4.2) also reads higher than GAT, but is recognised to be a more accurate instrument when calibrated against manometry (Kanngiesser *et al.* 2005, Boehm *et al.* 2008, Taylor personal communication – Appendix 3). The DCT allows direct trans-corneal measure of pressure (Siganos *et al.* 2004) and is based on Pascal's Law of Hydrostatic Pressure (Kanngiesser *et al.* 2005). Once shell stress (Buzard 1992, Young and Budynas 2002) is neutralised by the DCT casing Newton's Third Law holds, and only intraocular pressure is transmitted to the sensor. Apart from designing a curved, rather than flat, non-sensitised support annulus the theory seems identical to Tonopen and based on sound mechanical assumptions. The evident elimination of biomechanics and tear forces with the DCT, and Tonopen, reflect a theoretically more plausible measure of intracameral IOP.

Inclusion of manometry and DCT could have given more support for the conclusion, of the tonometers tested, the one most theoretically trustworthy is the Tonopen. DCT would seem a 21st century upgrade of the Tonopen, demonstrating excellent precision,

potentially enhanced due to gathering 100 IOP readings per second over 5 to 8 seconds (Kotecha *et al.* 2010). It would be beneficial for future studies assessing the GAT model assumptions to include the DCT; a shortcoming of this research.

While GAT was only affected by CCT, ORA-IOPg, while designed a GAT correlate, did not demonstrate dependency on CCT, rather ORA-CRF. As ORA-CRF is effectively defined by CCT (Luce and Taylor 2006) the two could essentially compete for affecter dominance. ORA-CRF eclipsing CCT as an affecter on this GAT mimic, while not impacting on GAT itself (Figure 2.2) is further evidence ORA-CRF is not a unique biomechanical measure as Luce and Taylor (2006) propose. Further, ORA-IOPcc, claimed a measure of IOP independent of CCT (Luce and Taylor 2006), is also impacted by ORA-CRF. The primary impact on ORA-IOPcc, at Node 0 was ORA-CH. Luce and Taylor (2006) indicate ORA-CH underpinned the calculation of ORA-IOPcc, claiming this ensures ORA-IOPcc is a measure of pressure less affected by corneal properties. Yet all ORA measures are derived from two applanation events which, like GAT, must be influenced by CCT. The complex DTA for ORA-IOPcc (Figure 2.4) does not include a single non-ORA estimate of biomechanics. ORA-CRF is highly correlated to CCT (Taylor *et al.* 2013). ORA-CH, determining ORA-IOPcc, is shown to be inter-related with ORA-CRF and CCT (Figure 2.1). It seems likely all ORA measures simply reflect the machine specific algorithm calculating every metric from the same two applanation points.

2.5 Conclusions

Of the instruments assessed, Tonopen alone was unaffected by the measured corneal biomechanics suggesting it reflects the most robust biomechanical model.

Regardless of the well-founded debate on the inadequacies of a CCT correction for GAT, DTA confirmed primacy of CCT. No other independent variables were included; ORA-CH and ORA-CRF were of no consequence. Regardless, the inter-dependency of CCT and corneal curvature was demonstrated. ORA-CH is also implicated in the co-dependency however the overall results lay doubt on the biomechanical integrity of this metric.

ORA-IOPcc does not appear independent of biomechanics being impacted by ORA-CRF, defined by CCT and ORA-CH. It appears unlikely ORA-CH and ORA-CRF can be considered robust independent measures of biomechanics, nor are they improvements

on CCT. The results suggest the ORA measures extracted from the waveform are simple expressions of the machine algorithm, all deduced from the same two applanation points.

Mechanical laws clearly predict the interdependency of IOP, corneal curvature, CCT and biomechanics. Regardless, no evidence could be supplied suggesting IOP itself impacts corneal biomechanical responses. This result is interpreted as reflective of the accuracy and validity of the measurements.

Chapter 3: Tonometer Agreement

Abstract

Aim: To assess how GAT, Tonopen and the two ORA measures of IOPg and IOPcc agree with each other. No tonometer is considered a reference standard, the results interpreted within a framework of biomechanical principles without presuming a tonometer hierarchy.

Results: Tonopen was found to record measures of IOP significantly higher than all tonometers tested. ORA-IOPg and ORA-IOPcc agree with GAT, although the two ORA measures do not agree with each other.

Conclusions: Without manometry is it necessarily implicit GAT is correct? If a design priority of ORA-IOPcc was to supply an improved GAT measure unaffected by corneal biomechanics it should not agree with GAT. Without disagreeing with GAT, ORA-IOPcc cannot be considered an improved GAT measure. Regardless of the radically different machine theory, Tonopen and ORA-IOPcc purportedly neutralise corneal biomechanics. Agreement would be anticipated. The discrepancy suggests at least one machine must fail in this goal.

3.1 Should all tonometers necessarily agree?

Theoretically tonometers should agree, they are, after all, attempting to measure the same phenomenon. However, inter and intra observer variability, manufacturing imprecision, machine operational imprecision, theoretical principles and assumptions of each tonometer design, objectivity of machine operation and natural physiological and temporal variations all contribute to clinical noise obscuring real variations. Further, Pepose *et al.* (2007) advocates IOP reflects a pressure reading filtered through the biomechanical signature of each individual cornea. The biomechanical signature is governed by more than Young's Modulus, a measure of material stiffness, in isolation. Comprehensively, corneal biomechanics is a reflection of geometry, incorporating thickness and topography, and material stiffness contingent on corneal microstructure (Whitford *et al.* 2015).

Certainly the European Committee for Standardisation (2009), defining the scope of International Standard ISO 8612:2009, state true IOP cannot be measured without recourse to manometry. The standard must accommodate innate variability of both test and reference instruments and specifies the minimum requirements and design compliance procedures for tonometers intended for routine clinical use.

Detailed in Chapter 1 (section 1.7.1), tolerances allowed in ISO 8612 account for error of both test and reference tonometers. Bland and Altman (1986) stipulate, when comparing instruments, the true reading is unknown. The Bland/Altman technique is to determine if a new instrument can be considered interchangeable with another; accuracy

of either instrument is not a consideration. The authors also stress the level of variation acceptable is a matter of judgement and should be defined in advance. The actual arithmetic process simply defines the statistical Limits of Agreement (LoA), acceptance the instruments are interchangeable is subjective and based on the specific clinical or experimental goals.

3.1.1 Study aim

Interchangeability of tonometers is not a consideration for this investigation. No tonometer is considered a reference standard; the results assess how different tonometers agree with each other rather than GAT. Results will be interpreted within a framework of biomechanical principles without presuming a tonometer hierarchy.

Tonometers investigated are the Goldmann Applanation Tonometer (GAT), Haag-Streit, Bern, Switzerland, TonoPen XL® (Tonopen), Bio-Rad, Glendale, California and the non-contact GAT mimic Ocular Response Analyzer® (ORA), Reichert Ophthalmic Instruments, Buffalo, New York.

3.2 Methods

A full description of data collection was presented in Chapter 2. Briefly, this was a retrospective analysis of data collected from healthy volunteers, confirmed via preliminary ocular examination, among patients, NHS employees and students and staff of Aston University, Birmingham, UK. A total of 91 right eyes were utilised for analysis.

If inclusion criteria were attained, the full Consent Form (Appendix 4) was explained. The research received institutional ethics approval via Aston University (Appendix 5) and complied with the tenets of Helsinki.

As described previously, tonometers investigated are GAT, Tonopen and ORA. The ORA records a GAT equivalent reading (ORA-IOPg) and a reading purportedly correcting GAT for CCT (ORA-IOPcc). The modelling principles of the three tonometers are presented in Chapter 1; GAT (section 1.3 and 1.4), Tonopen (section 1.7.2) and ORA (section 1.7.3).

The alternative instrument theory of the Tonopen warrants a brief re-emphasis. The Tonopen, consists of a 1.02mm diameter pressure sensitive plate embedded in a 3mm diameter non-sensitive annulus (Schwartz *et al*. 1966). The bending and boundary forces of the cornea are supported by the non-sensitive base plate, which also removes tear forces from the electrically sensitive zone. By neutralising biomechanics, the only force acting on the pressure sensitive zone, through the thin corneal shell, is the IOP, albeit artificially raised by the volume of intraocular fluid displaced; compensated within the instrument algorithm.

3.2.1 Statistical Analysis

The number of eyes was estimated via G Power version 3.1.9.2 (Faul *et al*. 2007) using the *a priori*, 2 tailed strategy with $\alpha = 0.05$, power = 0.8 (1-β). The sample available allowed a medium effect (0.3) to be detectable and yielded a sample size of 90.

Kolmogorov-Smirnov test demonstrated the Tonometer results, apart from ORA-IOPcc were not normally distributed; non-parametric tests were utilised. Kendall's Tau Coefficient evaluated Tonometer correlation. Wilcoxon Signed Rank Test estimated if the sample measures between two tonometers differed. These tests were performed using SPSS 22.0 (IBM 2014).

Limits of agreement between tonometers was assessed via the Bland and Altman (1986) graphical technique for comparing difference of means using Excel, XLSTAT, statistical software.

3.3 Results

Kendall's Tau Coefficient confirm all tonometers correlate (Table 3.1), as would be anticipated for instruments ostensibly measuring the same physiological phenomenon (Bland and Altman 1986). These results do not suggest agreement, precision or that the instruments are equally influenced by biomechanical factors.

	GAT	Tonopen	ORA-IOPg	ORA-IOPcc
GAT Sig 2 Tailed	1 .	0.513** 0.00	0.379** 0.00	0.339** 0.00
Tonopen Sig 2 Tailed		1	0.430** 0.00	0.355** 0.003
ORA-IOPg Sig 2 Tailed			1	0.665** 1
ORA-IOPcc Sig 2 Tailed				1

**. Correlation is significant at the 0.01 level (2-tailed). N=91

Abbreviations:
GAT: Goldmann Applanation Tonometer.
Tonopen: Self Explanatory.
ORA-IOPg: GAT correlated IOP: measured by ORA
ORA-IOPcc: Corneal compensated IOP: measured by ORA

Table 3.1 Kendall's Tau Correlation of Tonometers.

Wilcoxon Signed Rank Test and Bland-Altman plots of agreement are amalgamated into Figures 3.1 to 3.6. Agreement between GAT and its correlates ORA-IOPg and ORA-IOPcc was demonstrated. However, ORA-IOPg and ORA-IOPcc did not agree with each other. Tonopen does not agree with any of the applanating tonometers.

Figure 3.1
GAT v Tonopen

Related Samples Wilcoxon Signed Rank Test	
Null Hypothesis	**Decision**
Median of difference between GAT and Tonopen equals Zero	REJECT Null Hypothesis

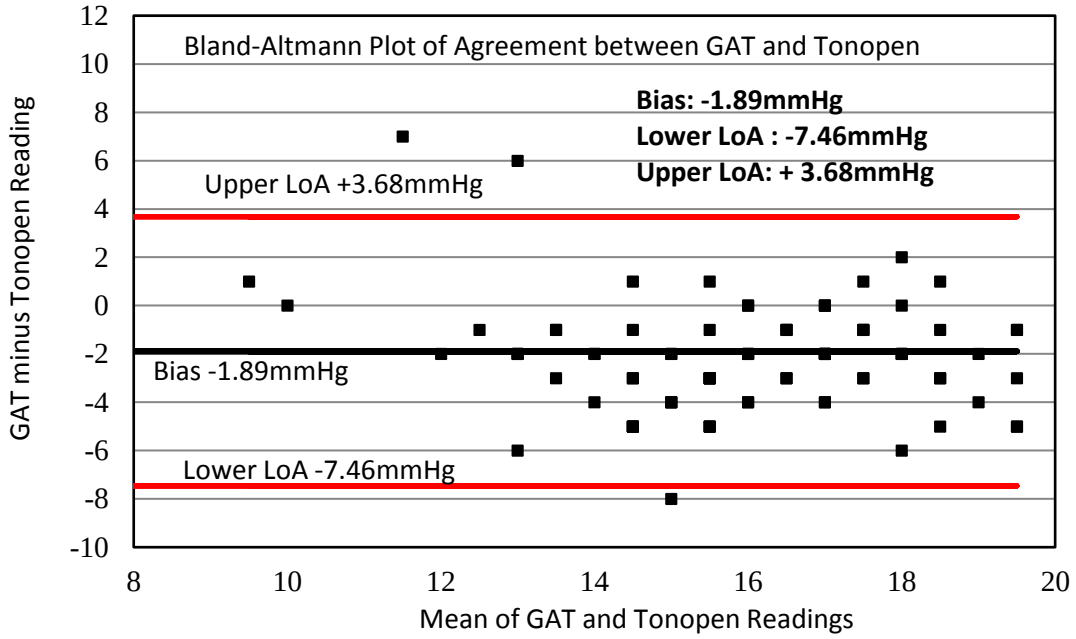


Figure 3.2
GAT v ORA-IOPg

Related Samples Wilcoxon Signed Rank Test	
Null Hypothesis	**Decision**
Median of difference between GAT and ORA-IOPg equals Zero	Accept Null Hypethesis

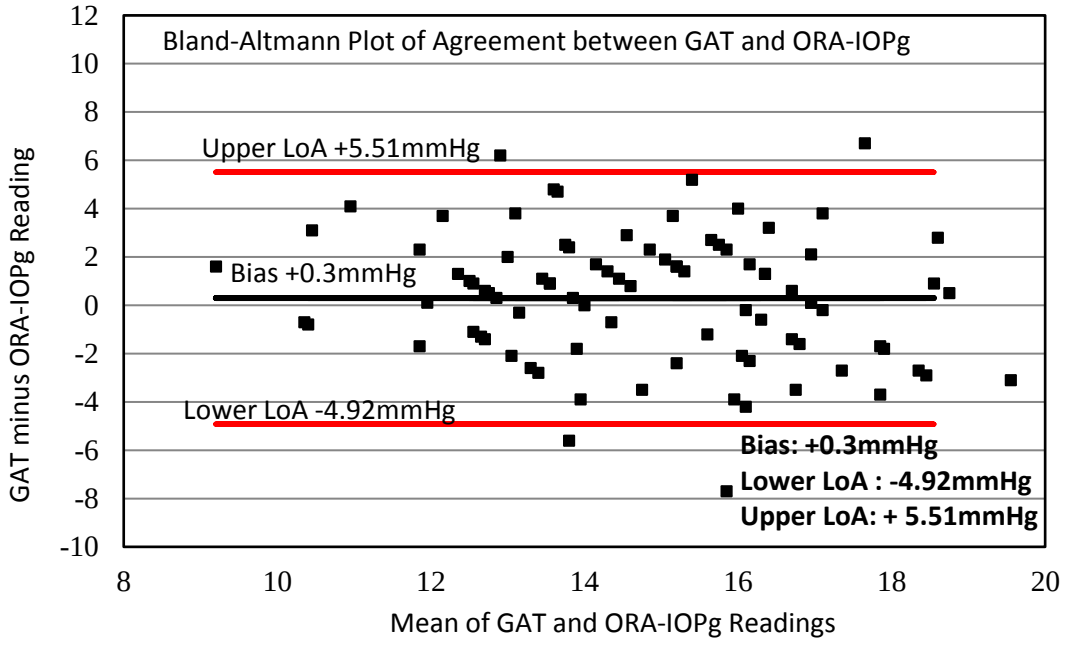


Figure 3.3
GAT v ORA-IOPcc

Related Samples Wilcoxon Signed Rank Test	
Null Hypothesis	**Decision**
Median of difference between GAT and ORA-IOPcc equals Zero	Accept Null Hypothesis

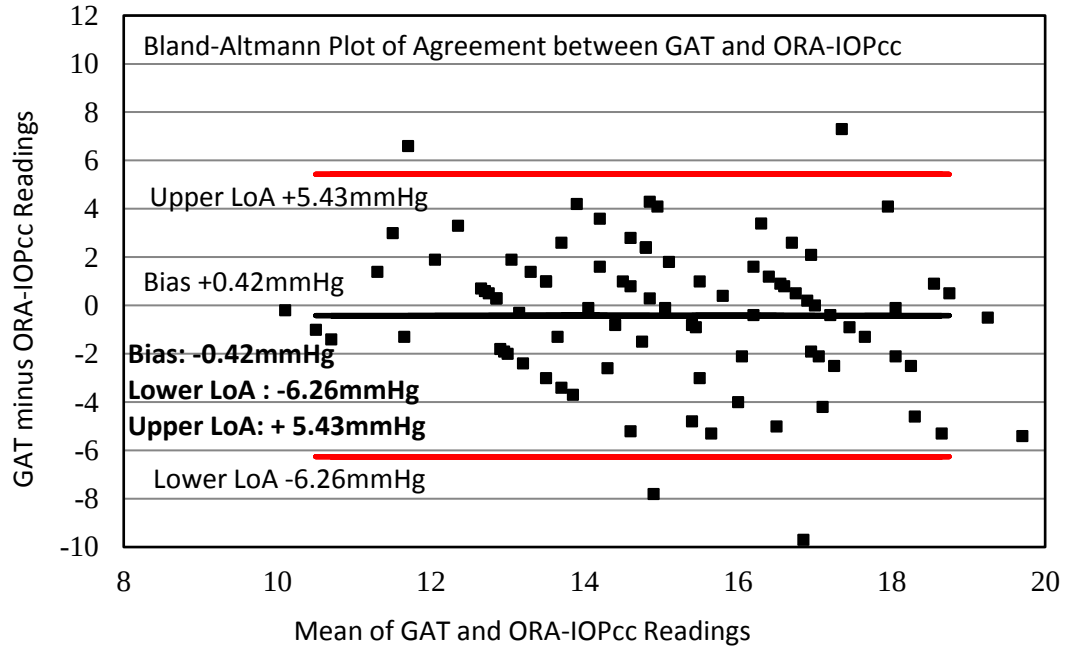


Figure 3.4
Tonopen v ORA-IOPg

Related Samples Wilcoxon Signed Rank Test	
Null Hypothesis	**Decision**
Median of difference between Tonopen and ORA-IOPg equals Zero	REJECT Null Hypothesis

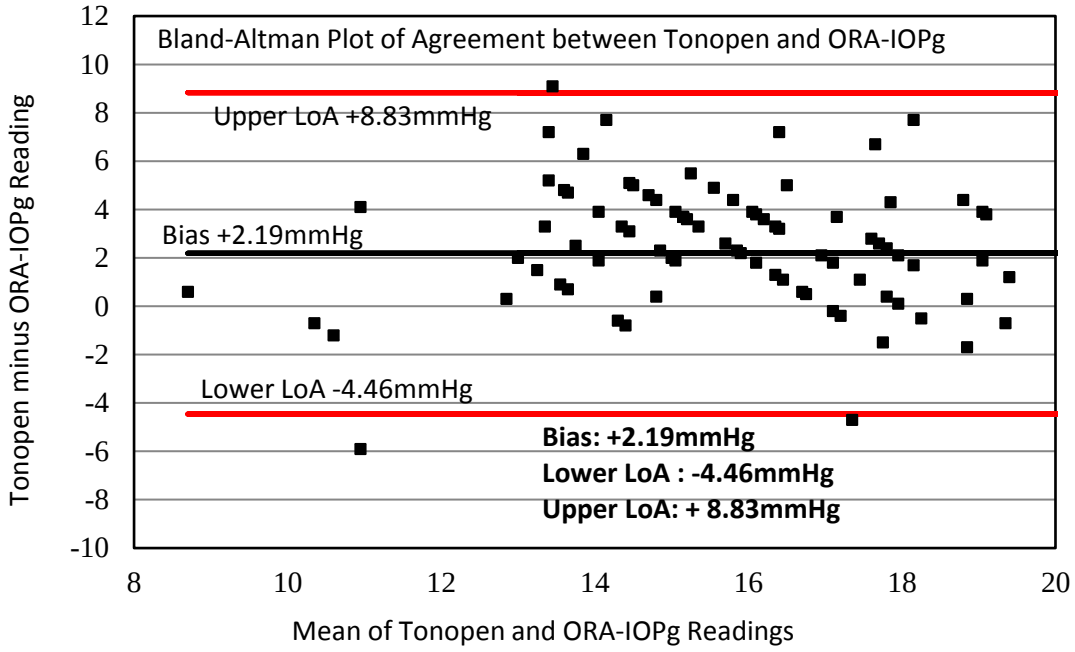


Figure 3.5
Tonopen v ORA-IOPcc

Related Samples Wilcoxon Signed Rank Test	
Null Hypothesis	**Decision**
Median of difference between Tonopen and ORA-IOPcc equals Zero	REJECT Null Hypothesis

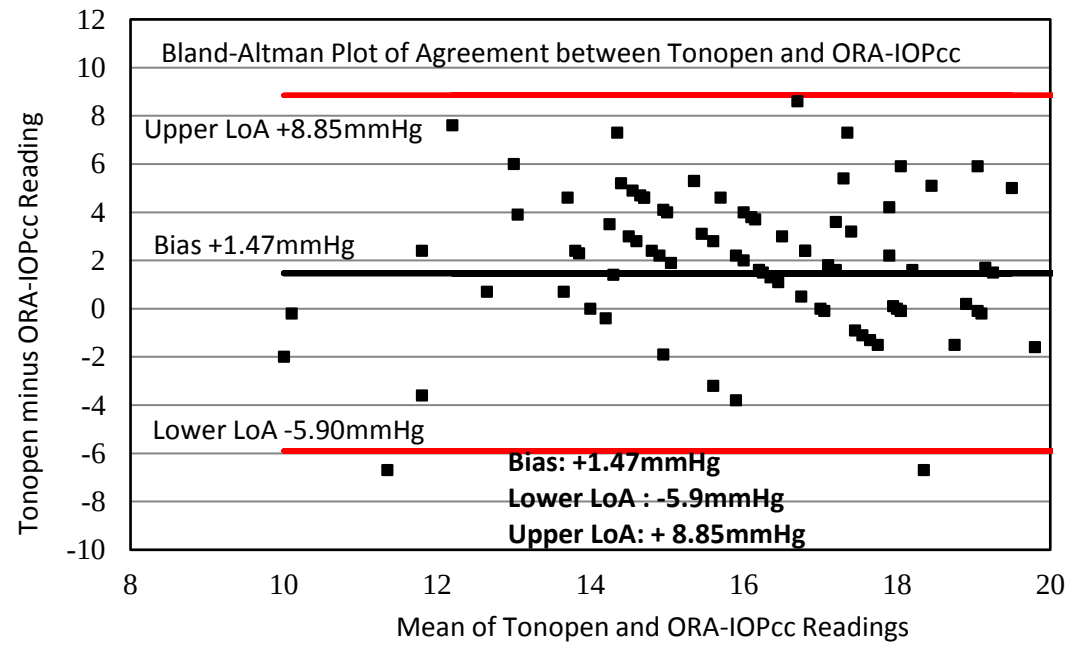
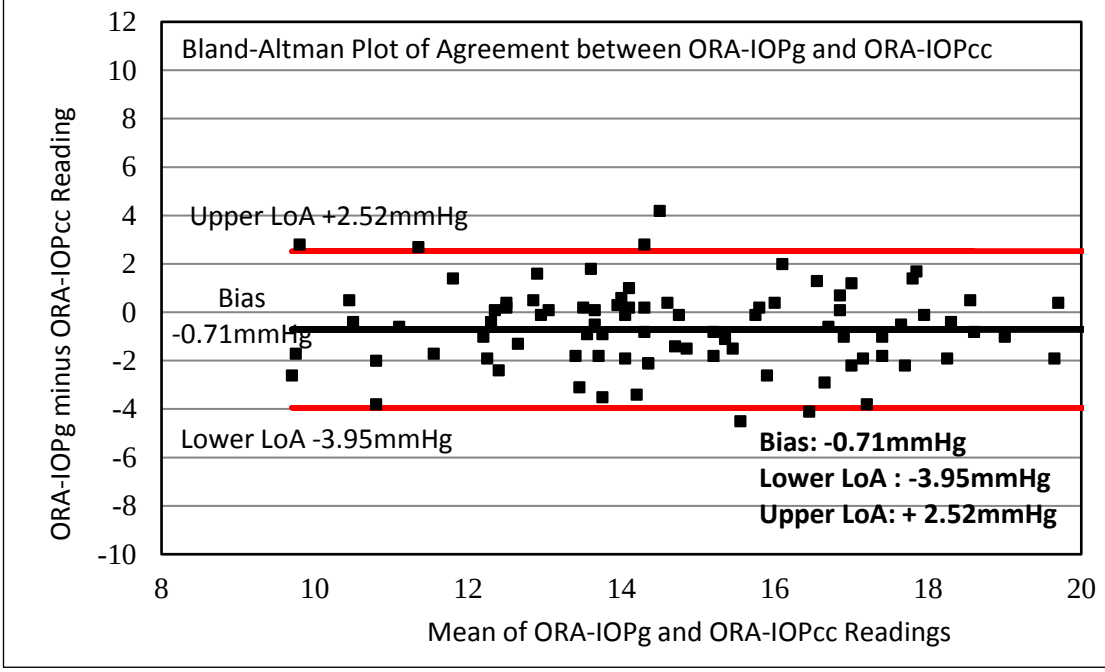


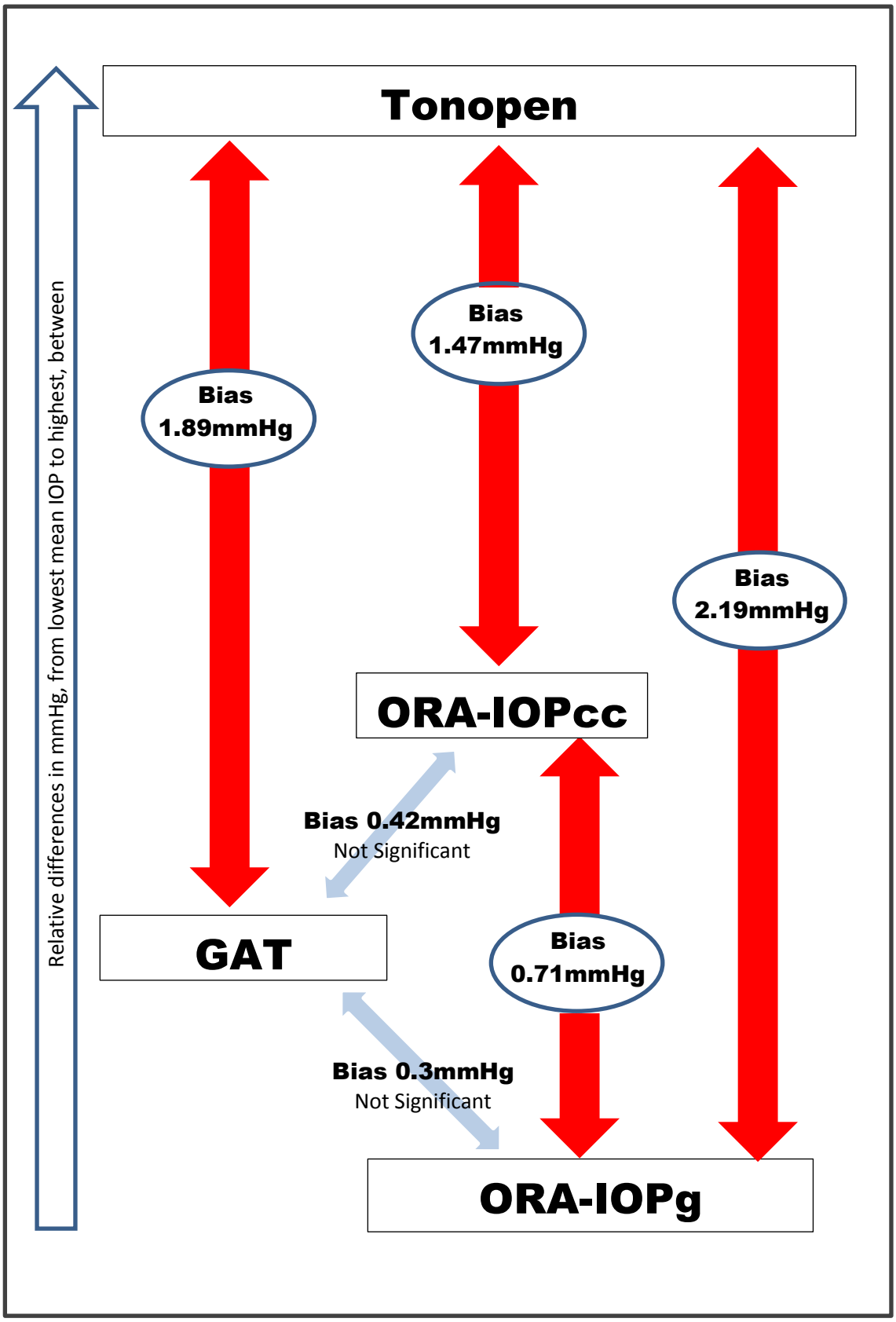
Figure 3.6
ORA-IOPg v ORA-IOPcc

Related Samples Wilcoxon Signed Rank Test	
Null Hypothesis	**Decision**
Median of difference between ORA-IOPg and ORA-IOPcc equals Zero	REJECT Null Hypothesis



The relative biases, calculated via the Bland-Altman plots of agreement (Figs 3.1 to 3.6) are schematically represented in Figure 3.7. Higher tonometer placement within the figure represents higher mean IOP measures for that instrument. The figure implies nothing about tonometer hierarchy or accuracy. Tonopen records highest, significantly higher than all tonometers tested. ORA-IOPcc was slightly higher than GAT which was slightly higher than ORA-IOPg, these were not significantly different. While both ORA metrics agreed with GAT, they did not agree with each other. Figure 3.7 demonstrates why this would be the case.

Figure 3.7 Statistical Bias of Tonometers Assessed



3.4 Discussion

3.4.1 ISO 8612 and Comparison to GAT

None of the machine comparisons comply with the ISO 8612 imperative, 95% of paired differences between the test and reference instrument must fall within ±5mmHg (European Committee for Standardisation 2009).

GAT showed no statistically significant bias compared to ORA-IOPg and ORA-IOPcc although the LoA for both measurements did not comply with ISO 8612 requirements.

Tonopen alone disagreed with GAT demonstrating the greatest bias of 1.89mmHg. Viewed as a convention Figure 3.7 could reinforce the understanding, since Tonopen does not agree with GAT it is less accurate. However, Bland and Altman (1986) stress their technique simply determines if instruments are interchangeable; accuracy of either machine is not a consideration. Additionally, the results represent statistical differences and do not necessarily reflect a clinically significant difference (Bland and Altman 1986).

Further, if claims of non-compliance to ISO 8612 are to be made, authors must adhere to ISO 8612 protocols as well as tolerances. The standards group stipulate a minimum of 40 eyes to be assessed for each of three categories of IOP range, 7 to 16mmHg, >16 to <23mmHg and ≥ 23mmHg; of the 91 eyes assessed 63 fell into the low IOP category, 28 on the middle and no eyes recorded GAT measures higher than 22mmHg. Results must be interpreted with the recognition ISO 8612 protocols were not satisfied.

3.4.2 Ocular Response Analyser measures

Only ORA-IOPg and ORA-IOPcc showed no statistically significant departure in bias from GAT. The ORA is a GAT mimic and GAT correspondence was a design priority. However, if, as advocated, ORA-IOPcc is a measure of IOP unaffected by corneal biomechanics (Luce and Taylor 2006) ORA-IOPcc should not agree with GAT. Surely the design goal has been lost if not the case?

Further, Tonopen did not agree with ORA-IOPcc. ORA-IOPcc is a measure purportedly independent of corneal biomechanics (Taylor *et al.* 2013). Yet Tonopen theory (Chapter 1 section 1.7.2) and the results of Chapter 2 demonstrate this instrument to be unaffected by the corneal biomechanical metrics collated. Regardless of the radically different machine theory, since both machines purportedly neutralise corneal biomechanics,

agreement would be anticipated. The discrepancy suggests at least one machine must fail in this goal.

Taylor (personal communication – Appendix 3) acknowledges the GAT paradigm poor, yet the design priority for the ORA remained a GAT correlate (Reichert Technologies 2012). The DCT, utilising a process neutralising corneal biomechanics, and evidenced as more accurate, records higher IOPs not corresponding to GAT. Taylor suggests this has limited its acceptance. Taylor argues the problem with GAT is not the number designated IOP, rather it is the fact the figure is contaminated by corneal artefact. Unlike the DCT, the ORA seems to be attempting to neutralise corneal biomechanics, while still agreeing with GAT. If GAT is confounded by corneal biomechanics, while ORA-IOPcc is not, these two design priorities are incompatible.

3.4.3 Inter-instrument Limits of Agreement

Limits of Agreement between all instruments were substantial.

If biomechanical theory (section 1.7.2) and experimental results (Chapter 2) of the tonopen and marketing claims of ORA-IOPcc (Taylor *et al.* 2013) are sound these instruments should demonstrate the tightest comparison. However, not only did the machines disagree in terms of bias, they demonstrated the greatest LoA of ±7.37mmHg.

Biases between ORA-IOPg and GAT as well as ORA-IOPcc and GAT were not statistically significant. However, the LoA were ±5.22mmHg, ±5.85mmHg respectively suggesting, while the biases demonstrate GAT agreement, the variability in the system is great.

Smallest was between ORA-IOPg and ORA-IOPcc, recording ±3.24mmHg. This undoubtedly reflects the identical instrument technology and theory, a single acquisition event for both measures eliminating machine variability; further the instrument is objective.

Instrument variability was not assessed via this experiment; repeatability of the instruments is investigated in Chapter 4 which may reveal alternative areas to explain inconsistency.

3.4.4 Tonometer Hierarchy

Without manometry is it necessarily implicit GAT is correct?

Regardless of convention, propagated by interpretations of ISO 8612, it is not necessarily the case tonometers should agree. The Schiőtz tonometer was superseded by GAT. Not because they agreed, but because they did not. Schiőtz demonstrated poor repeatability (Friedenwald 1937, Kronfeld 1945, Jackson 1955, Schottenstein 1996) and GAT was more accurate and repeatable. Unlike ORA-IOPcc, Tonopen, was never intended a GAT mimic. If, with its fundamentally different theoretical principles, Tonopen is a more accurate tonometer it would not be expected, nor was it demonstrated, to agree with GAT. It would be interesting to assess how well Tonopen agreed with DCT.

Henson and Harper (1998) queried the entrenched assumption non-contact tonometers (NCT) read higher than GAT. Only one NCT was assessed (ORA), however all rely on the same principle. The results indicate there is no significant difference between GAT and NCTs.

Tonopen, arguably supported by the most robust theoretical principles, recorded the highest. The Tonopen results correspond with the Dynamic Contour Tonometer (DCT). Using very similar theoretical principles, the DCT is evidenced to approximate intracameral pressure very well, but does read several mmHg higher than GAT (Kanngiesser *et al*. 2005, Boehm *et al*. 2008). A significant shortcoming of this research was the omission of the DCT. Both Tonopen and ORA-IOPcc are suggested to neutralise corneal biomechanics. Inclusion of DCT results may have aided interpretation of the discrepancy between the two machines.

3.5 Conclusions

Tonopen was found to record measures of IOP significantly higher than all tonometers tested. Conclusions about accuracy, however, cannot be made. The biomechanical principles of Tonopen, detailed in Chapter 1 (section 1.7.2), are theoretically robust and suggest neutralising of corneal biomechanics, rather than simply incorporating adjustments, to be possible. This claim was experimentally supported by the results presented in Chapter 2.

Conversely ORA-IOPcc, claimed a measure of IOP unaffected by corneal biomechanics, and as such a better indicator of real IOP than GAT (Luce and Taylor 2006), did not statistically differ from GAT. If a design priority of ORA-IOPcc was to supply an improved GAT measure independent of corneal biomechanics (Taylor *et al.* 2013) it should not agree with GAT. The design goal has been lost if the new measure does not differ from the old. There is no reason to adopt a new instrument increasing costs (Drexler and Fujimoto 2008, Radcliffe 2014), if the instrument does not represent improved clinical utility. Without disagreeing with GAT, ORA-IOPcc cannot be considered an improved GAT measure.

Chapter 4: Instrument Repeatability

Abstract

Aim: To assess the repeatability of all the instruments utilised in this thesis. IOP measurements of GAT, Tonopen and the two ORA measures of IOPg and IOPcc. Biomechanical markers of ultrasound pachymetry, Keratometry and the two Ocular Response Analyser measures of Corneal Hysteresis and Corneal Resistance Factor.
Results: Tonopen recorded the best CoR of ±4.5mmHg, followed by GAT (±4.7mmHg), ORA-IOPg (±4.9mmHg) and finally ORA-IOPcc (±5.7mmHg). Repeatability of ORA-CH, ORA-CRF and Keratometry were better, demonstrating, for the realistic experimental goals, acceptable repeatability. Pachymetry however showed a large CoR (±18.20µm).
Conclusions: The wide Coefficients of Repeatability of all the tonometers may mask real effects investigated in Chapter 5. Regardless of the objective nature of the machine operational system, ORA-IOPcc showed the poorest CoR suggesting fundamental problems with the machine algorithm. The ORA does not appear a robust replacement for GAT.
Poor pachymetry repeatability suggests a single reading is of limited value in guiding clinical decisions for the management of ocular hypertensives.

4.1 Introduction. Repeatability: Another Layer of Measurement Noise

Of the instruments assessed, Tonopen appears the most theoretically robust when considering neutralising corneal biomechanics. However, this does not imply other sources of measurement noise would be equally well controlled. Inter and intra observer variability, manufacturing imprecision, machine operational imprecision, objectivity of machine operation and natural physiological and temporal variations continue to plague the accurate measurement of IOP.

Measured IOP is simply a number, repeatability of the number is paramount. In order for two measurements to agree they must be repeatable (Ehrlich *et al.* 2010). A major drive to replace the Schiőtz was its variability due to fundamental design and manufacturing flaws (Schmidt 1959, 1960). Schiőtz (1920) presented corrections to the conversion curves as well as refinements to the instrument and yet, despite using an official Schiőtz tonometer supplied by the Norwegian company and certified by Professor Schiőtz, Friedenwald (1937) found it varied significantly from the 'Schiőtz Standard Tonometer'. Kronfeld (1945) checked 27 official standard Schiőtz instruments and none were compliant to specifications, while imitation instruments demonstrating poorer accuracy were widespread (Kronfeld 1945, Jackson 1955, Schottenstein 1996).

Repeatability will dictate agreement (Bland and Altman 1986). Bland and Altman (1986) explain if a traditional method is the more variable, a new method, even if perfect will not agree with the existing standard. If both methods have poor repeatability, the authors continue, the problem is amplified.

4.1.1 Study Aim

To assess the repeatability of the instruments utilised in this thesis. Coefficients of Repeatability (CoR) will help interpretation of significance of change induced by Orthokeratology in Chapter 5. Repeatability reflects another source of clinical noise potentially masking true measures.

Tonometers investigated are the Goldmann Applanation Tonometer (GAT), Haag-Streit, Bern, Switzerland, TonoPen XL® (Tonopen), Bio-Rad, Glendale, California and the non-contact GAT mimic Ocular Response Analyzer® (ORA), Reichert Ophthalmic Instruments, Buffalo, New York. The ORA records a GAT equivalent reading (ORA-IOPg) and a reading purportedly correcting GAT for CCT (ORA-IOPcc).

Biomechanical markers of Corneal Hysteresis (ORA-CH) and Corneal Resistance Factor (ORA-CRF), as measured by the ORA will also be assessed as well as Rodenstock Keratometry C-MES Munchen, and Ultrasound pachymeter (PachPen ACUTOME INC).

4.2 Methods

Repeatability data was collected as part of the Orthokeratology phase of the study (Chapter 5).

Thirty-five eyes, of thirty-five volunteers, fulfilling the inclusion criteria, were enrolled in the study. Average age was 35 (range 12 to 64) and included 10 males and 25 females. The sample consisted of 29 Caucasians and 6 Asians.

All data was collected at a community optometry clinic in Northumberland, UK. Recruitment was via word of mouth and the practice Newsletter (Appendix 6), also distributed via Facebook. Data collection commenced in August 2015 after receiving

institutional ethics approval via Aston University. The study complied with the tenets of Helsinki.

Inclusion Criteria	Exclusion Criteria
Age between 12-65 years old	Any family or personal history of glaucoma
Van Herick angles ≥3, Clear AC, Anterior chamber anatomy normal	Symptoms or signs of sub-acute angle closure or congestion.
Normal Discs, Full fields (Fast Threshold): no flagged reliability indices, no flagged global indices.	Any corneal abnormalities – scarring, oedema, severe tear deficiency,
Absence of any ocular abnormalities or risk factors.	Concurrent contact lens wear
Normal corneal topography (Scout) Corneal Astigmatism ≤0.75DC	Any previous therapeutic or refractive corneal and ocular procedure – including cross linking
Ability to give consent. <16 Gillick Competence confirmed and parental consent granted	Any reported systemic disease Hypertension, heart disease, diabetes, COPD, current or previous use of steroids

Table 4.1 Inclusion and Exclusion Criteria

A full eye examination ensured those enrolled were healthy with no signs of corneal abnormalities or ocular disease. Table 4.1 synopsises inclusion and exclusion criteria.

Ocular history excluded any family or personal history of glaucoma, as well as any symptoms of sub-acute angle closure and corneal or other pathologies. General health issues were also investigated; smoking, systolic blood pressure, heart rate, diabetes, current or previous use of steroids have all been shown to have some level of correlation with IOP (Carel *et al.* 1984). A proportion of the study group did smoke but no other health issues were reported. Fundoscopy showed all discs to be normal with healthy neural rims.

All subjects had normal fields confirmed by Medmont M700® Automated Perimeter, Medmont International Pty Ltd, Nunawading, Australia, using the 'Glaucoma Fast Threshold' strategy. False positive, false negative and fixation loss confirmed each candidate's reliability. The programme did not flag any of the global indices of Overall

Defect, Pattern Defect, Short-term Fluctuation and Cluster Analysis as statistically significant for the volunteers included in the research. The global indices are described by Medmont (2015) and compared to those of the Humphreys instrument by Landers *et al*. (2007).

Slit lamp biomicroscopy, Scout corneal topography and keratometry confirmed healthy corneas, anterior chambers and irides. All subjects had angles graded III or greater with the Van Herick method; only angles up to Grade II have been found on gonioscopic examination to be closable (Palmberg 1996).

Exclusion criteria were any corneal or ocular abnormalities, previous therapeutic or refractive corneal surgery, astigmatism greater than 0.75 dioptre and concurrent contact lens wear. Only one eye was selected to avoid interdependency of results (Newcombe and Duff 1987, Murdoch *et al*. 1998). The right eye was chosen unless it did not fulfil the inclusion criteria in which case the left only was utilised. A total of 39 patients were enrolled; two voluntarily chose to discontinue and two did not fulfil the inclusion criteria for either eye during the initial ocular assessment. If inclusion criteria were attained, the full Consent Form (Appendix 7) was explained by an experienced Clinical Receptionist who was fully versed of the experimental aims and protocols; this colleague also managed the experimental logistics.

Automated tests were collected by a single experienced support clinician, while keratometry, pachymetry, Tonopen and GAT by a single optometrist. This protocol was considered appropriate to mimic real world conditions.

Measurements were recorded within one hour between 9.00am and 11.00am; the follow-up appointment was diurnally matched. The second appointment was timed, to reduce subject inconvenience, to coincide with collection of their orthokeratology lens (part of the next research phase) and was also dictated by subject availability; the average interval to re-test was 36.5 days (±19.6), ranging from 4 to 76 days.

Order of measurements were from least invasive; Scout Topography, Keratometry, ORA (CH, CRF, IOPg, IOPcc) and ultrasound pachymetry. There is a well-documented decrease in recorded IOP with repeated GAT (Thorburn 1978, Evans and Wishart 1992, AlMubrad and Ogbuehi 2008). However, Tonopen has an equivalent applanation footprint. Consequently GAT and Tonopen were alternated as either the penultimate or ultimate measurement. The initial GAT/Tonopen sequence for individual subjects was maintained.

4.2.1 Statistical Analysis

The number of eyes was estimated via G Power version 3.1.9.2 using the *a priori* strategy with α = 0.05, power = 0.8 (1-β) and effect size 0.5.The sample size was determined by the needs of the orthokeratology experimental arm discussed in Chapter 5.

Kolmogorov-Smirnov test for biomechanical parameters demonstrated normality. The tonometers exhibited a mixture of normal and non-normal distributions.

The statistical and graphical technique introduced by Bland and Altman (1986) was utilised to ascertain the Coefficients of Repeatability (CoR) of the repeated measures. Excel, XLSTAT, statistical software was used for the Bland-Altman calculations.

4.3 Results

The Coefficients of Repeatability for all tonometers were broad indicating significant variability in repeatability. Tonopen recorded the best CoR of ±4.5mmHg, followed by GAT (±4.7mmHg), ORA-IOPg (±4.9mmHg) and finally ORA-IOPcc (±5.7mmHg). This high degree of variability of the ORA-IOPcc will contribute to the poor agreement between Tonopen and ORA-IOPcc discussed in Chapter 3.

Figure 4.1 Bland-Altman GAT Repeatability

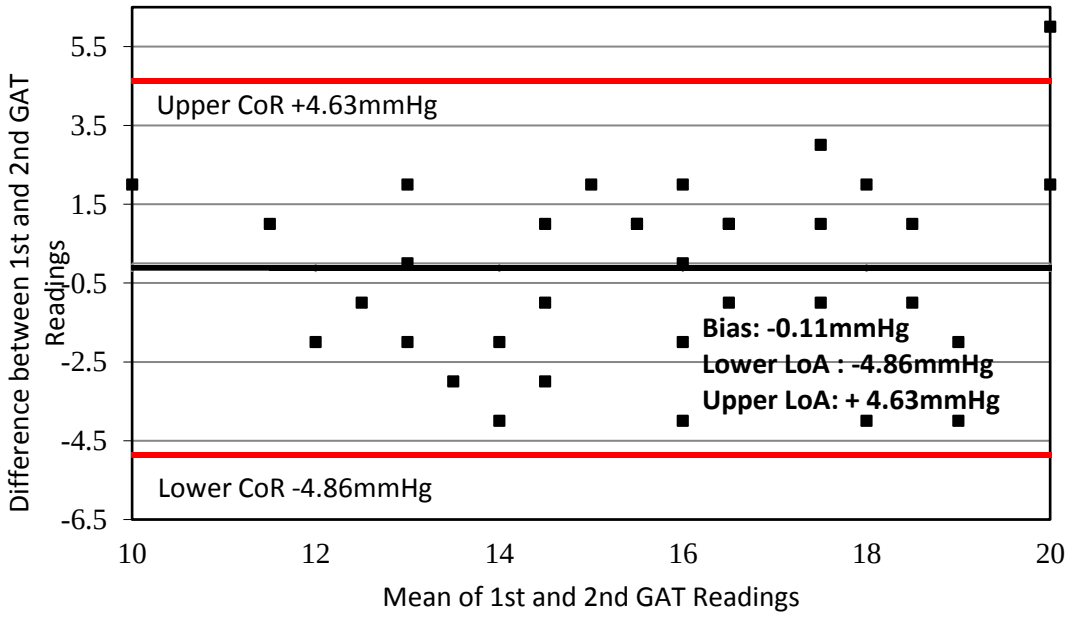


Figure 4.2 Bland-Altman Tonopen Repeatability

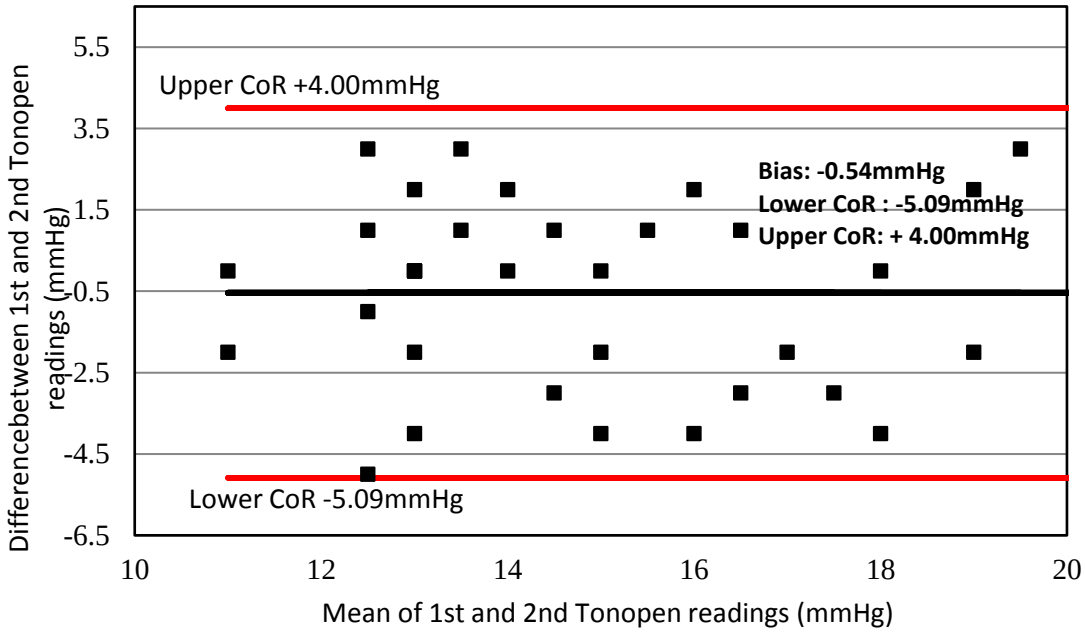


Figure 4.3 Bland-Altman ORA-IOPg Repeatability

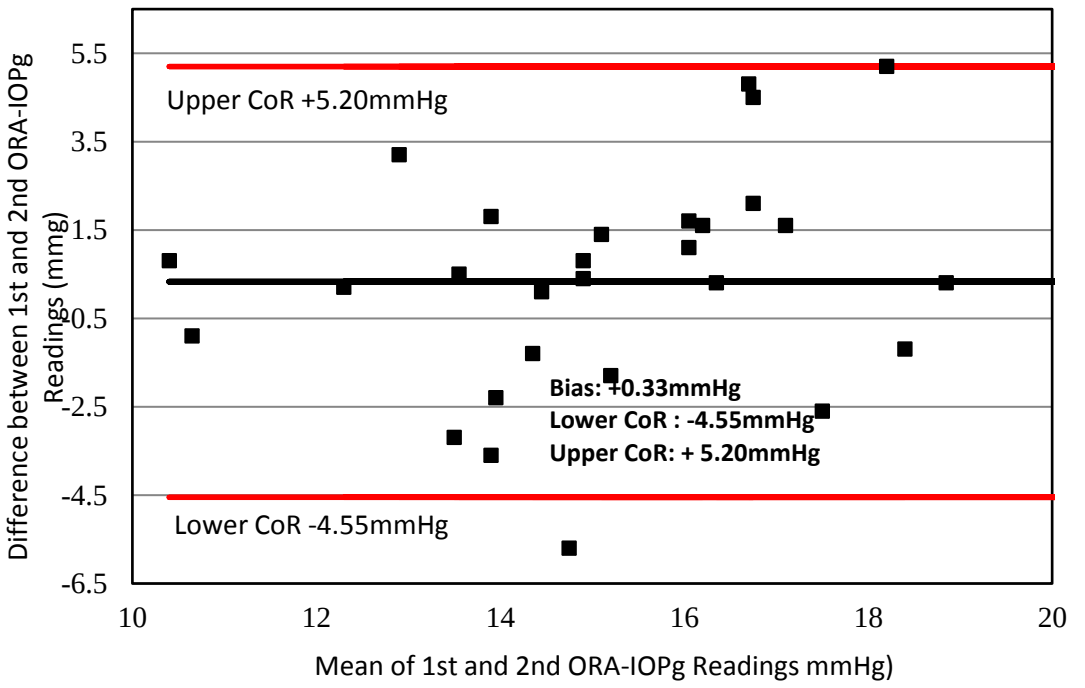


Figure 4.4 Bland-Altman ORA-IOPcc Repeatability

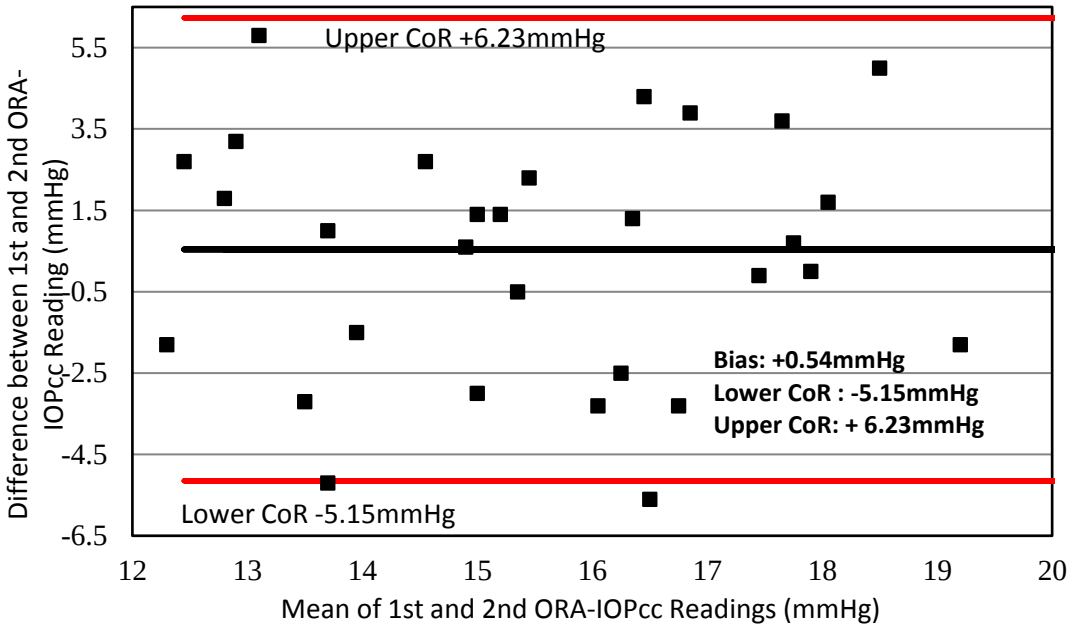


Table 4.2 banded the first and second readings of each tonometer according to the magnitude of difference. The automated measure of ORA-IOPcc showed the poorest repeatability with only 57% of second readings falling within ±2mmHg of the first, with 20% of second readings greater than 4mmHg. No differences were greater than ±6mmHg. If only ±3mmHg is considered the results are much closer with Tonopen recording 86% within this band, GAT and ORA-IOPg (83%) and ORA-IOPcc (80%).

Table 4.2 Banding of Differences between 1st and 2nd Tonometer Readings

	GAT	Tonopen	ORA-IOPg	ORA-IOPcc
<3mmHg	26 (74%) .	24 (69%)	26 (74%)	20 (57%)
3 to 4 mmHg	3 (9%)	6 (17%)	3 (9%)	8 (23%)
>4mmHg	6 (17%)	5 (14%)	6 (17%)	7 (20%)

Abbreviations:
GAT Goldmann Applanation Tonometer
ORA-IOPg Goldmann correlated IOP: measure by the ORA
ORA-IOPcc Corneal Compensated IOP: measured by the ORA

Repeatability of ORA-CH, ORA-CRF and Keratometry (Figs 4.5 to 4.7) were better, demonstrating, for the realistic experimental goals, acceptable repeatability.

Figure 4.5: Bland-Altman ORA-CH Repeatability

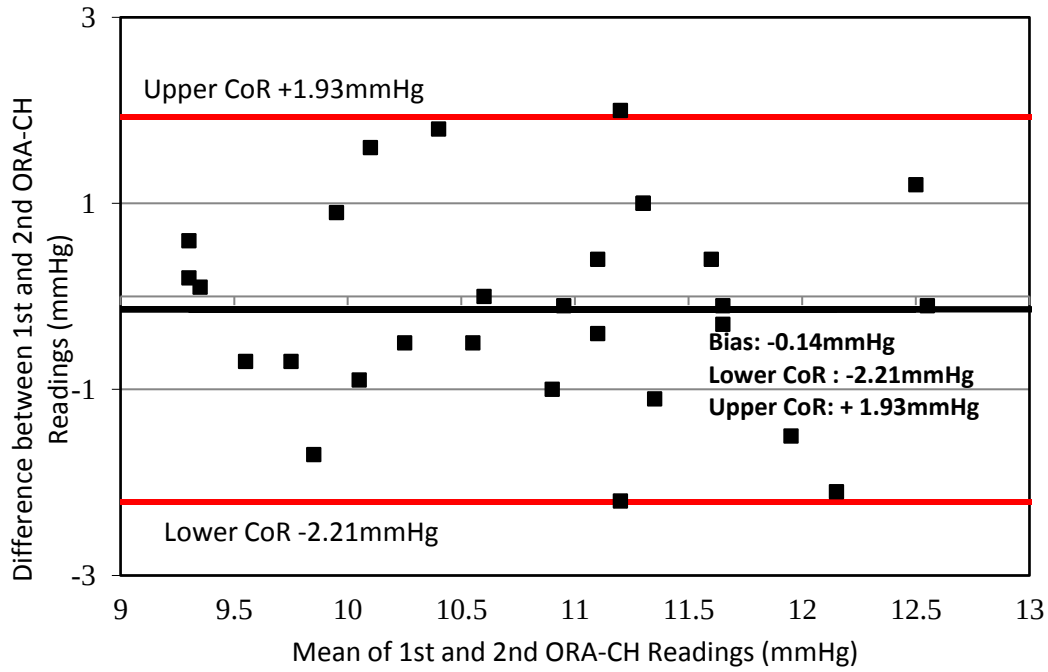


Figure 4.6: ORA-CRF Repeatability

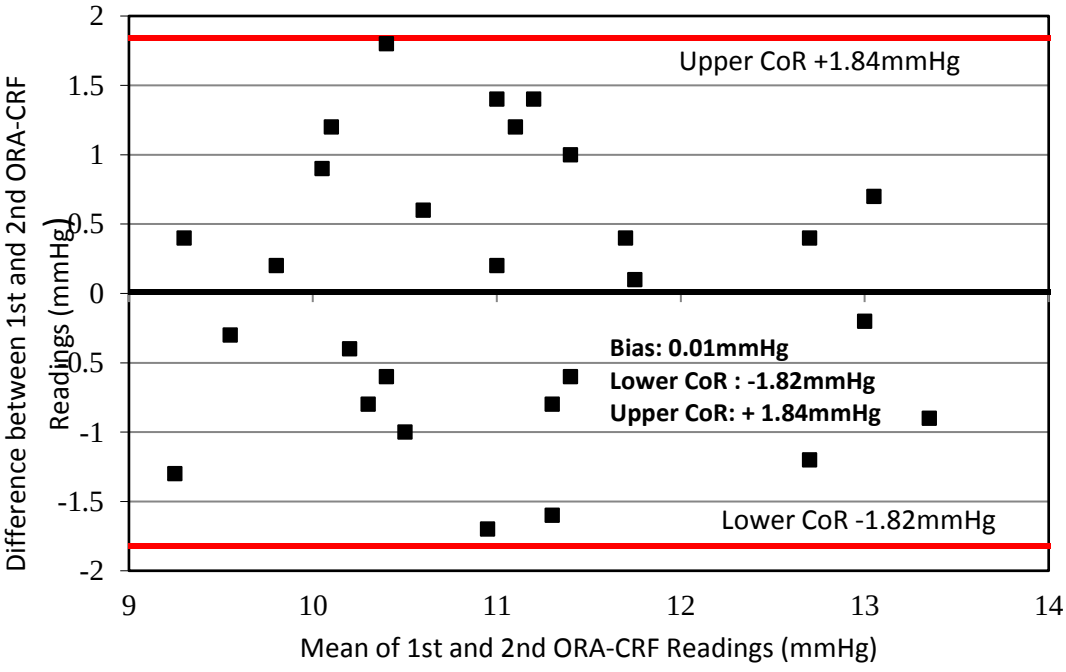
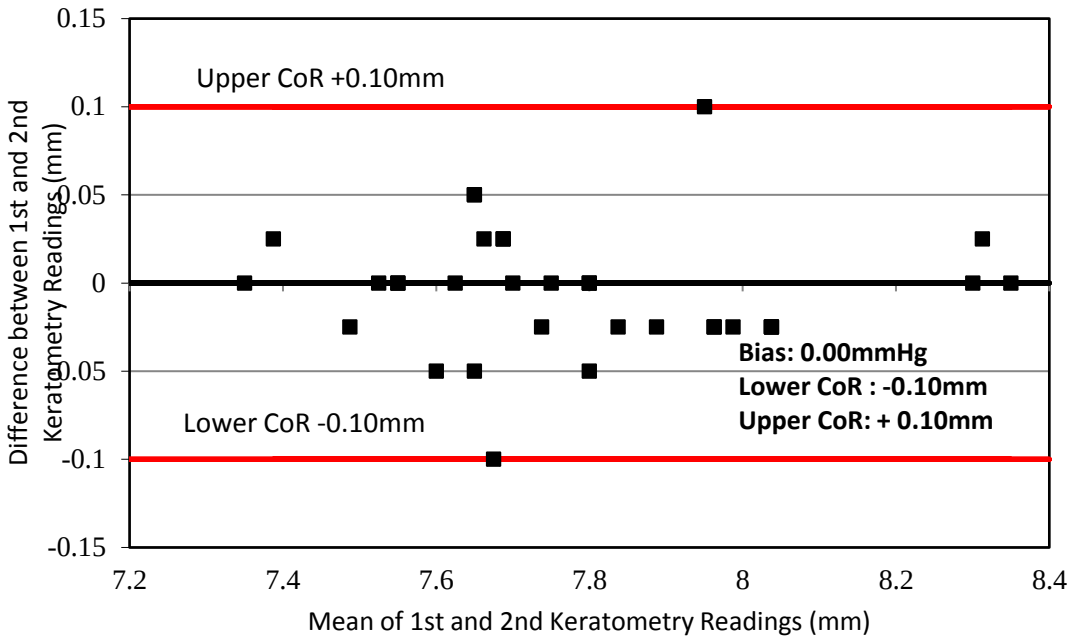


Figure 4.7: Bland-Altman Keratometry Repeatability



Pachymetry however showed quite a large CoR (Upper to Lower bounds of CoR ±18.20µm) (Fig 4.8). Table 4.3 splits the differences between first and second pachymetry readings into 5µm bands; only 54% of second readings were within ±5µm of the first with 26% between ±11 to 25µm.

Figure 4.8: Pachymetry Repeatability

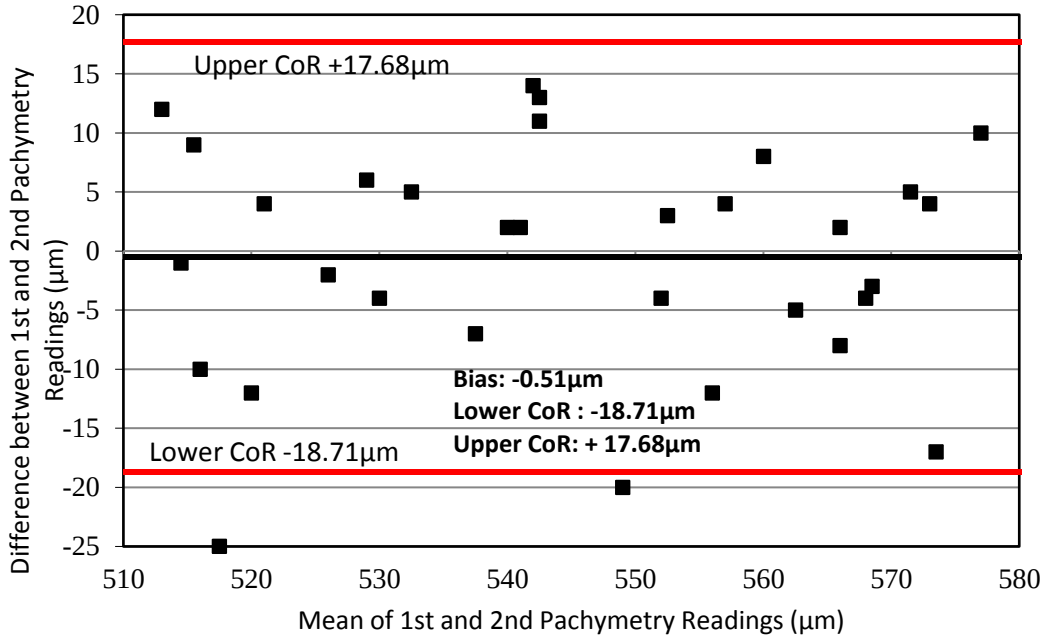


Table 4.3 Banding of Differences between 1st and 2nd Pachymetry Readings

	≤5µm	6 to 10µm	11 to 15µm	16 to 20µm	21 to 25µm
Ultrasound Pachymetry	19 (54%)	7 (20%)	6 (17%)	2 (6%)	1 (3%)

Table 4.4 summarises the Coefficients of Repeatability of all instruments assessed.

Table 4.4 Summary of Repeatability Results of Instruments assessed

	Upper CoR	Lower CoR	Bias1st to 2nd reading	Limits of Repeatability
GAT	+4.63mmHg	-4.86mmHg	-0.11mmHg	±4.73mmHg
Tonopen	+4.00mmHg	-5.09mmHg	-0.54mmHg	±4.55mmHg
ORA-IOPg	+5.20mmHg	-4.55mmHg	+0.33mmg	±4.88mmHg
ORA-IOPcc	+6.23mmHg	-5.15mmHg	+0.54mmHg	±5.69mmHg
ORA-CH	+1.93mmHg	-2.21mmHg	-0.14mmHg	±2.07mmHg
ORA-CRF	+1.84mmHg	-1.82mmHg	+0.01mmHg	±1.83mmHg
Keratometry	+0.10mm	-0.10mm	0.00mm	±0.10mm
Pachymetry	+17.68µm	-18.71µm	-0.51µm	±18.20µm

4.4 Discussion

What constitutes acceptable repeatability? Bland and Altman (1986) plots are a statistical and graphical tool defining, to 95% confidence, the agreement between two measures. Accepting the Coefficients of Repeatability as satisfactory is subjective and based on professional judgement directed by specific clinical requirements. The authors also indicate, ideally, the acceptable limits should be set in advance; reflecting as they do a perceived clinical imperative.

However, the idealised goal and feasibility may be incompatible. Sandner *et al*. (2005), for instance, recommend, for clinically interchangeable use, a limit of agreement of ±2mmHg with GAT is the minimum for acceptance. Since intra-observer variation with GAT is reported as high as -3.8 to +2.4 mmHg (Thorburn 1978), these expectations are unrealistic. Further, as Bland and Altman (1986) state, agreement is contingent on repeatability.

4.4.1 Tonometers

Smedowski *et al.* (2014) suggests a 10% reduction in visual field progression risk and 10% improvement in outcome for patients with OHT with a 1mmHg reduction in IOP. Further, the Clinical Guidelines (NHS North Tyneside, Newcastle and Northumberland 2012 – Appendix 9) for Ocular hypertension, specify, in the absence of other frank signs of glaucoma, if repeated GAT is >21mmHg referral to ophthalmology is indicated; a measure of 20mmHg does not necessitate referral. Clinically 1mmHg may be a critical demarcation directing management.

There are simply too many variables to ensure clinical expectations meet technical reality. Inter and intra observer variability, manufacturing imprecision, machine operational imprecision, theoretical principles and assumptions of tonometer design, objectivity of machine operation and natural physiological and temporal variations all contribute to clinical noise obscuring real variations.

This study specifically used an experienced clinical technician for automated measures and an optometrist for subjective tests, representative of real world conditions. The results therefore reflect machine, average intra-observer and unquantifiable temporal physiological variations.

Coefficients of Repeatability for all tonometers were broad. Tonopen recorded the best CoR of ±4.5mmHg, followed by GAT (±4.7mmHg), ORA-IOPg (±4.9mmHg) and finally ORA-IOPcc (±5.7mmHg).

The automated measure of ORA-IOPcc showed the poorest repeatability with only 57% of second readings falling within ±2mmHg of the first and 20% of second readings greater than 4mmHg (Table 4.2). If a machine design is inherently superior, as GAT was compared to Schiőtz, the introduction of objectivity into the data acquisition process should improve repeatability. The poorest repeatability of ORA-IOPcc, then, could suggest a fundamental flaw in the machine algorithm or operational principles, ORA-IOPg was actually more repeatable. Regardless of the claim ORA-IOPcc is a measure of intraocular pressure less affected by corneal biomechanics and CCT (Luce and Taylor 2006), the poor repeatability must compromise clinical value.

4.4.2 ORA-CH, ORA-CRF and Keratometry

The Coefficients of Repeatability for ORA-CH, ORA-CRF and Keratometry are considered, for the experimental goals, acceptable.

It is difficult to give a quantitative judgement on the ORA metrics since the real clinical implications of these measures remains speculative. The clinically acceptable CoR should reflect a measure's ability to discriminate normal from abnormal. Certainly baselines and agreed normal ranges remain elusive. While Luce and Taylor (2006) found Keratoconus, Fuchs Dystrophy, Primary Open Angle Glaucoma and Normal Tension Glaucoma to demonstrate general variation in ORA-CH and ORA-CRF readings compared to Normals, the overlap was huge making discriminatory decisions difficult. For this thesis disease discrimination was not the goal, rather a general investigation of corneal biomechanics in normal eyes. No advanced expectation of experimental imperatives (Bland and Altman 1986) was considered.

The experimental goals for Keratometry, were realised *post hoc*. For the investigation of an anticipated change in corneal curvature to variations in intracameral IOP (Chapter 2) the accuracy and precision of keratometry were inconsequential as the keratometry scale was recognised as too coarse to detect the subtle changes in corneal radius. In Chapter 5, the scale and repeatability are acceptable for the more dramatic impact of Orthokeratology on corneal curvature.

4.4.3 Ultrasound Pachymetry

Ultrasound Pachymetry did demonstrate a relatively large CoR (±18.20µm) (Fig 4.8); 9% of second readings varied by >15µm and 26% by >10µm (Table 4.3). The coefficient of repeatability, as defined by the British Standards Institute (Bland and Altman 1986) indicates 95% of differences between 1st and 2nd readings to be less than 2 standard deviations, in this case ±18.20µm.

Figure 4.9 shows the prophylactic treatment guidelines for Ocular Hypertensives (NICE 2009b). The central band from 555 to 590µm, only 35µm broad, ensures, given the CoR presented, even a mid-point CCT reading of 572.5µm cannot be assumed to give a true positive result.

Figure 4.9 NICE Recommendations for the Prophylactic Treatment of Ocular Hypertensives (NICE 2009b).

The data was not collected under idealised test conditions. The second measure was diurnally matched to the first, within one hour, but the interval between measures varied according to patient availability with an average of 36.5 days (±19.6), ranging from 4 to 76 days. Variation would logically reflect, not only machine and operator variability, but also natural physiological and temporal variations. This is still a measure of repeatability; reflecting routine clinical practice. Petrie and Sabin (2009) indicate repeatability refers to

a single observer repeating measures under identical conditions. The time between measures is not stipulated. Reproducibility assesses if different instruments or different observers produce identical results.

Shildkrot *et al.* (2005) found repeat CCT measurements to vary by 20µm in 20% of cases and 40µm in 5%. They affirm this level of variability could impact glaucoma management. Suzuki *et al.* (2003) reported significantly lower repeatability variability of 4.88±2.91. However the measurements were taken by a single experienced clinician within 5 minutes of each other. Shildkrot *et al*. (2005) indicate, design of reliability studies tend to positively bias results due to the stringent controls not reflective of routine clinical practice. Brandt et al. (2001), taking repeat measures over a much longer period (384.7±75.2 days) found poorer overall repeatability of 12.1±17.2µm. Further, with the same operator the variation was improved (7.3±12.3µm) but when multiple operators were involved repeatability dropped (12.8±17.7µm).
Similar to the current study, Shildkrot and colleagues (2005) mimicked routine clinical practice rather than replicating stringent repeatability studies. They concluded the variability reflects, not only reliability of the instrument but variability of CCT over the relevant test/retest period. Physiological variability, while confounding rigorous repeatability studies, more accurately reflects clinical reality and needs to be embraced.

Shildkrot *et al*. (2005), asserts standard practice is to take a single pachymetry reading. Why then, the authors argue, with the co-dependency of CCT and GAT in the current glaucoma management paradigm, is GAT repeatedly checked while a single pachymetry measure is considered adequate? No measurement should be utilised without confirmation. Further, all tests should incorporate an official baseline.

The recommendations of Shildkrot and colleagues (2005) would be to repeat pachymetry. If the measures are within 20µm the mean should be assumed as baseline. If the separation is greater, a third measure is necessary and the median of the three used as an estimate of CCT. However, if associated with a change in IOP, then closer follow-up would be recommended.

4.5 Conclusions

The Coefficients of Repeatability of all tonometers are wide. Real effects may be masked by general noise.

Regardless of the objective nature of the machine operational system, ORA-IOPcc showed the poorest CoR suggesting fundamental problems with the machine algorithm. Confirming suspicions the ORA does not appear a robust replacement for GAT.

The broad Coefficients of Repeatability for pachymetry re-enforce the opinion of Park *et al.* (2012) who impress the necessity of amalgamating all evidence before formulating a clinical management plan, irrespective of CCT.

Chapter 5: The impact of Corneal Flattening via Orthokeratology on GAT and the Ocular Response Analyser. Presenting an Alternative Interpretation of Corneal Hysteresis and Corneal Resistance Factor.

Abstract

Aim: Exaggerated corneal flattening via orthokeratology, with minimal or no change to CCT or microstructural corneal biomechanics, may demonstrate if an ablation effect, in isolation, affects GAT, its' non-contact mimic ORA, as well as the quasi-biomechanical measures of ORA-CH and ORA-CRF. Corneal flattening, in isolation, may also help clarify how the ORA metrics are obtained and how they may relate to global corneal biomechanics, incorporating topography, CCT and microstructure. An alternative interpretation of the relevance and utility of ORA-CH and ORA-CRF is presented.

Results: Despite exaggerated corneal flattening there was no statistical change to tonometry measures pre to post-orthokeratology of the applanation tonometers assessed.

Without affecting microstructural corneal biomechanical properties, corneal flattening induced by orthokeratology profoundly altered the measures of Corneal Hysteresis and Corneal Resistance Factor as measured by the Ocular Response analyser, purportedly *in vivo* measures of corneal biomechanics.

Conclusions: The orthokeratology results pose questions about the interpretation and utility of the ORA biomechanical markers of ORA-CH and ORA-CRF.

The results suggest ORA-CH and ORA-CRF reflect predominantly a response to the modification of corneal curvature. The results highlight the probability the ORA metrics do not reflect microstructural corneal biomechanics in any significant sense, if at all.

Exaggerated corneal shape change via orthokeratology was not found to significantly alter any tonometer readings. The lack of significance could reflect inherent measurement noise.

5.1 Introduction: Applanation

The foundation principle of the 'Imbert-Fick' construct (Imbert 1885, Fick 1888) and applanation tonometry generally (Goldmann and Schmidt 1957) is the creation of a plane surface. Logic impels an artificially flattened surface, post refractive ablation, must affect applanation tonometers. An imaginary corneal surface, perfectly flat, post ablation, must represent the end point of applanation. Neither GAT nor a non-contact equivalent would

need to apply any force at all to supply a reading. Indeed, Shaikh *et al.* (2002) report a single case where IOP with GAT was recorded as 0 (zero) post LASIK; IOP checked via ballottment (palpation) was estimated between 40 and 50mmHg. Can Schmidt's (1959, 1960) statement suggesting corneal curvature variation capable of inducing errors in GAT as rare, remain acceptable, especially with the increasing number of corneal modifications routinely undertaken?

Further, regardless of the Ocular Response Analyser (ORA) using an applanation process calibrated against GAT (Luce 2004, Taylor - personal communication – Appendix 3), Luce and Taylor (2006) propose the ORA measure of corneal compensated IOP (ORA-IOPcc) gives an estimate of IOP unaffected by corneal biomechanics. However, the calculation of ORA-IOPcc was based purely on pre and post LASIK clinical data (Terai *et al.* 2012). While Taylor *et al.* (2013) indicate the measure is adjusted for corneal biomechanics, demonstrating zero correlation to CCT, corneal shape was not a consideration.

Nor was shape considered when defining the proposed biomechanical measures of Corneal Hysteresis (ORA-CH) and Corneal Resistance Factor (ORA-CRF). Luce and Taylor (2006) specifically state ORA-CH could not be correlated to corneal shape, encouraging the investigators to believe they had quantified a totally new parameter.

Yet all ORA measures are anchored on two applanation points. The inward, traditional, measure is taken as the air pressure increases and the normally convex cornea is flattened to a plane surface. Inertia ensures the cornea proceeds into a concave configuration before returning, as the air plenum pressure decreases, through a second applanation point (Luce 2004). Time is the measured variable, IOP is inferred. Appreciation of the applanation process should make corneal shape a self-evident contributor to measurement anomalies for applanation tonometers as well as the biomechanical markers of ORA-CH and ORA-CRF.

Luce and Taylor (2006) propose ORA-CH is a measure of the viscous damping of the cornea while ORA-CRF is a measure of the cumulative effects of both viscous and elastic resistance of the cornea. The authors suggest ORA-CH quantifies biomechanical properties of the cornea; a view often re-cited. However, initially Luce made much more conservative claims of the clinical interpretation of these measures as representing the output of the Reichert ORA under the specific measurement conditions imposed by the ORA (Dupps 2007). The cautionary interpretation of the new metric, Luce and Taylor

(2006) suggest, reflects the limited understanding of what the waveforms actually represent. Luce (2005) further qualified the interpretation of ORA-CH as reflecting aggregate effects of CCT, corneal rigidity, hydration and other undetermined factors. The undetermined factors have not been clarified, although Luce (2005) includes system time delays in the instrument itself as a potential contributor. The term 'rigidity' was not defined by the author either. Biomechanically terms must be defined, 'Modulus of Rigidity' is not synonymous with 'Stiffness', a reflection of 'Young's Modulus of Elasticity'. Claims of a definitive interpretation of the ORA metrics are speculative.

The ORA metrics may reflect a selective interpretation of data significance. Indeed, Luce and Taylor (2006) only consider weakening of the corneal structure, as adjunctive to reduced CCT, to explain the universal reduction in both ORA-CRF and ORA-CH post LASIK. Yet the mechanical behaviour of the cornea, as predicted by biomechanical laws (Whitford *et al.* 2015) reflects not simply tissue microstructure but additionally CCT and topography (Ariza-Gracia *et al.* 2015).

5.1.1 Study Aim

Exaggerated corneal flattening via orthokeratology, with minimal or no change to CCT, may demonstrate if an ablation effect, in isolation, affects GAT, its' non-contact mimic ORA, as well as the quasi-biomechanical measures of ORA-CH and ORA-CRF. Orthokeratology, eliminates the complex, multifaceted alterations to CCT, corneal topography and corneal biomechanics engendered by refractive surgery.

Corneal flattening, in isolation, may also help clarify how the ORA metrics are obtained and how they may relate to global corneal biomechanics, incorporating topography, CCT and microstructure. An alternative interpretation of the relevance and utility of ORA-CH and ORA-CRF is presented.

5.2 Methods

Thirty-five eyes, of thirty-five volunteers, fulfilling the inclusion criteria, were enrolled in the study. The number of eyes was estimated via G Power version 3.1.9.2 using the *a priori* strategy with α = 0.05, power = 0.8 (1-β) and effect size 0.5. Prajapati *et al*. (2010) suggest the effect size should reflect experimental expectations. This sample size estimation matched that of Mark and Mark (2003) who measured GAT along the two principal meridians of astigmatic eyes and reported a strong and very significant shape effect with 30 eyes.

A full description of selection process and inclusion and exclusion criteria is presented in Chapter 4. Average age was 35 (range 12 to 64). The sample included 10 males and 25 females with 29 Caucasians and 6 Asians.

All data was collected at a community optometry clinic in Northumberland UK. Data collection commenced in August 2015 after receiving institutional ethics approval via Aston University and full consent form explained and signed (Appendix 7). The study complied with the tenets of Helsinki.

Tonometers utilised were Goldmann Applanation Tonometer (GAT), Haag-Streit, Bern, Switzerland and the non-contact GAT mimic Ocular Response Analyzer® (ORA), Reichert Ophthalmic Instruments, Buffalo, New York. The ORA records a GAT equivalent reading (ORA-IOPg) and a reading purportedly correcting GAT for CCT (ORA-IOPcc). Corneal Hysteresis (ORA-CH) and Corneal Resistance Factor (ORA-CRF), as measured by the Ocular Response Analyser, were also collated. The modelling principles of the two instruments are synopsised in Chapter 1; GAT (section 1.3 and 1.4) and ORA (section 1.7.3). Keratometry (Rodenstock, Munchen) and ultrasound Pachymeter (PachPen ACUTOME INC) were the final instruments to collect biomechanical data.

Order of measurements were from least invasive as detailed in Chapter 4. All measures, pre and post overnight orthokeratology lens wear, were taken between 9.00 and 11.00am with each individual's measurements matched for time of day.

Orthokeratology data was collected after a single overnight wear. This reflected logistical issues but was considered appropriate for the experimental requirements as dramatic visual improvement has been noted in as little time as 10-15 minutes of lens wear (Sridharan and Swarbrick 2003, Chen *et al*. 2009).

Orthokeratology lenses, EyeDream Boston XO, were ordered empirically via No7 Contact Lens Laboratory Limited using their proprietary algorithm for Orthokeratology linked to the Scout Topographer. The lenses were fitted in the practice by the optometrist the evening before overnight wear. A contact number for emergencies was given to each subject but this was never prevailed upon. Each subject returned the following morning. After checking for lens binding by the optometrist the lens was removed and discarded via the practice sharps bin. Five minutes was allowed before the data collection, using identical order as previously.

5.2.1 Statistical Analysis

Kolmogorov-Smirnov test demonstrated the biomechanical markers, both pre and post orthokeratology, were distributed normally. However the tonometer measures were not normally distributed. Both parametric and non-parametric tests were utilised.

All statistical analyses were performed using SPSS 22.0 (IBM 2014).

The Paired t-Test assessed the Null Hypothesis the difference between pre-OK and post-OK ORA-CH, ORA-CRF, CCT and Corneal Curvature was zero.

Kendall's Tau Correlation evaluated correlation between the biomechanical markers.

Wilcoxon Signed Rank Test estimated if the measure of IOP for each tonometer technique varied pre to post orthokeratology. The Bland-Altman plots of Coefficients of Repeatability, from Chapter 4, were included in the tonometer results to graphically demonstrate inherent variability of the tonometer measures, aiding interpretation of outcomes.

Employed previously in ophthalmic literature (Twa *et al.* 2005, Pancholi 2016, Rushton *et al.* 2016), Decision Tree Analysis (DTA), incorporating Chi-squared Automatic Interaction Detection (CHAID), was favoured over multiple regression analysis for a number of reasons. Firstly it does not necessitate normality (Pancholi 2016). Further, DTA accounts for all variables simultaneously, advantageous in this protocol as global effects are being assessed. The question being asked is whether biomechanical confounders of tonometry are inter-related. Modification of one metric may impact on others. DTA ensures outcome expectancies cannot confound the process.

The outcomes are displayed as a flow chart in a hierarchical form (Pancholi 2016). This highly visual display makes DTA easy to interpret. The researcher must identify the initial dependent variable, in this case tonometer readings, representing the target parameter other variables may affect (Wilkinson 1992). The stepwise CHAID algorithm questions whether this outcome is altered by the independent variables (CCT, Corneal Curvature, ORA-CH and ORA-CRF).

Kass (1980) indicates another strength of CHAID is the built in significance testing. The CHAID algorithm chooses the independent variable having the strongest interaction on the dependent one (Dunstone 2014, Rushton 2015). Twa *et al.* (2015) describe the tree presentation as consisting of nodes specifying a particular attribute of the data with the branches representing a test of each attribute's value. CHAID rejects insignificant cross tabulations ensuring the researcher's attention is drawn to potentially useful subdivisions, very useful for inexperienced researchers (Kass 1980).

Sample size and power calculations are inapplicable with DTA (Pancholi 2016). Regardless, simultaneous multiple hypothesis testing increases the possibility rare events could be interpreted as significant, potentially leading to a Type I error. A Bonferroni adjustment compensates for this risk by adjusting the alpha level for multiple testing (Ritschard 2013). Further splitting ceases when any branching fails to meet the test (Wilkinson 1992). Loh (2015) suggests a weakness of CHAID is the over-conservative nature of the Bonferroni adjustment, however for the sample size available a conservative approach to significance was considered prudent.

5.3 Results

Of the biomechanical parameters considered, only CCT showed no statistically significant change pre to post Orthokeratology (Table 5.1).
This allows the isolation of corneal curvature from CCT, a feature not possible with refractive surgery.

As anticipated corneal curvature was significantly flattened by orthokeratology. The statistical changes in ORA-CH and ORA-CRF are more difficult to explain in biomechanical terms; it seems unlikely they represent true changes in corneal biomechanical microstructure.

Table 5.1 Paired t Test. Mean Difference between Pre-OK and Post-OK: ORA-CH, ORA-CRF, CCT and Corneal Curvature

	Paired Differences (34 degrees of freedom)						
				95% Confidence Interval of the Difference			
	Mean	Std Dev'n	Std Error Mean	Upper	Lower	t	Sig 2 tailed
ORACH(Pre/Post OK)	0.76	1.11	0.19	0.38	1.14	4.08	.000
ORACRF(Pre/Post OK)	0.68	1.07	0.18	0.31	1.05	3.74	.001
CCTus (Pre/Post OK)	0.23	14.11	2.39	-4.62	5.08	0.10	.924
CCave (Pre/Post OK)	-0.15	0.16	.027	-0.20	-0.09	-5.48	.000

Abbreviations:

ORACH	Corneal Hysteresis: measured by the Ocular Response Analyser
ORACRF	Corneal Resistance Factor: measured by the Ocular Response Analyser
CCTus	Central Corneal Thickness: measured by Ultrasound Pachymetry
CCave	Average Spherical Corneal Curvature

Table 5.2 Kendall's Tau Correlation of Biomechanical Markers Pre and Post Orthokeratology.

	CCave..Pre	ORACH..Pre	ORACRF..Pre
CCave..Pre Sig 2 Tailed	1	-0.378* 0.25	-0.484** 0.003
CCTus..Pre Sig 2 Tailed	+0.001 0.997	+0.487** 0.003	+0.533** 0.002
CCave..Post Sig 2 Tailed	1	-0.225 0.194	-0.298 0.082
CCTus..Post Sig 2 Tailed		+0.407* 0.015	+0.515** 0.002

**. Correlation is significant at the 0.01 level (2-tailed). N=35
*. Correlation is significant at the 0.05 level (2-tailed)

Abbreviations:

CCave..Pre	Average Spherical Corneal Curvature Pre Orthokeratology
CCave..Post	Average Spherical Corneal Curvature Post Orthokeratology
CCTus..Pre	Central Corneal Thickness (Ultrasound Pachymetry) Pre Orthokeratology
CCTus..Post	Central Corneal Thickness (Ultrasound Pachymetry) Post Orthokeratology
ORACH..Pre	ORA Corneal Hysteresis Pre Orthokeratology
ORACH..Post	ORA Corneal Hysteresis Post Orthokeratology
ORACRF..Pre	ORA Corneal Resistance Factor Pre Orthokeratology
ORACRF..Post	ORA Corneal Resistance Factor Post Orthokeratology

Prior to manipulating corneal morphology with orthokeratology, ORA-CH and ORA-CRF were positively correlated to CCT. Conversely, as corneal curvature increased (flattens) ORA-CH and ORA-CRF statistically decreased (Table 5.2).

Compared to pre-orthokeratology biomechanical markers, post orthokeratology CCT remained positively correlated to ORA-CH and ORA-CRF while corneal flattening removed any significant correlation between corneal curvature and the two ORA quasi-biomechanical markers.

Contrary to expectations there was no statistical change in tonometry measures pre to post-OK for GAT or ORA (Figures 5.1 to 5.3). The Bland-Altman plots of the Coefficients of Repeatability (CoR), taken from Chapter 4, graphically demonstrate the significant variability in repeatability of all tonometer measures. This must mask subtle alterations.

Figure 5.1 Wilcoxon Signed Rank Test of Agreement between Pre and Post OK GAT measures with Bland Altman graphic of GAT Repeatability from Chapter 4

Related Samples Wilcoxon Signed Rank Test	
Null Hypothesis	**Decision**
Median of difference between PreOK GAT and PostOK GAT equals zero	Accept Null Hypothesis

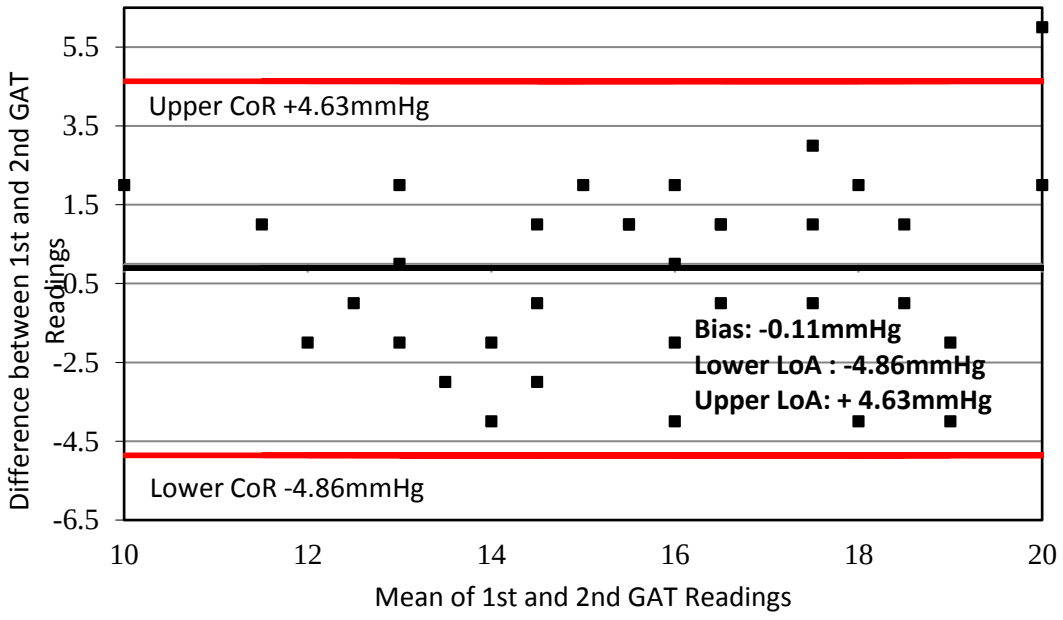


Figure 5.2 Wilcoxon Signed Rank Test of Agreement between Pre and Post OK ORA-IOPg measures with Bland Altman graphic of GAT Repeatability from Chapter 4

Related Samples Wilcoxon Signed Rank Test	
Null Hypothesis	**Decision**
Median of difference between PreOK ORA-IOPg and PostOK ORA-IOPg equals zero	Accept Null Hypothesis

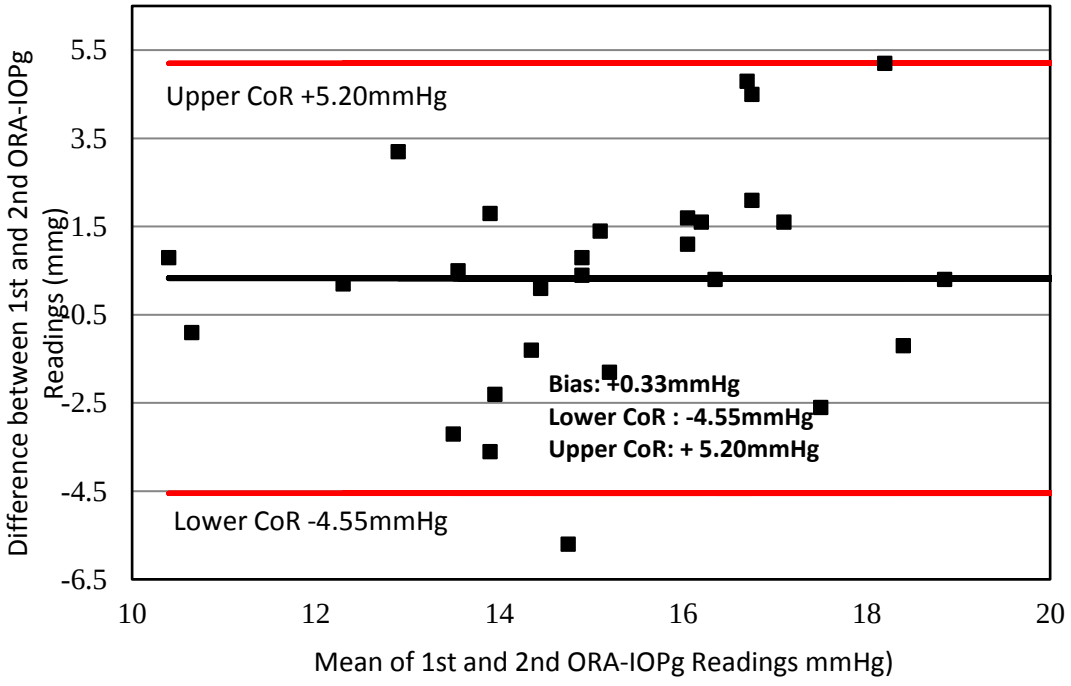
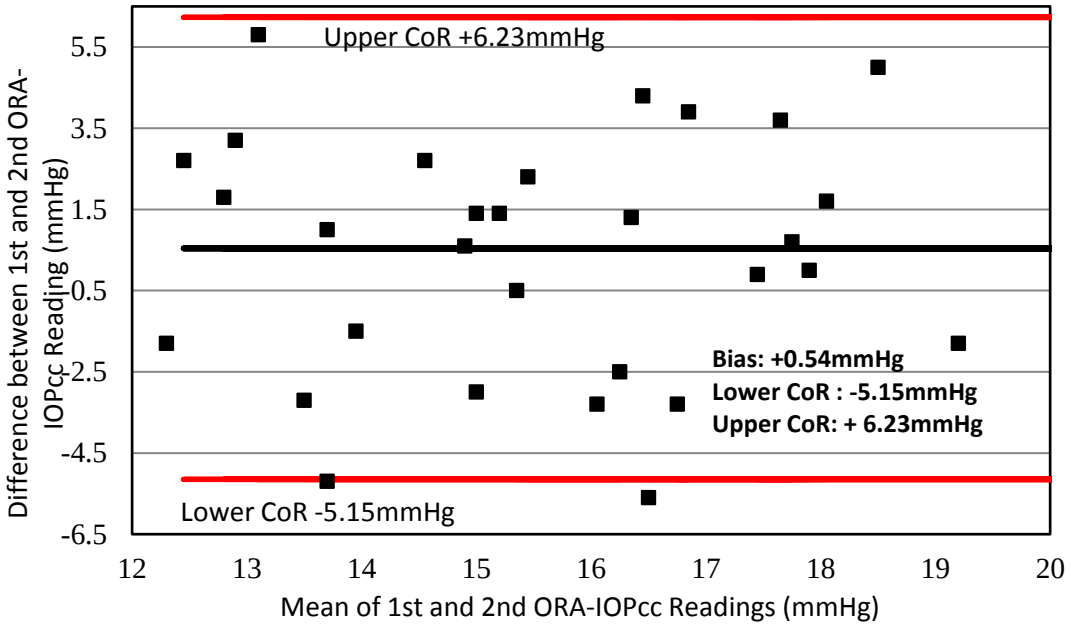


Figure 5.3 Wilcoxon Signed Rank Test of Agreement between Pre and Post OK ORA-IOPcc measures with Bland Altman graphic of GAT Repeatability from Chapter 4

Related Samples Wilcoxon Signed Rank Test	
Null Hypothesis	**Decision**
Median of difference between PreOK ORA-IOPg and PostOK ORA-IOPcc equals zero	Accept Null Hypothesis



Clinically these results support the original GAT assumption, even extreme curvature variation does not affect GAT readings (Goldmann and Schmidt 1957).

Figures 5.4a to 5.6b demonstrate the global impact orthokeratology had on applanation tonometers. The variations between pre and post orthokeratology will be interpreted as the result of significant changes in corneal shape, despite the fact changes in ORA-CH and ORA-CRF were also annotated (Table 5.1). This interpretation is open to dispute; a full rationale is presented in the discussion.

GAT and its design correlate mimic ORA-IOPg, Pre-Orthokeratology, were impacted solely by ORA-CRF (Figures 5.4a and 5.5a).

Post-Orthokeratology the independent variables increased for both GAT and ORA-IOPg with ORA-CRF remaining dominant but with ORA-CH and CCT contributing (Figures 5.4b and 5.5b). Corneal Curvature (CCave..post) did not register on either Decision Tree Analysis, regardless of being the primary modified parameter.

Figure 5.4a Classification Tree – Impact of CCT, CC, ORA-CH and ORA-CRF on Pre-Orthokeratology GAT

Growing Method: CHAID
Dependent Variable: GAT..Pre
Independent Variables: CCTus..Pre, CCave..Pre, ORACRF..Pre, ORACH..Pre
Independent Varibales Included: ORACRF..Pre

Abbreviations
GAT..Pre: GAT pre Orthokeratology
CCTus..Pre: Ultrasound Pachymetry pre Orthokeratology
CCave,,Pre: Average Spherical Corneal Curvature pre Orthokeratology
ORACH..Pre: Corneal Hysteresis pre Orthokeratology
ORACRF..Pre: Corneal Resistance Factor pre Orthokeratology

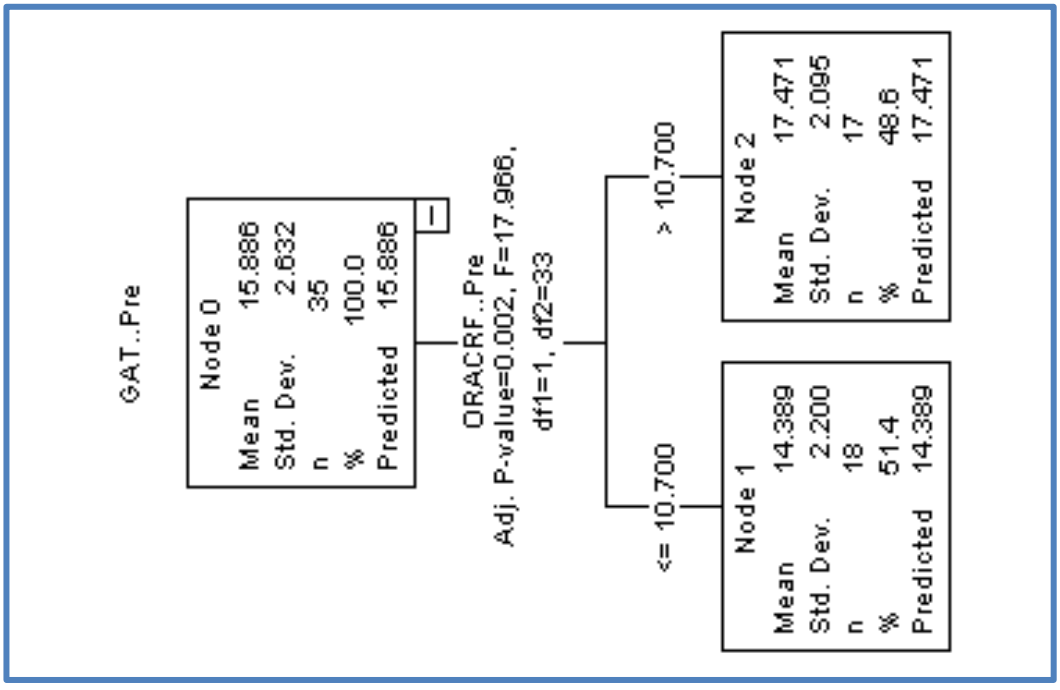


Figure 5.4b Classification Tree – Impact of CCT, CC, ORA-CH and ORA-CRF on Post-Orthokeratology GAT

Growing Method: CHAID

Dependent Variable: GAT..Post

Independent Variables: CCTus..Post, CCave..Post, ORACRF..Post, ORACH..Post

Independent Varibales Included: ORACRF..Post, ORACH..Post, CCTus..Post

Abbreviations
GAT..Post: GAT post Orthokeratology
CCTus..Post: Ultrasound Pachymetry post Orthokeratology
CCave..Post: Average Spherical Corneal Curvature post Orthokeratology
ORACH..Post: Corneal Hysteresis post Orthokeratology
ORACRF..Post: Corneal Resistance Factor post Orthokeratology

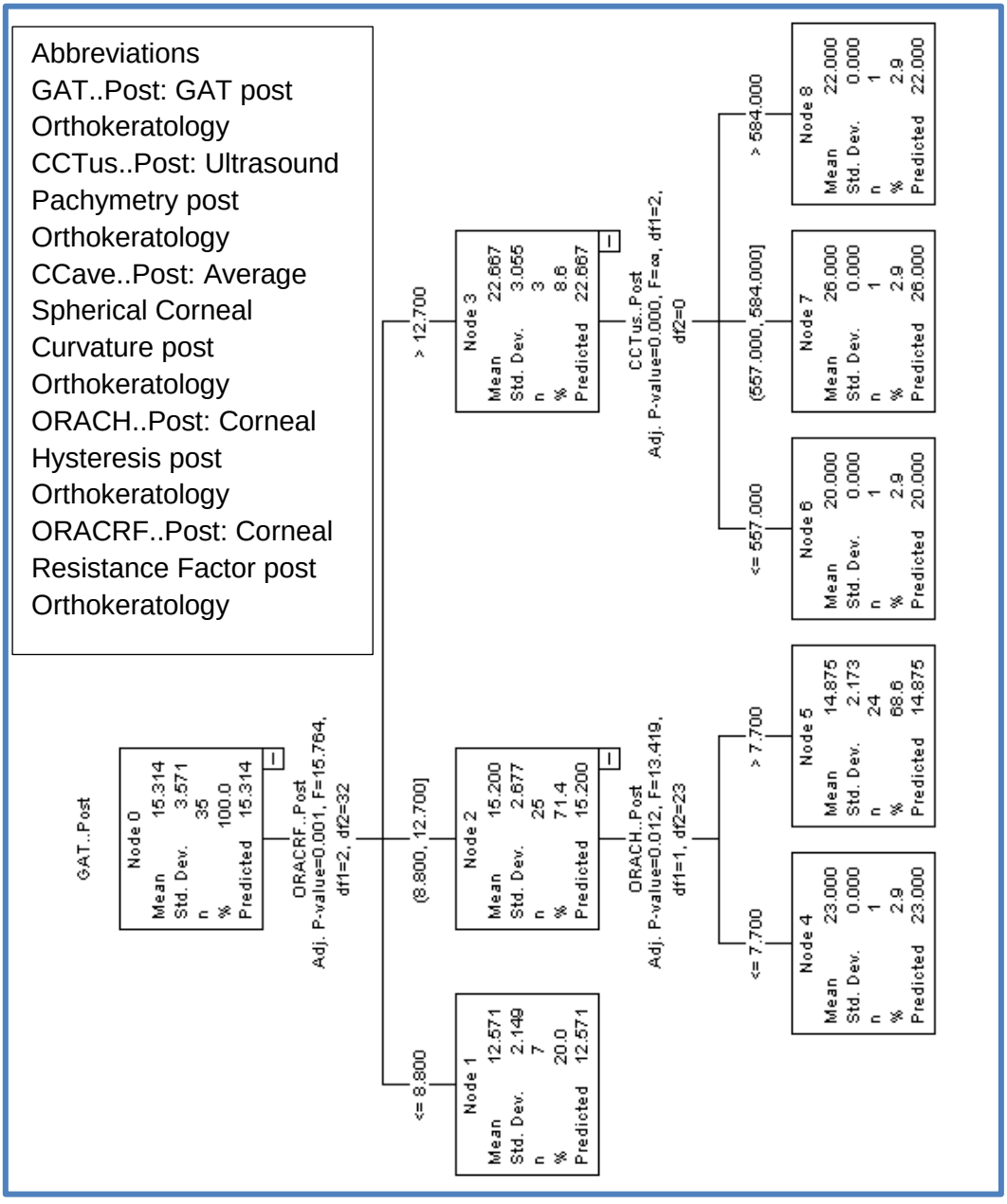


Figure 5.5a Classification Tree – Impact of CCT, CC, ORA-CH and ORA-CRF on Pre-OK ORA-IOPg

Growing Method: CHAID

Dependent Variable: ORAIOPg..Pre

Independent Variables: CCTus..Pre, CCave..Pre, ORACRF..Pre, ORACH..Pre

Independent Varibales Included: ORACRF..Pre

Abbreviations

ORAIOPg..Pre: GAT equivalent ORA IOP pre Orthokeratology
CCTus..Pre: Ultrasound Pachymetry pre Orthokeratology
CCave..Pre: Average Spherical Corneal Curvature pre Orthokeratology
ORACH..Pre: Corneal Hysteresis pre Orthokeratology
ORACRF..Pre: Corneal Resistance Factor pre Orthokeratology

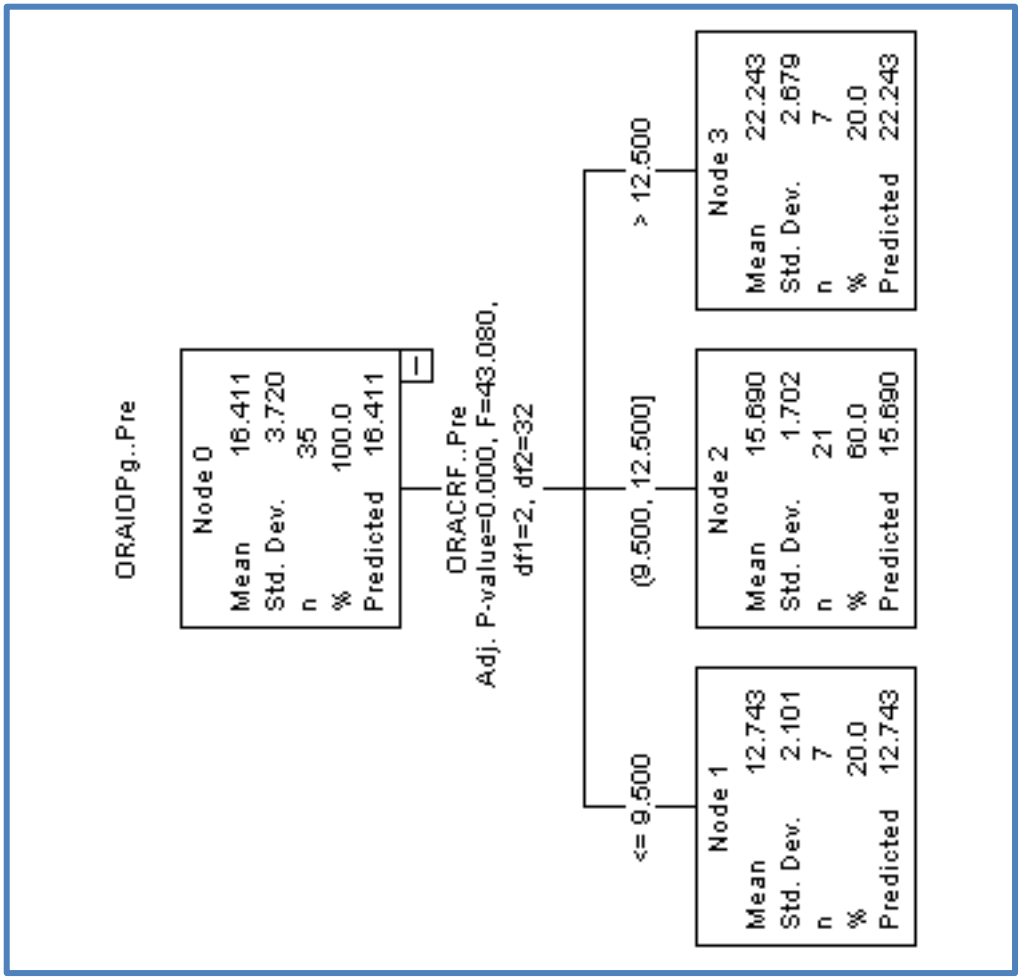


Figure 5.5b Classification Tree – Impact of CCT, CC, ORA-CH and ORA-CRF on Post-OK ORA-IOPg

Growing Method: CHAID

Dependent Variable: ORAIOPg..Post

Independent Variables: CCTus..Post, CCave..Post, ORACRF..Post, ORACH..Post

Independent Varibales Included: ORACRF..Post, ORACH..Post, CCTus..Post

Abbreviations

ORAIOPg..Post: ORA GAT equivalent ORA IOP post Orthokeratology

CCTus..Post: Ultrasound Pachymetry post Orthokeratology

CCave..Post: Average Spherical Corneal Curvature post Orthokeratology

ORACH..Post: Corneal Hysteresis post Orthokeratology

ORACRF..Post: Corneal Resistance Factor post Orthokeratology

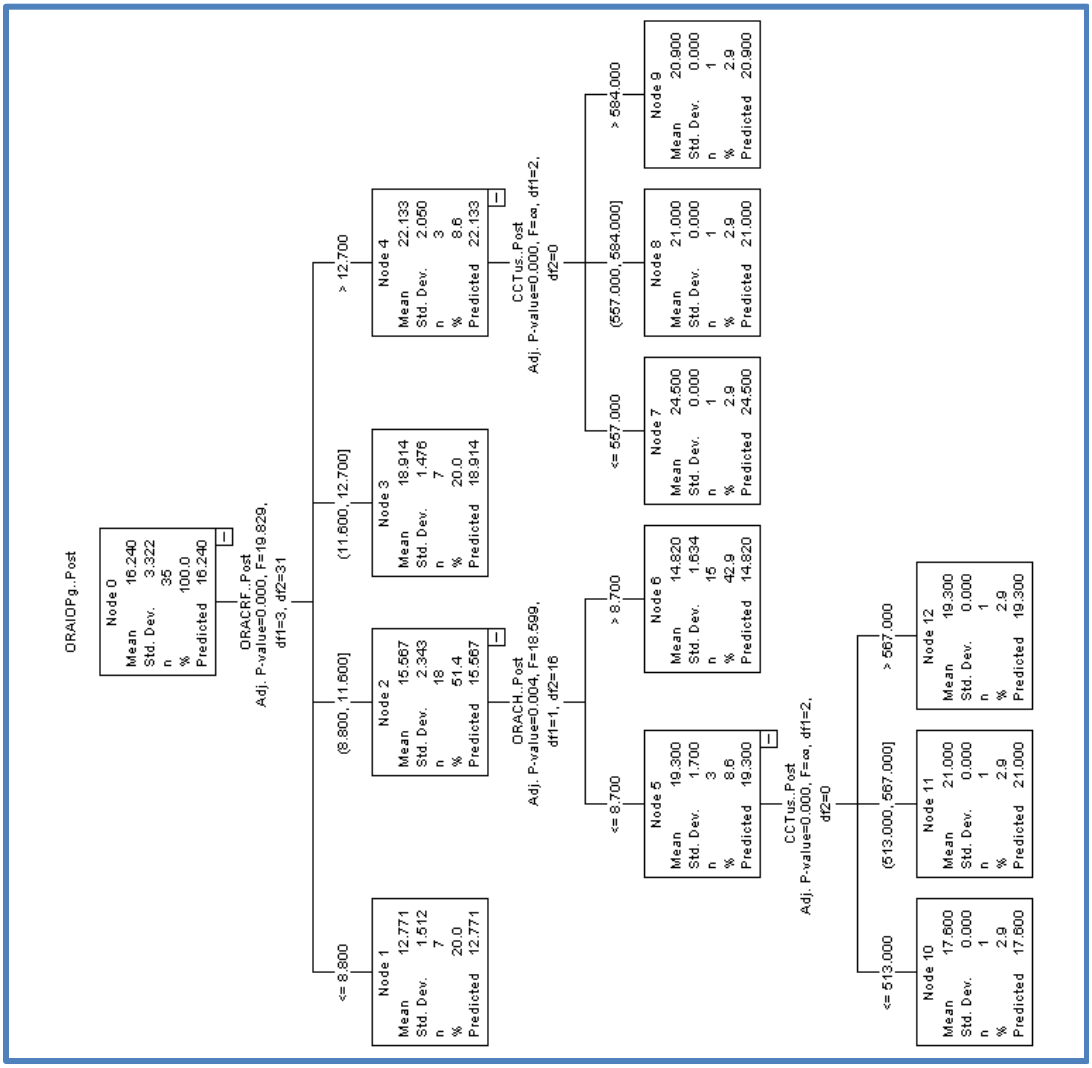


Figure 5.6a Classification Tree – Impact of CCT, CC, ORA-CH and ORA-CRF on Pre-OK ORA-IOPcc

Growing Method: CHAID

Dependent Variable: ORAIOPcc..Pre

Independent Variables: CCTus..Pre, CCave..Pre, ORACRF..Pre, ORACH..Pre

Independent Varibales Included: ORACRF..Pre, ORACH..Pre, CCave..Pre

Abbreviations

ORAIOPcc..Pre: ORA Corneal Compensated IOP pre Orthokeratology

CCTus..Pre: Ultrasound Pachymetry pre Orthokeratology

CCave..Pre: Average Spherical Corneal Curvature pre Orthokeratology

ORACH..Pre: Corneal Hysteresis pre Orthokeratology

ORACRF..Pre: Corneal Resistance Factor pre Orthokeratology

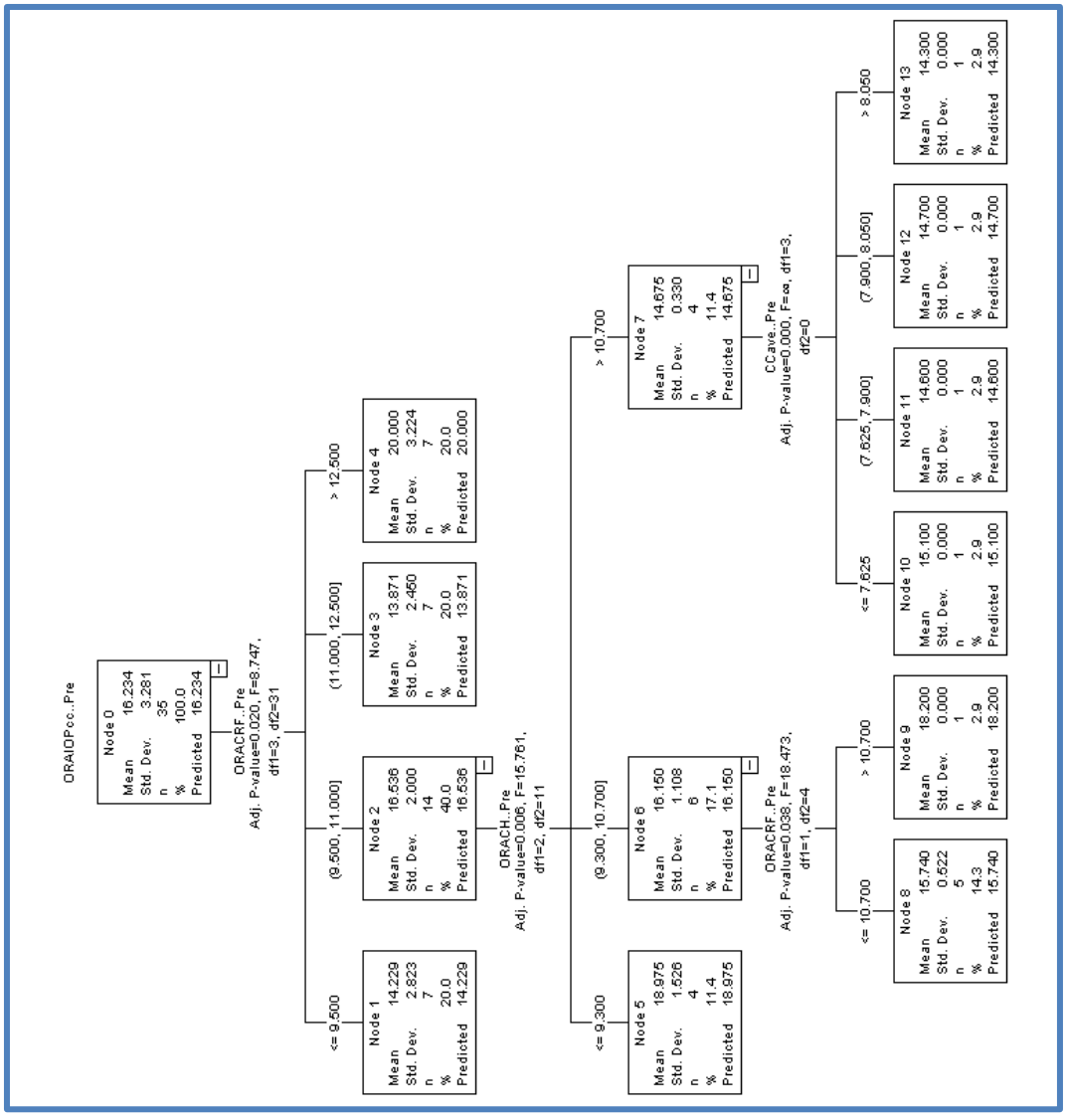
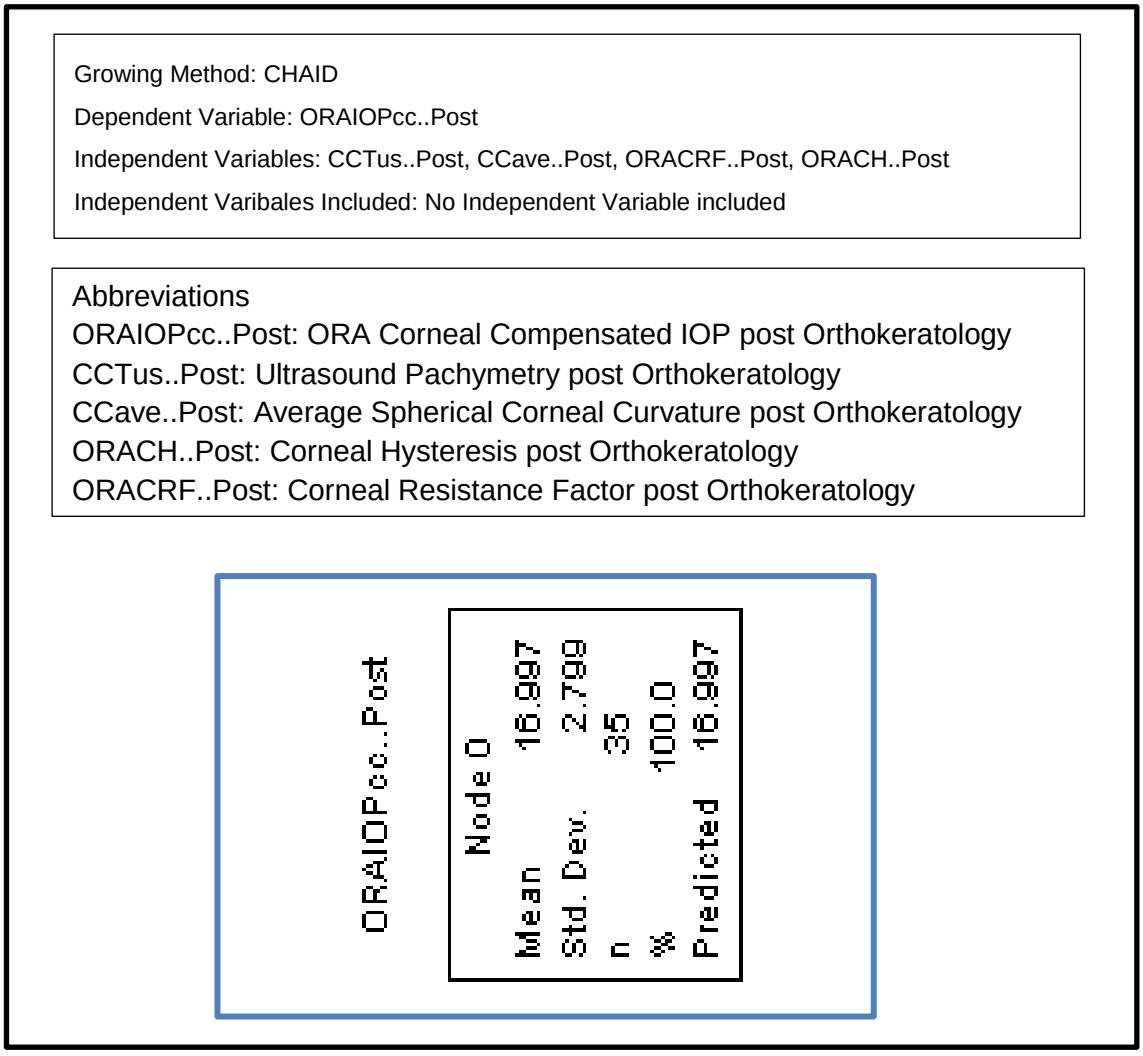


Figure 5.6b Classification Tree – Impact of CCT, CC, ORA-CH and ORA-CRF on Post-OK ORA-IOPcc



Conversely, the ORA IOP estimate purportedly adjusted for corneal properties, ORA-IOPcc, demonstrated a simplification of the DTA pre to post Orthokeratology. Prior to overnight lens wear ORA-IOPcc was impacted by ORA-CRF, ORA-CH and corneal curvature (Figure 5.6a). CCT was not noted as an affecter but rather its correlate, ORA-CRF (Luce and Taylor 2006, Taylor *et al.* 2013). After a single overnight orthokeratology lens wear no independent variables were found (Figure 5.6b).

Assuming independence of parameters is unwise, modification of a single parameter impacts on others.

5.4 Discussion

The orthokeratology results pose more questions about the interpretation and utility of the ORA biomechanical markers of ORA-CH and ORA-CRF than about the initial query of how corneal ablation affects applanation tonometry.

Regardless of the results, it remains an intuitive expectation ablation must impact applanation tonometry. Visually GAT reduced from 15.89 to 15.31mmHg, ORA-IOPg from 16.41 to 16.24mmHg while ORA-IOPcc increased from 16.23 to 17mmHg pre to post orthokeratology, but these were not significant. Tonometer repeatability (Bland Altman Figures 5.1 to 5.3 - GAT ±4.73, ORA-IOPg ±4.88, ORA-IOPcc ±5.69mmHg) was too inconsistent. Reducing the effect size to 0.1 (smallest effect) but maintaining power at 80% estimated a sample size of 779 (G Power version 3.1.9.2). Increasing the power to 0.95 but maintaining α at 0.05 and effect size as large (0.5) predicted a sample size of 42. These experimental modifications may have demonstrated a difference, if one exists. Sources of measurement noise are numerous and cumulative effects appear substantial.

Additionally, the end point of myopia reduction with orthokeratology is not a suitably flattened cornea but a sphericalised one with eccentricity zero (Mountford 1997, Sridharan and Swarbrick 2003). The cornea then, while relatively moulded, is still spherical. The effect of corneal flattening on applanation tonometry, if possible to isolate from the simultaneous alterations to CCT and corneal biomechanics, may be more pronounced with refractive surgery. No papers specifically considering this possibility have been cited, pre-eminence of CCT and biomechanics is always assumed.

Shildkrot *et al.* (2005) indicate a natural circadian variation in CCT with higher CCT noted overnight, returning to normal within 1 to 2 hours upon eye opening. The authors also indicate CCT is noted to change due to subtle contact lens induced corneal oedema. However, the subjects were awake for at least 2 hours prior to attendance for lens removal. Further, no statistical change in CCT was noted, indicating the absence of stromal oedema affecting corneal biomechanics.

Flattening of corneal curvature had no direct impact on IOP measures. Corneal curvature (CCave..post) did not register on any Post-Orthokeratology DTA. Regardless, modification of corneal curvature, interpreted as the primary change despite changes in ORA-CH and ORA-CRF noted (Table 5.1), dramatically altered the Decision Tree Analysis of tonometer affecters.

Figures 5.4a to 5.6b demonstrate the global impact of orthokeratology on applanation tonometers. GAT and its design correlate mimic ORA-IOPg, pre-Orthokeratology, were impacted solely by ORA-CRF (Figures 5.4a and 5.5a). This is in variance with the normal data (Chapter 2) where GAT was affected solely by CCT (Figure 2.2). ORA-IOPg showed complex inter-relationships (Figure 2.3) albeit with ORA-CRF as the primary affecter. As ORA-CRF is effectively defined by CCT (Luce and Taylor 2006) the two could essentially compete for affecter dominance. The different sample size and ranges for the orthokeratology group could explain the replacement of CCT with ORA-CRF.

Post-Orthokeratology the independent variables increased for both GAT and ORA-IOPg with ORA-CRF remaining dominant but with ORA-CH and CCT contributing (Figures 5.4b and 5.5b). This supports the contention corneal biomechanics, a well-accepted confounder of tonometry, needs to be viewed in a continuum, whole eye framework. Assuming independence of parameters is unwise and modification of individual parameters may unintentionally impact on others.

Conversely, ORA-IOPcc demonstrated a simplification of the Decision Tree Analysis pre to post orthokeratology. While impacted by ORA-CRF, ORA-CH and corneal curvature (Figure 5.6a) prior to treatment, after a single overnight orthokeratology lens wear no independent variables were found (Figure 5.6b). *Prima facie*, the complete absence of biomechanical affecters on ORA-IOPcc post orthokeratology supports the contention of Luce and Taylor (2006) and Taylor *et al.* (2013) ORA-IOPcc is a new measure of IOP independent of CCT and biomechanics.

However, the orthokeratology results eliminated the apparent impact of CCT (or ORA-CRF) and corneal biomechanics on ORA-IOPcc, without actually modifying the former nor, it will be argued, the latter.

While Taylor *et al*. (2013) indicates ORA-IOPcc is adjusted for corneal biomechanics, attributing the responses post LASIK to weakening of corneal structure adjunctive to reduced CCT (Luce and Taylor 2006), corneal shape may have been the primary modification sampled. This supports the claim the ORA algorithm was based on incomplete modelling assumptions.

While open to a wide range of interpretations depending on the understanding of what the ORA metrics represent and how they are calculated, the contention presented is all ORA metrics, not simply ORA-IOPcc, reflect predominantly a response to modification of corneal curvature.

Of the biomechanical markers assessed only CCT was statistically unaffected by orthokeratology. Corneal curvature, ORA-CH and ORA-CRF were modified. Regardless, it is postulated as unlikely corneal microstructural biomechanics, predominantly defined by the stroma (Pandolfi and Manganiello 2006, Elsheikh *et a*l. (2008b), could be so significantly modified by 12 hours of orthokeratology. It seems more likely the ORA variations reflect the proprietary data acquisition algorithm based on two applanation episodes. If this is the case the changes induced in the ORA metrics highlight the probability these do not reflect microstructural corneal biomechanics in any significant sense, if at all.

Pandolfi and Manganiello (2006) suggest the stroma constitutes 90% of the corneal thickness, but more importantly this layer defines the mechanical behaviour of the cornea. Certainly all papers cited for corneal modelling solely consider the stroma. The current view indicates the orthokeratology effect represents central epithelial thinning (Alharbi and Swarbrick 2003, Choo *et al.* 2008) involving re-distribution of epithelium from the central to mid-peripheral cornea (Nichols *et al.* 2000), rather than alterations to the stromal bed. Unlike refractive surgery, stromal tissue is not removed during orthokeratology. The biomechanical behaviour of the corneal stroma, virtually incompressible (Liu and Roberts 2005) does not allow for corneal compression. The upshot is a lack of evidence orthokeratology alters stromal or endothelial microstructural biomechanics (Swarbrick 2006).
Schipper *et al*. (1995) state epithelium is flexible but incompressible, as would be expected of a membranous container of non-gaseous fluid. Hence the re-distribution of epithelium during orthokeratology. Initially, compressive force deforms the epithelial cells with elongation of adjacent cells in the mid-periphery suggesting transfer of intracellular contents. Primary roles of the epithelium include a protective barrier function, controlling stromal swelling and absorption of oxygen and nutrition for the avascular cornea (Elsheikh *et al.* 2008b).Yeh *et al.* (2013) did not report reduced epithelial barrier function post orthokeratology, a significant observation explaining the apparent lack of stromal and endothelial biomechanical alteration.

Elsheikh *et al.* (2008b) suggest epithelial stiffness to be appreciably lower than the stroma's and can, for modelling purposes, be ignored.

Viewed in this context, the orthokeratology results suggest unlikely the ORA metrics quantify biomechanical properties of the cornea as Luce and Taylor (2006) claim. Rather they seem to reflect the data acquisition process and do not appear robust surrogates for CCT or unique mechanical metrics. Neither bear any direct relation to classical

biomechanical constitutive functions, particularly Young's Modulus of Elasticity (Dupps 2007, Lau and Pye 2011, Terai *et al*. 2012, Piñero and Alcón 2014). A true hysteretic response cannot be defined by two instantaneous NCT readings (Lau and Pye 2011), an infinite number of individual hysteretic curves could pass through the same two points. The measures are also machine specific, reflecting machine variables and the undisclosed proprietary algorithms. Luce (2005) includes system time delays in the instrument itself as a potential contributor. Chang *et al.* (2010) and Ishii *et al.* (2013) suggest the waveform reflects a whole eye response indicating ORA-CH may be derived from internal structures. These authors describe ORA-CH as a determinant of biometry in the anterior and posterior segments. Further, the corneal response also reflects a bending response of the cornea, with the introduction of shear forces and associated boundary conditions (Ariza-Garcia 2015).

These results actually imply corneal shape a dominant contributor to the ORA metrics. Certainty, the pre-orthokeratology correlation clearly demonstrate, despite not modifying CCT or corneal microstructure, as corneal curvature flattens ORA-CH and ORA-CRF reduce (Table 5.2). Extrapolating the trend lines suggest, as the cornea continues to flatten ORA-CH and ORA-CRF would approach zero, without any change to internal biomechanics. Could a perfectly flat cornea, post ablation, register zero tension as well as zero ORA-CH and ORA-CRF? The results suggest, regardless of manufacturer claims, the probability ORA-CH and ORA-CRF reflect changes in corneal shape, as much if not more, than corneal biomechanics.

5.5 Conclusions

The orthokeratology results pose questions about the interpretation and utility of the ORA biomechanical markers of ORA-CH and ORA-CRF.

All ORA metrics, not simply ORA-IOPcc, appear to reflect predominantly a response to the modification of corneal curvature. The interpretation of data based on pre and post LASIK measurements (Terai *et al.* 2012) made no allowance for changes in corneal curvature suggesting the ORA algorithm is based on incomplete modelling assumptions.

Exaggerated corneal shape change via orthokeratology was not found to significantly alter any tonometer readings. The lack of significance could reflect inherent measurement noise.

Chapter 6: Tear Attraction (N') and the GAT Biomechanical Model

Abstract

Aim: Success of the GAT model is conditional on M' (elasticity of the cornea pushing toward the tonometer) equalling N' (surface tension of the tears attracting the probe). By design definition if this is not the case the model and GAT fail. Despite constituting 50% of the GAT model patches, there is no consensus on tear force magnitude. Values in the literature range from 0.45mmHg to 4.7mmHg. This chapter investigates from original source material, the origins of the primary tear force estimates. Manipulating tear dimensions and concentrations will assess this anchor assumption's magnitude and variability.

Results: No model estimating N' magnitude was accepted. A new model representing tear bridge forces at stable, end point, applanation is presented and tested.

Conclusions: Tear forces are minimal, in the order of only 0.4mmHg. This creates a challenge to explain how, under the GAT model assumptions, the tonometer can underestimate IOP in thin corneas.

6.1 Introduction: The GAT Equation

Fundamental to the GAT model is the equation:

$$IOP_T + M' = IOP_{GAT} + N' \qquad \textbf{(6.1)}\ \text{GAT Model}$$

(Adapted from Goldmann and Schmidt 1957, 1961).

Where:

IOP_T: True Intracameral IOP (albeit slightly raised by ocular volume displacement)

IOP_{GAT}: Pressure recorded by GAT (assumed equivalent to Force/Area) acting on the cornea.

M': Elasticity of the cornea pushing toward the tonometer.

N': Surface tension of the tear fluid pulling the tonometer probe toward the cornea.

The model dictates, for GAT to be accurate, the tear force drawing the applanation body toward the cornea must be equal, but opposite, to corneal resistance opposing applanation: $M' = N'$.

Inadequacies of this model are now well accepted. Current research trends concentrate on corneal biomechanics; central corneal thickness (CCT) and Corneal Hysteresis (CH) and Corneal Resistance Factor (CRF), as measured by the Ocular Response Analyser (ORA). Corneal biomechanics is well established as a confounder of accurate applanation tonometry (Argus 1995, Wilensky 1999, Damji *et al.* 2003, Brandt 2004, Liu and Roberts 2005, Liu and He 2009, Roberts 2014, Śródka 2010, 2011, 2013, Elsheikh *et al.* 2006).

This, of course, is only half the model's assumptions. Whitacre and Stein (1993), citing Schwartz *et al.* (1966), indicate the surface tension of the tears pulling the tonometer toward the cornea is equivalent to 4.15mmHg of pressure. The authors suggest this is an indirect measure of the average cornea's resistance to indentation; only true if this figure and the GAT model equation (6.1) are accepted. Scant research has considered the potential variability tear forces may have on the accuracy of GAT; despite tear forces representing 50% of the GAT model patches. What do tear forces represent, can stability be presumed and indeed is the magnitude necessarily significant?

Liu and Roberts (2005) striving to calculate the impact of corneal biomechanics on IOP measurement generated a working equation for their model. Effectively a replication of the GAT model equation 6.1, Liu and Roberts' formula substituted the symbol 's' for surface tension forces rather than N' and reaffirmed its magnitude to be 4.15mmHg (N'=s=4.15mmHg). Their paper's title did not mention Goldmann Applanation Tonometry (GAT), however it specifically considered biomechanics relating to this instrument; a vital inclusion. Vital because the equation of Goldmann and Schmidt (1959, 1961) represents a phenomenological arrangement specifically applying to GAT rather than a constitutive function of tonometry. Regardless, Glass *et al.* (2008) investigating corneal biomechanics using the non-contact ORA, present Liu and Robert's (2005) equation as a constitutive function. The authors indicate the pressure (s), of magnitude 4.15mmHg, is created on the surface of the cornea by the tear film. The authors reason this is the case because the cornea is convex. Their logic follows when the cornea is concave, during the maximum pressure plenum of the ORA flow, this tear force is reversed and pulls the cornea back toward applanation and habitual convexity. The interpretation reflects a profound misunderstanding of capillary forces, surface tension and scale of impact and indeed defies Newton's three laws of Motion.

Tear interactions with GAT involve a combination of inter-molecular forces; interactions not possible without juxtaposed surfaces.

6.1.1 Tear Bridges

6.1.1.1 Surface Tension

Surface Tension is the property of a liquid surface ensuring it adopts a form minimising its outer surface area (van Honschoten *et al*. 2010), formed exclusively when a sharp

change in density between adjoining phases exists (Bar-Meir 2013). A conventional explanation of surface tension indicates a surface molecule, rather than experiencing equal forces of attraction in every direction within an encapsulating liquid, will only experience forces created by adjacent and internal molecules resulting in stronger attractions at the surface. This molecular force, effectively holding a liquid together, is a 'cohesive' force (Kralchevsky and Nagayama 2001). This cohesive force will necessarily oppose the internal, repulsive, forces between molecules within the bulk liquid generating pressure (Trefethen 1969).

Bar-Meir (2013) indicates the relationship between surface tension and the pressure differential across the interface is based on geometry. A stable geometry necessitates the pressure differential across the interface must be balanced by the surface tension; if this were not the case the surface would expand. The full derivation is simplified to the recognised equation of Young-Laplace (Skσæveland 2012):

$$\Delta P = \sigma(\frac{1}{R_1} + \frac{1}{R_2}) \qquad \textbf{(6.2)}\ \text{Young-Laplace equation}$$

This represents the pressure difference (ΔP) over an interface and applies specifically to a static fluid experiencing no outside forces (Verges *et al.* 2001). While σ is the surface tension of the fluid, the bracketed expression is a purely geometric factor for shape with the two principle radii (Skσæveland 2012). If the denser material was spherical the equation could be simplified to ΔP = 2σ/R (Bar-Meir 2013).

At equilibrium the surface tension neutralises the pressure differential across the interface, ensuring the surface remains uniform and smooth with no force acting normally to the surface (van Honschoten *et al.* 2010). An undisturbed tear layer will be at equilibrium and therefore cannot generate, in isolation, a force opposing IOP. Forces, normal to the surface, result with the introduction of an extra interface into the system (Neeson *et al*. 2014) allowing a liquid meniscus bridging the two surfaces to form (Kim 2012).
The absence of juxtaposed surfaces with non-contact tonometry ensures bridging forces are impossible.

6.1.1.2 Capillary Forces

Capillary 'adhesive' forces bond particles and surfaces due to inter-molecular interactions (Yang *et al.* 2014). Capillary forces are only manifest at extremely small distances; indeed at a molecular level (Finn 1999). In a capillary tube, edge molecules, as well as experiencing surface tension cohesion, encounter 'adhesive', capillary forces, between the liquid and solid surface (Yang *et al.* 2014). The behaviour of a liquid within a capillary tube reflects competition between cohesive and adhesive forces. If the adhesion forces are greater than cohesive the liquid will 'wet' the surface, resulting in spread along the vessel walls in defiance of gravity (Finn 1999, Xu and Fan 2004). The adhesive force between the two surfaces depends on the liquid surface tension and shape of the meniscus (Kim 2012). If, as would be the case with a capillary tube of mercury, the cohesive forces exceed adhesive then the meniscus will be convex and the surface will not wet.

6.1.1.3 Tear Bridge Forces

The forces of attraction considered in the GAT model reflect a combination of molecular interactions commonly termed 'bridging' forces; forces only effective when the surfaces are in very close proximity. Upon GAT contact with the tear layer no additional external forces are added to the system; the microscopic forces between liquid and surface molecules become dominant (Xu and Fan 2004). Kralchevsky and Nagayama (2001) suggests the liquid bridge force is a combination of surface tension and meniscus capillary pressure. This would imply the force acting on the GAT probe is a result of the cohesive surface tension of the meniscus re-establishing equilibrium. The dimensions of the meniscus however will be dependent on the adhesive capillary forces between the tonometer and corneal surfaces, dictating the contact angle of the meniscus.

Tear bridge geometry is clearly focal to the attractive forces between surfaces. Authors considering the potential impact of corneal curvature on GAT do so purely anatomically; the intuitive expectation a greater force would be required to flatten a steeper cornea (Holladay *et al.* 1983, Whitacre and Stein 1993, Kohlhaas *et al*. 1995, Mark and Mark 2003, Liu and Roberts 2005). Corneal curvature, however, helps dictate tear bridge geometry, and hence tear bridge force. Changes in the tear film dimensions may compensate or compound potential errors in GAT measurement created by corneal shape.

6.1.1.4 Can Tear Bridging be Normalised?

The magnitude of 4.15mmHg for tear forces (Liu and Roberts 2005, Glass *et al.* 2008) appears to originate from Schwartz *et al.* (1966) who cautioned on the difficulty in estimating this figure accurately. Indeed, Kralchevsky and Nagayama (2001), Neeson *et al.* (2014) and Goldmann and Schmidt (1957) indicate under specific conditions bridge forces can be attractive, neutral or repulsive.

Certainly, Chihara (2008) does not support the automatic acceptance of an absolute figure for surface tension, reporting ranges quoted in the literature from 1 to 4.67mmHg. The mathematical calculations of Elsheikh *et al.* (2006), Elsheikh and Wang (2007) and Elsheikh *et al.* (2011), suggest a surface tension equivalent of only 0.45mmHg, while Kwon *et al*. (2008) published the highest estimate of 4.7mmHg. Chihara (2008) indicates the precise effects of tear film attraction are not well understood.

An absolute magnitude for this attraction force was not stipulated by Goldmann and Schmidt (1957). Rather, they found experimentally on 10 living eyes manometic readings equalling GAT when the applanation zone diameter was less than 4mm; concluding N'=M' at and below this applanation diameter. However, the authors confess it is unknown whether N'=M' is optimally fulfilled in living patients but, without supporting arguments, did not expect errors to exceed 1mmHg. At odds with this statement the authors also suggest a wide fluorescein ring (2mm) gave readings 2mmHg higher than measurements taken with a ring width of 0.2mm.

Rabinovich *et al.* (2005) illustrate the liquid bridge force between a plane and sphere is dependent on the surface tension(γ), volume (V), embracing angle (α), contact angle (Θ) and also the height (H) of the bridge at its narrowest point (Fig 6.1).

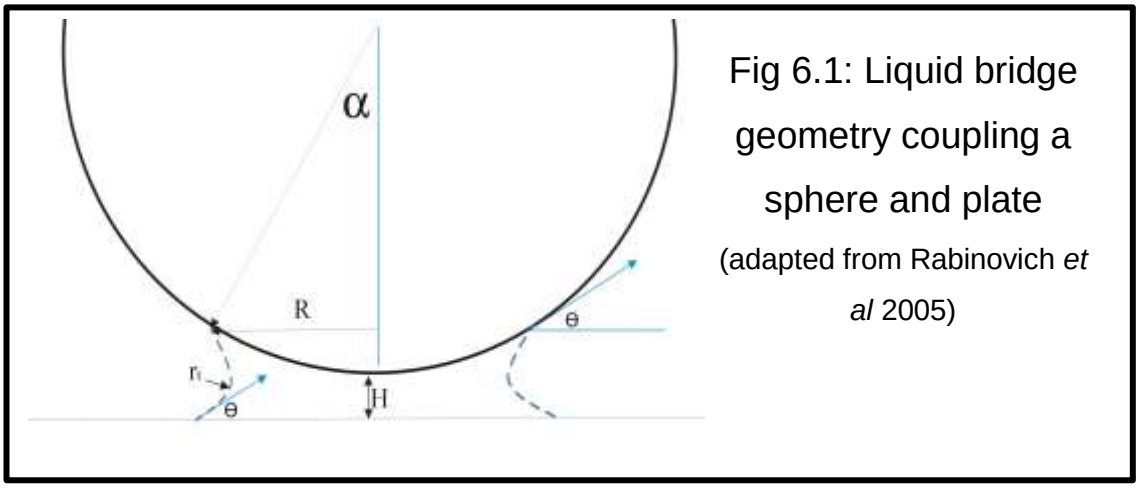


Fig 6.1: Liquid bridge geometry coupling a sphere and plate (adapted from Rabinovich *et al* 2005)

Tear bridge volume is critical to total tear forces (Rabinovich and colleagues 2005), yet is highly variable. McGinnigle *et al.* (2012) suggested tear thickness for normal eyes to be 6µm while dry eye values may be as low as 2µm. Peng *et al.* (2014), Siddique and Braun (2015) and McGinnigle *et al.* (2012) also showed tear evaporation in normal eyes drives tear volume reduction.

Wettability of the corneal and tonometer surfaces will also affect tear forces; a wettable surface will have greater attraction. Goldmann and Schmidt (1957) were very conscious unless the tonometer probe is meticulously maintained a repulsive force could be created. The authors presented a very specific and complicated regimen to clean the probe; a routine not emulated in clinical practice (Whitacre and Stein1993).

Surface tension is also variable. The surface tension constant for pure water is approximately 0.0728N/m (Nagyová and Tiffany 1999, Elsheikh *et al*. 2006). Puinhas *et al.* (2013) indicate, while tears comprise 98.2% water, the remaining 1.8% solids represent over 500 different proteins. These solids reduce the surface tension to approximately 42-46mN/m (≈0.045N/m) (Nagyová and Tiffany 1999), a drop of virtually 40%. If 1.8% solids can reduce the tear surface tension by 40%, natural variations in tear osmolarity, due to intrinsic and extrinsic factors, could significantly affect GAT. Any process increasing tear chemical concentration must reduce the surface tension. Meta-analysis performed by Tomlinson and colleagues (2006) found a range of tear osmolarities in the literature from 283.3 (lowest bound of normal subjects) to 349.5 mOsmol/L (highest bound in ‘dry eye’ patients). Lemp and colleagues (2011) catalogue age, androgen deficiency, environmental stress, blinking abnormalities, autoimmune disease, systemic drugs, ocular surgery, contact lens wear and fluid preservatives as potential drivers for increasing tear osmolarity. Lee *et al.* (2000) also indicate tear secretion and tear film stability is decreased with laser refractive surgery. As well as evaporation concentrating the tear chemistry (Sweeney *et al.* 2013, Peng *et al.* 2014), the inflammatory process increases the concentration of soluble and cellular inflammatory mediators into the tears (Pflugfelder 2004). Finally, surface tension is also dependent on surface polar lipids (Siddique and Braun 2015) and Wang *et al*. (2015) report the level of fatty-acids and non-polarised lipids are reduced in Meibomian Gland Dysfunction.

It would seem unlikely tear bridge dimensions and chemistry can be normalised. Schwartz *et al.* (1966) indicate this is a major limitation of GAT. The surface tension is dependent, not only on its chemical constituents but the surface quality of the tonometer

probe, the amount of fluid on the cornea prior to applanation and the shape of the surfaces defining tear bridge geometry. The true magnitude and variability of tear forces have never been adequately quantified.

6.1.2 Study Aim

The estimate of tear forces presented by Schwartz *et al.* (1966) and Kwon *et al.* (2008) is tenfold larger than estimated by Elsheikh *et al.* (2006), Elsheikh and Wang (2007) and Elsheikh *et al.* (2011). These groups outlined their calculations it would seem valuable to review, compare and critique their methodologies.

Following this process an alternative mathematical model for tear bridge forces will be presented. Once formulated, the potential effects of individual variables, chemical and geometric, on these forces will be estimated and implications for the GAT model considered.

6.2 Calculation of Attraction of the Tear Meniscus on the GAT Probe Presented by Schwartz et al. (1966)

Figure 6.2 reproduces, verbatim (page 624), the derivation Schwartz and colleagues (1966) present supporting the proposition tear forces (P_C) equate to a pressure equivalent of 4.15mmHg. The authors stress this is an approximation as the exact radius of the tear-cornea-tonometer interface is required, not simply the diameter of the GAT probe. A radius of 1.7mm was arbitrarily specified as reasonable for an applanation radius of 1.53mm.

A number of additional approximations are incorporated.

The surface tension constant for tears is assumed, by Schwartz *et al.* (1966), to be 50dyn/cm (0.05N/m), although Braun (2012) suggest 0.046N/m is now the accepted standard for theoretical studies (Units of measure of Surface Tension are outlined in Appendix 10).

Further, Schwartz and colleagues (1966) caution the contact angle of the tears will be modified by the tonometer surface quality and the addition of the anaesthetic and fluorescein. The contact angle at the cornea will also vary according to corneal surface integrity and wettability.

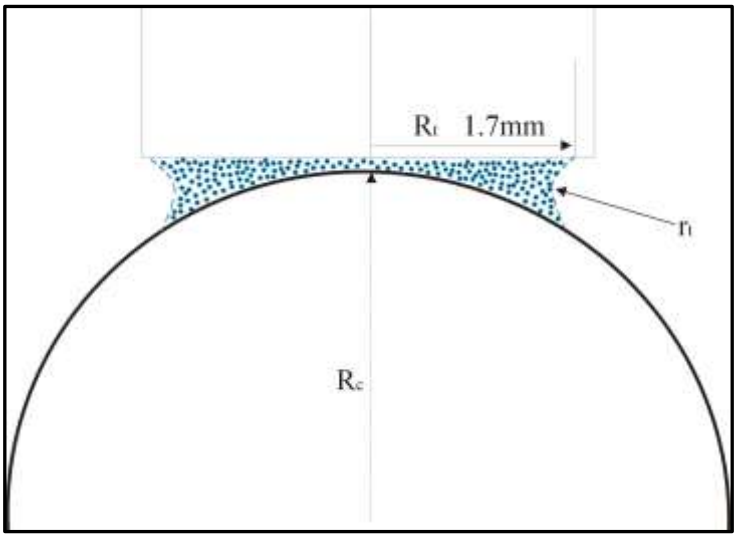


Figure 6.2

Accurate reproduction of the mathematical calculations of Schwartz *et al* (1966- page 624) for Pc: Tear force drawing GAT probe toward the cornea.

The pressure drop across the tear surface is:

$$\Delta p = \gamma \left(-\frac{1}{R_t} + \frac{1}{r_t}\right).$$ Schwartz Equation (86)

Where γ is the surface tension constant of the tears. The contact angle, and hence the radius (r_t) depends in part on the spreading distance R_t. Hence the tonometer surface and anaesthetic are factors on the size of (r_t).

As the tonometer contacts the layer of tears on the cornea, a fluid layer spreads over part of the tonometer surface. If the radius of curvature of the cornea is R_c, then if $R_t^2 << R_c^2$, it follows that:

$$r_t = \frac{1}{4}\frac{R_t^2}{R_c}$$ and hence:

$$P_c = \pi\gamma\left(-\frac{R_c^2}{R_t} + \frac{4R_c^3}{R_t^2}\right)$$ Schwartz Equation (87)

The surface tension constant γ is known to be about 50dyn/cm. So if R_t = 1.7mm (a reasonable choice for an applanation radius of 1.5mm) and R_c = 8mm, then:

$\Delta p = 5.55 \times 10^3$ dyn/cm² = 4.15mmHg.

Hence the force P_c at the contact area for GAT [$A = \pi(1.53)^2 mm^2$] is approximately 0.415 grams.

6.2.1 Derivation of Δp

The Schwartz and colleagues' (1966) estimate for the pressure drop across the tear meniscus/air interface was based on the Young-Laplace equation.

$$\Delta p = \gamma \left(-\frac{1}{R_t} + \frac{1}{r_t}\right). \quad \textbf{(6.3)}$$ Young-Laplace Equation (Schwartz *et al*. 1966)

(Note: The negative sign reflects the concave curve of the tear meniscus)

Young-Laplace equation has two unknowns, Δp, the pressure differential between outside and inside, and r_t, the radius of the tear meniscus at the edge of the wetted zone; as such cannot be solved.

The estimate of r_t appears to have been estimated via simple trigonometry. The derivation is not presented by the authors, however a proposed calculation is presented in Figure 6.3.

To estimate the meniscus curvature, Schwartz *et al.* (1966) assumed the tear meniscus radius of curvature (r_t) to be circular with cornea and GAT contact points tangential to the circle diameter, not a chord. The equation below (Eq 6.4) was presented (Figure 6.2) as an approximation of the tear meniscus radius:

$$r_t \approx \frac{1}{4}\frac{R_t^2}{R_c} \quad \textbf{(6.4)}$$ Tear meniscus radius approximation (Schwartz *et al*. 1966)

Where:
R_t: Spreading distance, approximated to 1.7mm, but dependent on the tear contact angle
R_c: Radius of curvature of the anterior corneal surface. Given a value of 8mm by Schwartz and colleagues (1966) and 7.7mm by Kwon *et al.* (2008).

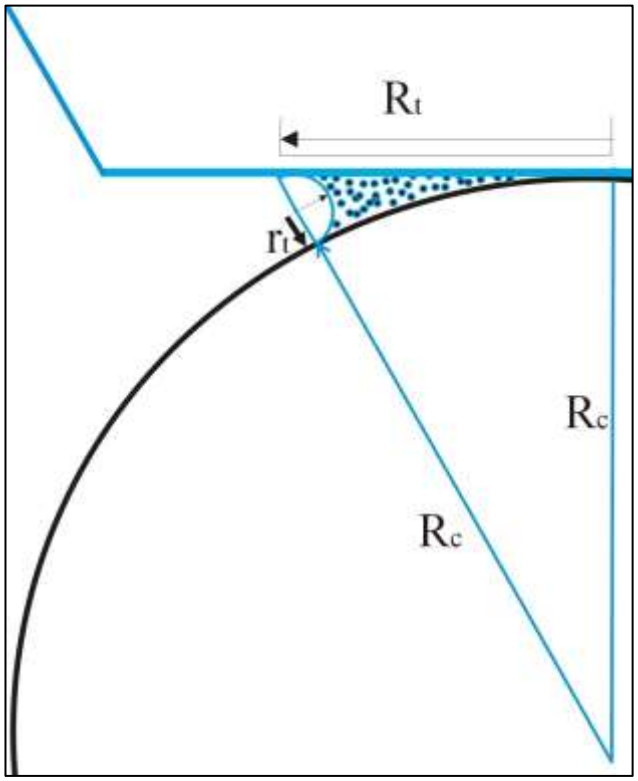


Figure 6.3

Proposed Tear Geometry Trigonometry for calculation of radius of curvature of the tear meniscus (rt) presented by Schwartz *et al* (1966)

Pythagoras theorum for right-angled triangles, 'The square of the hypotenuse is equal to the sum of the squares on the other two sides'.

From the construct above: $(R_c + 2r_t)^2 = R_c^2 + R_t^2$

Equals: $\cancel{R_c^2} + 4\,R_c\,r_t + 4r_t^2 = \cancel{R_c^2} + R_t^2$

Since: $4r_t^2 << R_c\,r_t$ this function can be ignored:

Such: $4\,R_c\,r_t + \cancel{4r_t^2} = R_t^2$

Hence: $4\,R_c\,r_t \approx R_t^2$

Giving: $r_t \approx \frac{1}{4}\,R_t^2 / R_c$

The Schwartz *et al.* (1966) assumption of a corneal radius of curvature of 8mm and tear bridge diameter of 1.7mm yields a radius of the tear meniscus of 0.009cm.

Inserting equation 6.4, approximating the radius of curvature of the tear meniscus, into the Young-Laplace equation presented by Schwartz *et al.* (1966) gives:

$$\Delta p = \gamma \left(-\frac{1}{R_t} + \frac{1}{\frac{1}{4}\frac{(R_t)^2}{R_c}} \right)$$

Simplifying:

$$\Delta p = \gamma \left(-\frac{1}{R_t} + \frac{4R_c}{(R_t)^2} \right)$$

(6.5) Equation for Δp
[Schwartz Equation (87) Plate 6.2]

This equation only gives the pressure differential across the meniscus interface. This does not represent the force (P_c) pulling the tonometer toward the cornea. However, Kwon and co-workers (2008) simply emulated the initial stage, calculated Δp, converted this figure to a pressure, 4.7mmHg, and presented this as the tear force of attraction. Figure 6.4 outlines their calculations and tear force estimation.

Figure 6.4 Calculation of Tear Force presented by Kwon *et al* (2008).

Vitally, Kwon and co-workers used a tear bridge radius of 1.53 (GAT applanation diameter) rather than 1.7mm; a tear meniscus not extending beyond the GAT probe. The authors accepted the estimate of 50dyn/cm for surface tension constant, but assumed a corneal curvature of 7.7mm. Hence:

$$\Delta p = 50 dyn/cm \left(-\frac{1}{0.153} + \frac{4(0.77)}{(0.153)^2} \right)$$

$$= 6371 dyn/cm^2$$

Since there are 10000cm² in 1m² and 1dyn = 10^{-5}N this figure can be converted to Pascals.

$$P = F/A = \frac{6371\text{dyn}}{cm^2} = \frac{0.06371N}{cm^2} = \frac{637.1N}{m^2} = \text{Pa}$$

Thus a tear force created by the tear bridge applying across the entire GAT surface is 637.1Pa (0.6371kPa).

Since 1mmHg = 0.1333kPa (European Committee for Standardisation 2009) this figure equates to:

$$\frac{0.6371\ kPa}{0.1333\ kPa} = 4.7\text{mmHg.}$$

While Kwon and colleagues (2008) did not complete the full process, their calculations are included as they highlight a potential flaw in the mathematical model and geometric assumptions proposed by Schwartz and colleagues. Kwon *et al.* (2008) incorrectly assumed a radius of the tear annulus (R_t) to be 1.53mm, the radius of the GAT contact zone. Stipulating R_t to be only 1.53mm ensured the dimensions sampled for the calculations were under the GAT probe and therefore void of tears. Despite no tear bridge being sampled, the closed nature of the mathematical model yielded a result actually greater than the 4.15mmHg presented by Schwartz and colleagues (1966).

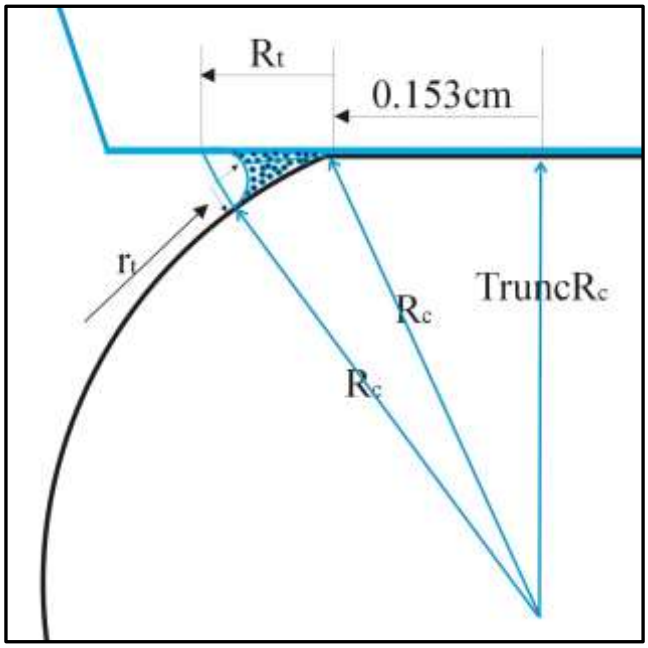


Figure 6.5:

Tear Geometry and Trigonometry for calculation of radius of curvature of the tear meniscus (r_t) at End Point, stable, Tonometry.

STEP 1: To calculate the truncated dimension from centre of corneal curve to applanated cornea:

Pythagoras: $(\text{Trunc}R_c)^2 + (0.153)^2 = R_c^2$

Hence: $\text{Trunc}R_c = \sqrt{(R_c^2 - (0.153)^2)}$

STEP 2: To calculate radius of tear meniscus (r_t), insert result for TruncRc in a modified Schwartz *et al* (1966) Pythagorean Triangle (Hypotenuse ($R_c + 2r_t$):

$$(R_c + 2r_t)^2 = (\text{Trunc}R_c)^2 + (R_t + 0.153)^2$$

$$(R_c + 2r_t) = \sqrt{[(\text{Trunc}R_c)^2 + (R_t + 0.153)^2]}$$

$$(r_t) = \{\sqrt{[(\text{Trunc}R_c)^2 + (R_t + 0.153)^2]} - R_c\}/2$$

The critical impact of tear bridge geometry and volume can be demonstrated by comparing the approximation of tear meniscus radius (r_t) presented by Schwartz *et al.* (1966) (Figures 6.2, 6.3) with that proposed in Figure 6.5. The trigonometry of Schwartz *et al.* (1966) represents a state of flux as the GAT probe is drawn toward the cornea. The two step trigonometry outlined in Figure 6.5 estimates the tear meniscus curvature when the GAT probe has applanated the cornea to a radius of 1.53mm with all lacrimal fluid pushed beyond the contact zone (Amdur 1960).

The tear annulus, beyond the GAT is the critical bridging force geometry of the GAT model. Inserting Schwartz and colleagues' estimate of corneal curvature (8mm) and radius from the centre of the GAT probe to the edge of the tear annulus (1.7mm) into the calculation in Figure 6.5 yields a radius of curvature of the tear meniscus of only 0.0017cm rather than the 0.009cm using the Schwartz *et al*. trigonometry in Figure 6.3.

A tear meniscus radius of 0.0017cm yields a Δp of 29138dyn/cm while the Schwartz *et al.* (1966) approximation for r_t of 0.009 yields a 5342dyn/cm. The smaller radius predicted at end point GAT predicts a 5.5x larger pressure differential across the meniscus interface with an equivalent impact on the estimation of tear forces. As predicted by Young-Laplace, a vessel with smaller radii will have greater pressure differential than a larger diameter container. Extrapolating, this model would predict the minimal tear meniscus in a pathologically dry eye would have greater pull on the GAT probe. A situation counterintuitive and reflects the fact the Young-Laplace equation only applies to very simple geometric forms with two radii.

6.2.2 Derivation of P_c

The actual equation, presented by Schwartz *et al.* (1966) calculating the tear force (P_c), projected over the entire surface of the GAT probe, is presented as:

$$Pc = \pi\gamma\left(-\frac{R_c^2}{R_t} + \frac{4R_c^3}{R_t^2}\right)$$

(6.6) Force of Tear attraction on the GAT probe presented by Schwartz *et al.* (1966) (Equation 87 – Figure 6.2)

However, a comprehensive derivation of this final equation is not presented (Figure 6.2); its logic is not apparent.

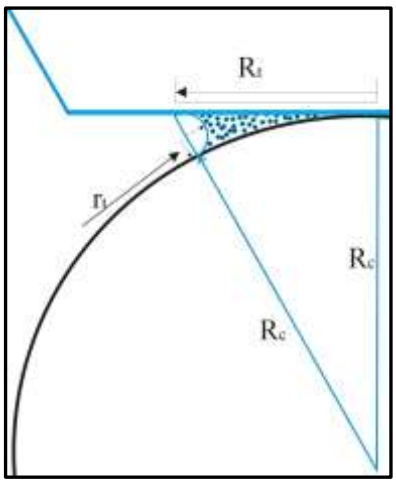


Figure 6.6:

Proposed derivation of equation 6.6 (Schwartz *et al.* 1966 eq 87: Figure 6.2)

$$\Delta p = \gamma \left(-\frac{1}{R_t} + \frac{4R_c}{(R_t)^2} \right)$$

Equation 6.6 Equation for Δp [Schwartz *et al*. Figure 6.2]

DERIVATION#1 Workings to achieve Schwartz *et al*. equation for P_c (Eq 6.6 and Schwartz *et al*. eq. 87 in Figure 6.2):

Area of a Circle to calculate area over which force is applied πr^2

However radius incorporated is R_c (radius of curvature of the cornea) rather than R_t (radius of the Tear Bridge):

Multiplying Equation 7.6 by the area of a circle: $\text{Area} = \pi(R_c)^2$ gives:

$$P_c = \pi(R_c)^2 \gamma\left(-\frac{1}{R_t} + \frac{4R_c}{(R_t)^2} \right)$$

Simplifying: $$P_c = \pi\gamma\left(-\frac{(R_c)^2}{R_t} + \frac{4(R_c)^3}{(R_t)^2} \right)$$

DERIVATION#2 A more appropriate calculation would utilise R_t rather than R_c. Area of Total Tear Bridge Circle – $\pi(R_t)^2$

$$P_c = \pi(R_t)^2 \gamma\left(-\frac{1}{R_t} + \frac{4R_c}{(R_t)^2} \right)$$

$$P_c = \pi\gamma\left(-\frac{(R_t)^2}{R_t} + \frac{4(R_t)^2 R_c}{(R_t)^2} \right)$$

$$P_c = \pi\gamma\left(-R_t + 4R_c \right)$$

The equation for P_c can be derived, as in Figure 6.6 (DERIVATION#1), however the rationale for incorporating R_c (Radius of curvature of the cornea) is not evident. The area over which the force is applied would need either the radius of the GAT probe (1.53mm) or the radius of the tear bridge (R_t = 1.7mm) rather than the radius of the cornea (R_c). A more plausible equation utilising R_t (DERIVATION#2) is also presented.
The figure of 4.15mmHg as representing attractive force of the tear meniscus is based on a flawed derivation.

6.2.3 Tear Attraction at GAT Equilibrium: Calculation Presented by Elsheikh *et al.* (2006) and Elsheikh and Wang (2007)

Contrasting to the calculations of Schwartz *et al.* (1966), Elsheikh and co-workers (2006, 2007) specifically considered the tear forces on the GAT probe perimeter at end-point, stable, applanation. The tear force was recognised to apply only at the circumference of the GAT probe with a radius of 1.53mm.

The surface tension of tears was assumed 0.0455N/m (45.5dym/cm) rather than 50 dyn/cm assumed by Schwartz *et al.* (1966). The researchers explain the surface tension acts along the circumference of the applanation body, although the film does not appear to be imbued with volume beyond the probe circumference.

$$\text{Circumference of a circle} = 2\pi r$$

$$2 \times \pi \times 0.153\text{cm} = 0.96\text{cm}.$$

The tear film equivalent force, along this circumference, is assumed to approximate the tear film surface tension (0.045N/m, or 45dyn/cm) multiplied by the GAT circumference and divided by the area of the GAT probe.

$$45.5\text{dyn/cm} \times 0.96\text{cm} = 43.68\text{dyn}$$

To convert to a pressure reading this force must be divided by the area of the GAT probe.

$$A=\pi r^2 = 0.0735cm^2$$

$$P=F/A = \frac{43.68dyn}{0.0735cm^2} = 594dyn/cm^2$$

Since there are $10000cm^2$ in $1m^2$ and 1dyn = 10^{-5}N this figure can be converted to Pascals.

$$P = F/A = \frac{594\text{dyn}}{cm^2} = \frac{0.00594N}{cm^2} = \frac{59.4N}{m^2} = Pa$$

Thus a tear force created by the thin circumferential meniscus applying across the entire GAT surface is 59.4Pa (0.059kPa).

Since 1mmHg = 0.1333kPa (European Committee for Standardisation 2009) this figure equates to:

$$\frac{0.059\ kPa}{0.1333\ kPa} = 0.45mmHg.$$

This figure is tenfold lower than the estimate suggested by Schwartz *et al.* (1966) or Kwon *et al*. (2008). However, these calculations completely ignore tear volume. A surface tension force, without defining tear bridge volume and associated meniscus height and radius of curvature, reflects an overly simplistic mathematical model. Tear bridging forces must incorporate both surface tension of the meniscus (Chen *et al.* 2011) and Laplace pressure within the bridge (Xu and Fan 2004).

6.3 Proposed Equation for Combined Tear Bridge Attraction at GAT Applanation Equilibrium

The Young-Laplace equation simply defines the pressure differential across an interface between two phases, the pressure differential being balanced by the surface tension. A liquid sphere with the capillary forces encapsulating a denser liquid, ensures the smaller the radius of curvature of the envelope the higher the pressure differential. The geometry

reflected by the Young-Laplace equation is not adequate to model the complex tear bridge annulus representing end point GAT.

Chen *et al*. (2011) and van Honschoten *et al*. (2010) indicate total bridge force will be a combination of hydrostatic pressure, described by van Honschoten and colleagues as negative Laplace pressure, and the surface tension around the circumference. Chen *et al.* (2011) combine the two complimentary forces, Surface Tension Force and Hydrostatic Pressure as:

$$\text{Surface Tension Force: } 2\pi(R_t)\gamma \quad \textbf{(6.7)}$$

$$\text{Hydrostatic Pressure: } \pi R_t^2\gamma\left(\frac{1}{r_t} - \frac{1}{R_t}\right) \quad \textbf{(6.8)}$$

Combining:

$$\text{Generic Bridge Force} = [2\pi(R_t)\gamma] + [\pi R_t^2\gamma\left(\frac{1}{r_t} - \frac{1}{R_t}\right)]$$

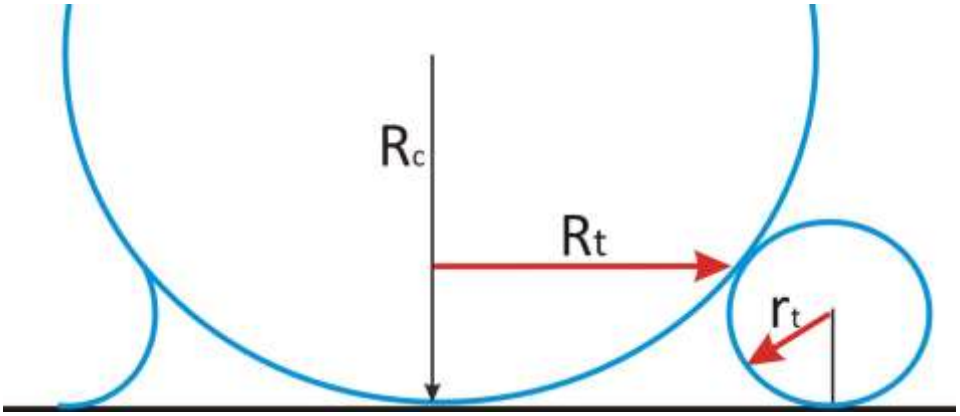
(6.9) Total Tear Bridge Force between Sphere and Plane at point of benign touch (adapted from Chen *et al.* 2011)

Where:

γ: Surface Tension

R_t: Radius of tear bridge at narrowest point

r_t: Radius of curvature of the meniscus



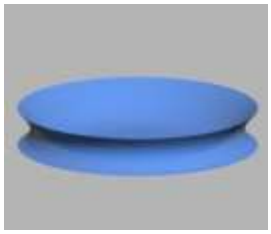
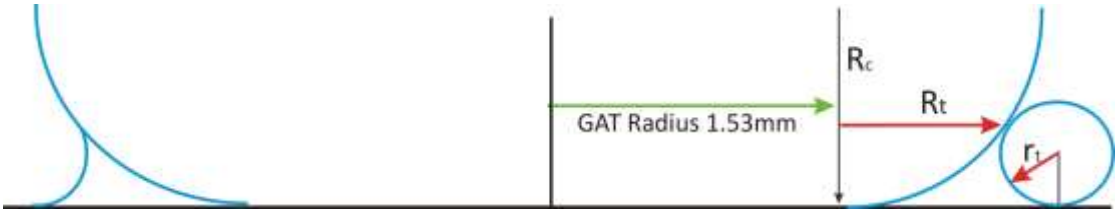


Figure 6.7 Cross Sectional Tear Bridge Geometry, with 3D simulation, between Plane and Curved Surface: Surface Contact at tangent to sphere.

Figure 6.7 represents a tear bridge with symmetry around a single contact point with a circumference of (≈2πRt). It does not replicate the full GAT annulus dimensions. To extend this to the entire GAT tear bridge annulus, as in Figure 6.8, the unaltered cross sectional geometry in Figure 6.7 must be enlarged proportionally to the extended circumference of the total GAT annulus.

Figure 6.8 Cross Sectional Tear Bridge Geometry as in Figure 6.7 but extended to full GAT Tear Bridge Annulus.



Aston University

Illustration removed for copyright restrictions

Equation 6.10 gives the proportional increase required to adjust Equation 6.9 for the full GAT tear annulus:

$$\text{Ratio } \frac{\text{Total Annulus Area at end point applanation (Fig 6.8)}}{Point\ Contact\ Bridge\ Area\ (Fig\ 6.7)} = \frac{(\pi(0.153+R_t)^2)-(\pi(0.153)^2)}{\pi(R_t)^2}$$

Simplifying: $\frac{(0.153+R_t)^2-(0.153)^2}{(R_t)^2}$

(6.10) Ratio: Increase in area of GAT Tear Bridge Annulus versus Area of Point Contact Tear Bridge Area

Combining equations 6.9 and 6.10 gives a proposed mathematical model to estimate the tear bridge forces drawing the GAT probe toward the eye at end point, stable applanation.

$$\text{Total GAT Tear Bridge Force} = \left([2\pi(R_t)\gamma] + [\pi R_t^2\gamma(\frac{1}{r_t} - \frac{1}{R_t})]\right)\text{X}\left(\frac{(0.153+R_t)^2-(0.153)^2}{(R_t)^2}\right)$$

(6.11) Total Tear Bridge Force on GAT

6.4 *Estimation of Tear Bridge Attraction at GAT Applanation Equilibrium*

6.4.1 Normalised Eye

To estimate an approximate order of magnitude for the tear forces within the tear bridge at stable, end point, applanation, tear chemistry and geometry have been normalised. Figure 6.9 demonstrates the tear bridge geometry.

An anterior corneal radius of curvature of 7.8mm reflects a Gullstrand Le-Grand standard eye (Fincham and Freeman 1980). An applanation zone radius of 1.53mm (Goldmann and Schmidt 1957). The tear annulus meniscus is assumed to extend 0.39mm beyond the applanated zone in accordance with the estimate presented by Whitacre and Stein (1993). The radius of curvature of the tear meniscus is calculated using the trigonomic construct outlined in Figure 6.5 and will vary according to the width of the tear annulus, extending from the GAT circumference, and Corneal Curvature.

A surface tension for tears was assumed to be 46mN/m (0.046N/m) as an established standard for theoretical studies (Braun 2012).

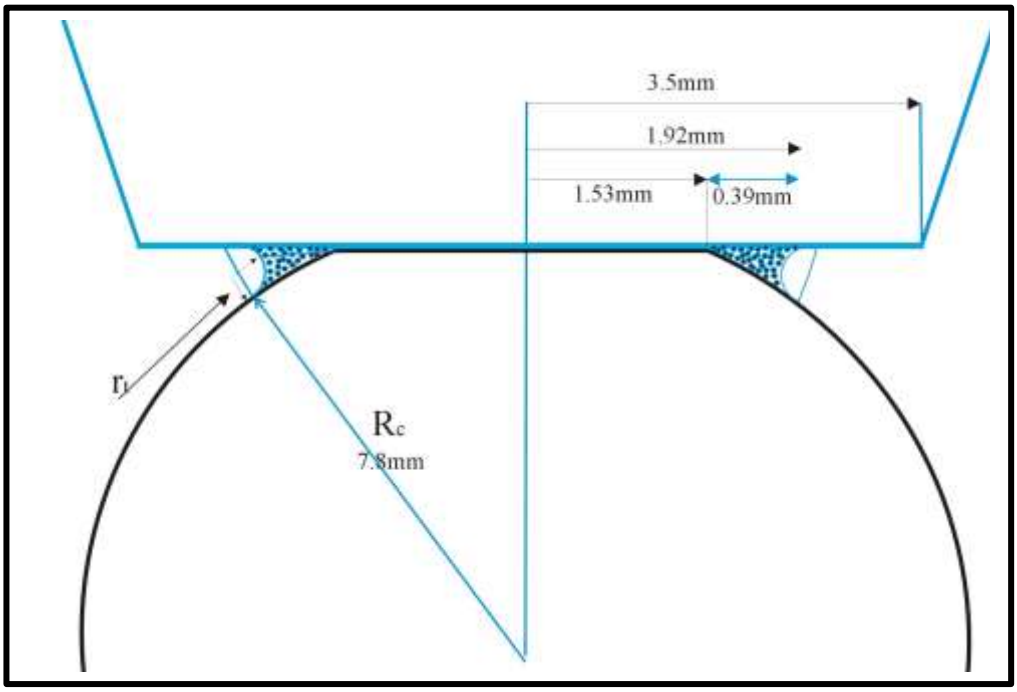


Fig 6.9: Geometry and Dimensions of tear bridge annulus of Normalised Eye at end point GAT

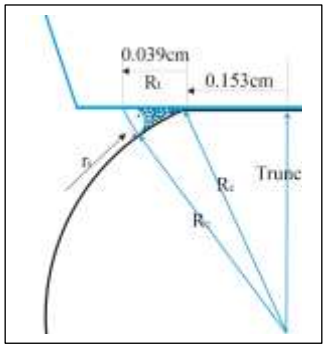
Inserting the dimensions for the standard Eye, GAT and Tears into equation 6.11:

$$\left([2\pi(R_t)\gamma] + [\pi R_t^2 \gamma(\frac{1}{r_t} - \frac{1}{R_t})]\right) \times \left(\frac{(0.153+R_t)^2-(0.153)^2}{(R_t)^2}\right)$$

Equation 6.7: $$[2\pi(R_t)\gamma] = [2\pi(0.039cm)46]$$

$$= 11.27 dyn/cm$$

r_t : from Figure 6.5



Step 1

TruncRc = $\sqrt{(0.78^2 - (0.153)^2)} = 0.765cm$

Step 2

$(r_t) = \{\sqrt{[(0.765)^2 + (0.192)^2]} - 0.78\}/2 = 0.0043cm$

Equation 6.8:

$$[\pi R_t^2 \gamma(\frac{1}{r_t} - \frac{1}{R_t})] = [\pi(0.039)^2 46(\frac{1}{0.0043} - \frac{1}{0.039})]$$

$$= 45.62\text{dyn/cm}$$

Adding the two forces (Eq 6.7 and Eq 6.8) gives: 56.89dyn/cm

Extrapolating to the total area of Tear Bridge Annulus

$$\text{Ratio: } \left(\frac{(0.153+R_t)^2-(0.153)^2}{(R_t)^2}\right)$$

$$= \left(\frac{(0.153+0.039)^2-(0.153)^2}{(0.039)^2}\right) = 8.85\text{xlarger}$$

The total GAT tear bridge annulus is 8.85 times larger than the area of the tear bridge at point contact (Figure 6.7) giving:

$$\text{Total Bridge Force} = (\text{Eq6.7+Eq6.8})\text{x}8.85 = 56.89 \text{ x } 8.85$$

$$= 501\text{dyn/cm}^2$$

$$P = F/A = \frac{501\text{dyn}}{cm^2} = \frac{0.00501N}{cm^2} = \frac{50.1N}{m^2} = 50.1\text{Pa } (0.0501\text{kPa})$$

Drawing the GAT probe toward the cornea.

Since 1mmHg = 0.1333kPa (European Committee for Standardisation 2009) this figure equates to:

$$\frac{0.0501\ kPa}{0.1333\ kPa} \approx 0.38\text{mmHg.}$$

This calculation indicates the tear bridge force at end point hydrostatic, applanation is minimal and over tenfold lower than the estimate of Schwartz *et al.* (1966).

6.4.2 Variation in Tear and Corneal Parameters: Effect on tear bridge attraction

An Excel spreadsheet was created to generate variations in corneal curvature, tear annulus width and tear surface tension (Appendix 11).

Ranges for normal corneal curvatures were set at 6.9mm and 9.0mm; sampled from the normative data in Chapters 2 and 3. A literature search did not reveal broader ranges; Mehravaran *et al.* (2013) publishing data from 400 normal right eyes presented a range of only 8.84 to 7.1mm (mean 7.79mm± 0.31mm) while Mashige (2013) reporting results from 9 studies including Caucasian, Indian, Chinese and African subjects reported ranges from 8.75 to 7.03mm. Haigis (2008), considering post refractive surgery corneas published a corneal curvature of 10.96mm; 11.00mm was incorporated into the spreadsheet.

Four widths of tear annulus were included; 0.01mm to mimic a severely tear deficient eye and 0.39mm representing an optimum width presented by Whitacre and Stein (1993). Broader annulus widths of 1mm and 2mm reflect the possibility of excessive enlargement of the fluorescein ring; Goldmann and Schmidt (1957) mentioned 2mm as an extreme.

The results of these changes on tear bridge forces, with a controlled surface tension of 46dyn/cm (Braun 2012), are collated in Table 6.1.

Table 6.1: GAT Tear Bridge Forces as Defined by Corneal Curvature and Meniscus Width

$\gamma = 46$ dyn/cm	0.39mm	0.01mm	1mm	2mm
Corneal Curvature	Tear Bridge Annulus Width			
6.9mm (Frampton)	0.34mmHg	0.33mmHg	0.35mmHg	0.37mmHg
7.8mm (Gullstrand)	0.38mmHg	0.37mmHg	0.39 mmHg	0.41mmHg
8.0mm (Schwartz *et al.* 1966)	0.39mmHg	0.38mmHg	0.4 mmHg	0.42mmHg
9.0mm (Frampton)	0.43mmHg	0.42mmHg	0.44mmHg	0.46mmHg
11mm (Haigis 2008)	0.52mmHg	0.51mmHg	0.53mmHg	0.54mmHg

Engineered alterations to tear annulus geometry, while affecting the force attracting the GAT probe toward the eye, generated clinically insignificant alterations. This reflects the meagre magnitude of the tear force. Variations ranged from 0.33mmHg in a very steep cornea (radius 6.9mm) in a severe dry eye with annulus of only 0.01mm to 0.54mmHg with annulus 2mm wide post refractive surgery.

The surface tension was arbitrarily altered from a standard figure of 46dyn/cm (Braun 2012). 35dyn/cm, mimics hyperosmolarity indicative of ocular surface dryness (Tomlinson *et al.* 2006, Benelli *et al.* 2010, Lemp *et al*. 2011), while 60dyn/cm suggests the instillation of saline to augment tear volume prior to a GAT reading. Extreme alterations to tear osmolarity are also demonstrated (Table 6.2) to have little impact on tear forces.

Table 6.2: GAT Tear Bridge Forces with varying geometries and Surface Tension

Corneal Curvature	Surface Tension	Tear Bridge Annulus Width		
	γ	**0.01mm**	**0.39mm**	**2mm**
6.9mm (Frampton)	35dyn/cm	0.25mmHg	0.26mmHg	0.28mmHg
	60dyn/cm	0.43mmHg	0.44mmHg	0.48mmHg
7.8mm (Gullstrand)	35dyn/cm	0.28mmHg	0.29mmHg	0.31mmHg
	60dyn/cm	0.48mmHg	0.49mmHg	0.53mmHg
9.0mm (Frampton)	35dyn/cm	0.32mmHg	0.33mmHg	0.35mmHg
	60dyn/cm	0.55mmHg	0.56mmHg	0.6mmHg
11mm (Haigis 2008)	35dyn/cm	0.39mmHg	0.39mmHg	0.41mmHg
	60dyn/cm	0.67mmHg	0.67mmHg	0.71mmHg

6.5 Discussion

These results refute the unequivocal claim (Whitacre and Stein 1993, Liu and Roberts 2005, Glass *et al*. 2008, Damji *et al*. 2003) tear film attraction equates to a pressure of 4.15mmHg. A standardised eye and GAT geometry yielded a magnitude for tear film attraction of only 0.38mmHg.

The full derivations were included specifically to allow critique. This is not a mathematician's solution. A mathematician would present an elegant equation modelling the tear annulus. This is not elegant. A mathematical model believed to most accurately reflect the cross sectional tear geometry was found and then expanded proportionally to encompass the entire area of the tear bridge annulus. The methodology appears robust. The flaws in the calculations of Schwartz and colleagues (1966) and Elsheikh *et al.* (2006) are demonstrated. Further, the calculations of Schwartz and colleagues predict as the tear meniscus diminishes the force of attraction increases. This is counterintuitive; the Young-Laplace equation is not adequate, in isolation, to model the complex tear bridge annulus at end point GAT. Acceptance of the new tear annulus model is supported by the observation as tear dimensions shrink, pressure equivalents also reduce; 0.41mmHg for a normalised eye with tear annulus of 2mm reduces to 0.37mmHg when the annulus width is 0.01mm.

Schwartz and colleagues (1966) approximated the tear meniscus as a circular arc. The proposed tear model maintains this assumption. This simplification is not without precedent (Chen *et al*. 2011). The magnitude of the forces and equivalent pressures involved support the adequacy of this expedient; a more comprehensive tear annulus model would not alter tear force magnitudes to any significant extent.

This figure does not refute the GAT mathematical model (equation 6.1). An actual magnitude for tear and elastic forces was never stipulated by Goldmann and Schmidt (1957). The model simply necessitates the two forces neutralise each other. Based solely on Schwartz and colleagues' estimate of tear force, Whitacre and Stein (1993) and Mardelli *et al*. (1997) assume corneal resistance equivalent to 4mmHg. Schwartz *et al.* (1966) however estimated resistance to be 0.8mmHg while Śródka (2010, 2011) suggested a figure of 1mmHg. Regardless, Śródka (2010), supporting the estimate of tear force presented by Elsheikh *et al*. (2006) of 0.45mmHg, indicates this level is well below measurement accuracy and operator variability, so wonders why correct for it at all.

6.5.1 'Modulus of Rigidity' and GAT

More significantly, preservation of the GAT model necessitates acceptance the elastic forces are equally minor. While this challenges experimental observations, it actually supports a primary qualification of the Imbert-Fick construct, and by association GAT. The thinner the cornea becomes, the closer it approximates an infinitely thin, perfectly elastic and flexible surface stipulated as fundamental to the acceptance of the 'Imbert-Fick' construct (Schottenstein 1996). GAT should, in compliance with the 'Imbert-Fick' caveats, more closely approximate intracameral IOP in the thinnest corneas.

CCT adjustment nomograms, however, do not support the theory. It is well accepted GAT underestimates true IOP in corneas thinner than 520µm. Yet, if all extraneous forces are neutralised at 520µm, ensuring the only force pushing back toward the tonometer is IOP, Śródka (2013), ponders how, in thinner corneas, the external tonometer pressure can be lower than the internal ocular pressure? The GAT model only allows one possibility; under thinner corneal dimensions, force N', pulling the tonometer toward the cornea, must be greater than the corneal elastic forces pushing back. Tear force magnitudes estimated prohibit this possibility.

The magnitude for tear force proposed is incompatible with the experimental and modelled biomechanical evidence. The correction factors incorporated into the GAT model (M': elasticity of the cornea, N': surface tension of the tear fluid) are potentially too slight to impact on the variations noted.

There must be other forces, not considered by Imbert, Fick or Goldmann, implicated. Regardless of Schmidt (1959) stating categorically ocular rigidity is completely eliminated with GAT, rigidity of the cornea may explain discrepancies. Goldmann and Schmidt (1957) were simply considering Friedenwald's 'Coefficient of Ocular Rigidity', which Liu and He (2009), quite precisely, describe as a measure of overall globe distensibility. Shearing forces, mechanically defined by the 'Modulus of Rigidity', as the cornea is bent around the circumference of the GAT probe, were not incorporated in the GAT model but will impact. Śródka (2010) suggests these flexural forces of the bent cornea, appear to pull the GAT probe toward the cornea rather than repel it.

Śródka (2010) explains at applanation equilibrium the peripheral corneal shell has to contain the full IOP inflation load, while the applanated zone of the shell, still at

equilibrium, exhibits a different pressure profile. Representing a boundary stress condition (Young and Budynas 2002), a shear force at the circumference of the applanation disc is necessary to balance the equilibrium; a shear pressure acting toward the inside of the eye.

If this is accepted it means the entire tonometry doctrine cannot be satisfied in the real eyeball, regardless of calibration dimensions, since, as Sródka (2009) explains, the law is based on false assumptions.

6.5.2 Measurement Accuracy: Dictated by the tears

While the magnitude of the tear forces cannot realistically affect GAT, Goldmann and Schmidt (1957) do indicate a wide fluorescein ring (2mm) gave readings 2mmHg higher than measurements taken with a ring width of 0.2mm. This reflects measurement accuracy rather than tear attraction variations. Accuracy will depend on precise imaging and alignment of the rings. Excessive or deficient tears will cause the fluorescent rings to be too broad or narrow allowing respectively over and under estimation of pressure (Akram *et al.* 2009). Moses (1960) and Roper (1980) explain it is the apex of the tear meniscus, at the point of cornea and GAT contact, which defines the applanation area and consequent accuracy. The meniscus apex, containing less fluorescein than the base, will be less visible with inadequate fluorescein resulting in reading inaccuracy of 5.62mmHg (Roper 1980). If the apex is sufficiently dim it may be missed entirely (Moses 1960). Measurements from GAT without fluorescein differed significantly from measurements with fluorescein (Bright *et al*. 1981, Arend *et al*. 2014). Hypofluorescence, caused by inadequate fluorescein concentrations or quenching, will also give an apparently narrower ring (Whitacre and Stein 1993).

By incorporating modern technologies and manufacturing processes Goldmann and Schmidt were able to produce a markedly more accurate and repeatable instrument compared to its predecessor, Schiőtz (Chapter 1, Section 1.4.2). Tears would appear inconsequential to the GAT model but a primary contributor to GAT measurement inaccuracy; an instrument eliminating tear artefact would seem reasonable.

6.6 Conclusions

Precise tear volume and fluorescein concentrations are critical to the accurate recording of a GAT measurement but have insignificant impact on the forces affecting the instrument. Since tear bridging forces appear minimal it would seem more appropriate to eliminate this area of measurement noise.

Further, the tear bridging results highlight the lack of consensus on GAT corrections. The GAT model patches N′ and M′ never accurately represented the forces and resistances affecting GAT. Śródka (2013) suggests shear forces are the primary source of inconsistency. These need to be investigated if corrections for GAT are to be realised although it may be expedient to neutralise rather than compensate for corneal biomechanics.

Chapter 7: Recommendations

7.1 Clinical Implications

This research does not expect or imply a clear and immediate change to clinical practice. A view supported by historical precedence.

Kirstein *et al.* (2011) and Kniestedt *et al*. (2008) suggest Digital Palpation Tonometry was the original 'Gold Standard' after Bowman reported its importance in 1826 (Chakrabarti *et al.* 2009, Stamper 2011). While the Schiőtz instrument, introduced in 1905 (Schiőtz 1905), is accepted the second 'Gold Standard' (Ritch and Caronia 2000), mechanical tonometers were not immediately embraced.

In 1908 Isador Schnabel, discussing mechanical tonometry, told the Vienna Ophthalmology Society 'to expect little from this test since digital tonometry by an expert is a much more accurate test' (Brandt 2004). A reflection of contemporary expert opinion. Chakrabarti and co-authors (2009) suggest ophthalmologists of the time felt so confident with their palpation skills, mechanical devices were considered inferior. While consideration of the refinements made by Goldmann and Schmidt half a century later may support their scepticism, there is little doubt clinical familiarity with alternatives constrain innovation. A barrier GAT had to overcome.

Katavisto (1964) states impression tonometers such as the Schiőtz were in much more general use than any other at that time. Starrels (1979), twenty years after the introduction of GAT, lists advantages of Schiőtz as familiarity, low cost, portability and ease of operation. An immediate conversion to GAT does not appear to have been the case and the arguments presented by Starrels in 1979 of low cost and familiarity, to support the continued use of Schiőtz, help maintain the continued use of GAT today (Brandt 2004, NICE 2009b).

Ehrlich *et al*. (2010) do express the view while a more accurate measure of IOP is appealing abandonment of GAT could disrupt continuity of care. Furthermore, Drexler and Fujimoto (2008), Radcliffe (2014) and Yao and Crosson (2014) comment clinicians do not accept new instrumentation increasing the time and cost of examination. De Moraes *et al.* (2008) warn, regardless of technological improvements, since virtually all

literature and clinical trials were based on GAT, re-defining the standard would necessitate re-defining statistical norms and targets; a logistical and educational morass.

7.1.1 Clinical arguments

Which is most important, accuracy in measuring intracameral IOP, agreement with GAT, repeatability or the ability to continuously monitor IOP fluctuations?

7.1.1.1 Is an absolute measure of Intracameral Pressure a Clinical Imperative? The argument in support of GAT.

A current definition of glaucoma is 'a progressive optic neuropathy associated with characteristic structural damage to the optic nerve and associated with characteristic visual field defects' (Foster *et al.* 2002, Kroese and Burton 2003, Bell 2014). Raised IOP is no longer included in the definition. IOP is classified as a risk factor (Kroese and Burton 2003) but crucially remains the sole modifiable characteristic of the disease (Ehrlich *et al.* 2012, Bell 2014).

Damji *et al.* (2003), assessing the challenges of 21st century tonometry, indicate optic nerve assessment remains, currently, the gold standard for diagnosing and monitoring glaucoma. This strategy does necessitate identification of morphological change in the optic nerve, representing potentially irreversible damage. One of the major aims of the Ocular Hypertensive Treatment Study (OHTS) was to identify non-glaucomatous patients who would benefit from prophylactic treatment.

The OHTS showed hypotensive medication halved the conversion rate of ocular hypertension (OHT) to glaucoma; at least over a 5 year period (Kass *et al*. 2002). Evidence supporting, perhaps, the benefit of prophylactic treatment. However, as early as the 1960s, evidence was presented showing only a minority of ocular hypertensive patients develop glaucomatous optic nerve damage (Palmberg 2002). Further, the 50% reduction in conversion observed in the OHTS represented a drop from 9.4% to 4.4% (EGS 2003) of the sample group of over 1600 participants (Feuer *et al.* 2002). Over 90% of untreated patients did not convert while half the treated patients went on to be

classified as Primary Open Angle Glaucoma (POAG) despite treatment (European Glaucoma Society 2003, Kass *et al.* 2002).

The OHTS Manual of Procedures (2001) reported, at that time, an estimated annual cost of glaucoma medication in the US to be $300 million with little evidence of societal health benefits. The document further considered the adverse drug effects on individuals as well as costs in time and lost productivity to the community. Since OHT has a 10 to 15 times greater prevalence than POAG (Chang-Godinich 2014) there is a clear need to identify and treat those ocular hypertensives at higher risk of conversion without inappropriately treating those at low risk. Gordon *et al.* (2002) concluded Baseline Age, Horizontal and Vertical CD ratios, Pattern Standard Deviation (PSD), IOP and Central Corneal Thickness (CCT) are strong predictive factors of conversion. The European Glaucoma Society (2003) suggests treatment should be offered to moderate risk patients, based on age, medical status, life expectancy and treatment benefit.

Even when the decision to treat is dependent on an IOP level, as in the prophylactic treatment of ocular hypertensives, is an absolute measure of IOP or simply an accepted frame of reference, necessary?

Mills (2000) suggest an absolute measure of IOP is not usually important, rather a comparison to a standard baseline. This is not a recently expressed opinion. Maklakoff stressed tonometry does not measure absolute IOP but rather should be used to assess relative pressure changes (Kniestedt *et al.* 2008). Cridland (1917), reviewing 11 years of Schiőtz use, stressed the importance of considering the relative reading of the instrument and not the supposed pressure equivalent.

This supports the contention, since instrument evaluations are predominantly concerned with assessing a new tonometer as a clinically viable tool, comparison to GAT is acceptable. It is, after all, the instrument of choice in ophthalmology clinics and as such constitutes the final arbiter for accepted pressure.

7.1.1.2 Agreement with GAT. Instrument Repeatability and the necessity to improve accuracy.

While the argument in support of maintaining GAT is persuasive, it is now widely accepted the standard is flawed.

No other modern authors cited have considered GAT evolution from first principles and within context of physical and biomechanical laws. The Imbert (1885), Fick (1888) and Goldmann and Schmidt (1957, 1961) models have been demonstrated as biomechanically unsound (Chapter 1, Sections 1.3 and 1.4). This supports the view of Śródka (2010) who suggests there is no theoretical justification for the calibration values. It may explain why, regardless of the substantial academic investment in striving to correct the instrument, none of the proposals adequately explain inadequacies. Corrections proposed for GAT proliferate (Orssengo and Pye 1999, Kwon *et a*l. 2008, Elsheikh *et al.* 2011, Kaushik *et al*. 2012, Khan 2014) and modelled and experimental results highlight errors (Argus 1995, Wilensky 1999, Damji *et al.* 2003, Brandt 2004, Liu and Roberts 2005, Liu and He 2009, Roberts 2014, Śródka 2010, 2011, 2013, Elsheikh *et al.* 2006).

Regardless of accuracy in measuring intracameral IOP, none of these endeavours would be necessary if the GAT model was an accurate representation of the forces and resistances involved in applanation tonometry. GAT measurement could be relied upon to represent a standardised measure, designated IOP, repeatable and reproducible.

CCT corrections emphasise GAT cannot be standardised, readings have to be adjusted. However, CCT is an imperfect surrogate for corneal biomechanics (Brandt 2004, Liu and Roberts 2005, Hamilton and Pye 2008, Young 2014). Its utility has been questioned (Hager *et al.* 2008, Boehm *et al.* 2008, Brandt 2004 and Doughty and Zaman 2000) and no correction has been validated (Brandt 2004). CCT seems inter-related with other biomechanical parameters, an expectation supported by biomechanical principles. Investigated in Chapter 2, global effects of corneal morphology dilute the individual impact of CCT. Decision Tree Analysis (DTA) demonstrated CCT to be effected by corneal curvature and the quasi-biomechanical markers of ORA-CH and ORA-CRF.

Despite this, CCT remains the pre-eminent correction for GAT, supported by DTA in Chapter 2. This does not imply CCT corrections are not compromised. The underestimation of IOP by GAT in thin corneas, discussed in Chapter 6, highlights this point. Rather, CCT pre-eminence will remain until Young's Modulus, or a robust

surrogate, can be measured *in vivo*. Corneal Hysterisis (ORA-CH) and Corneal Resistance Factor (ORA-CRF) do not represent robust alternatives. An unforeseen outcome in Chapter 5, with modification of corneal curvature via orthokeratology without altering CCT or corneal biomechanics, was the measured alterations to both ORA metrics. While open to a wide range of interpretations depending on the understanding of what the ORA metrics represent and how they are calculated, the contention presented is they represent, predominantly, a response to the modification of corneal curvature. It seems likely the ORA metrics reflect the proprietary data acquisition algorithm based on two applanation episodes. If this is the case ORA-CH and ORA-CRF do not reflect corneal biomechanics in any significant sense, if at all.

An absolute magnitude for M', or N', was not stipulated by Goldmann and Schmidt (1957). Assuming the model assumptions to be true, the designers reverse engineered and found the probe dimensions when GAT readings equalled manometry. Only under these specific design arrangements, arrangements potentially too narrow to encompass all physiological and pathological variability, can GAT be assumed equal to true IOP.

Further, the tear bridging results presented in Chapter 6 highlight the lack of consensus on GAT corrections. Tear forces seem insignificant and cannot explain the underestimation of IOP by GAT in thin corneas. Further, if the GAT model is accepted, this implies M', designated elasticity by Goldmann and Schmidt (1957) is equally inconsequential. The thinner a cornea becomes the closer it approximates the infinitely thin, flexible membrane stipulated as ideal for the Imbert-Fick construct. Underestimation of pressure in thin corneas contravenes this presumed Imbert-Fick fundamental.

The original GAT model parameter of corneal elasticity (M') seems unable to accurately represent the forces and resistances affecting GAT. Never explained by Goldmann and Schmidt (1957), it remains conjecture the authors employed the descriptor ‘elasticity’ to represent the biomechanical law of ‘Young’s Modulus’; they certainly did not use the term ‘rigidity’ in a constitutive biomechanical sense. Yet the cornea’s modulus of rigidity and the shear forces and boundary condition around the circumference of the GAT probe as the cornea is flexed certainly create forces not incorporated in the simple GAT biomechanical model.

The tear forces, while given significance within the GAT equation, are too slight to counteract the biomechanical factors. Variations in GAT readings resulting in alterations in tear volume appear the result of loss of accuracy in distinguishing the mire alignment end point.

The merit of maintaining GAT as an assumed standardised, repeatable measure, appears unsound when other instruments are based on more robust biomechanical theory.

7.1.1.3 The argument for improved Accuracy

Ehrlich *et al.* (2012) re-confirm IOP remains the only modifiable risk factor and treatment path for eyes with glaucoma; logically greater accuracy and reduction in confounding factors should be valuable.

Özcura *et al.* (2008) and the European Committee for Standardisation (2009) maintain without direct and invasive manometry it remains impossible to measure true IOP. A sentiment echoed by Schmidt (1960) who acknowledged, regardless of the obvious technological refinements incorporated in the GAT, the ideal tonometer would be a compensated membrane manometer. Further, Goldmann and Schmidt (1957) admit the use of coarse methods to model the eye and suggest their conclusions may represent first approximations; a self-critique warranting more regular re-affirmation.

Acknowledging true IOP cannot be measured without recourse to manometry (European Committee for Standardisation 2009), International Standard ISO 8612:2009 simply specifies the minimum requirements for tonometers intended for routine clinical use. While ISO 8612 may be acceptable to expedite commercial release of new tonometers, designers fundamentally questioning the GAT model need to calibrate their machines against a more robust standard.

Certainly all tonometers designated 'Gold Standard' have been calibrated against manometry; digital palpation (McLean 1919), Schiőtz (Schiőtz 1905) and GAT machines (Goldmann and Schmidt 1957, 1961). Innovative technologies must do likewise. Comparison to a current standard will always bias interpretation.

Regardless of convention, propagated by interpretations of ISO 8612, it is not necessarily the case tonometers should agree with GAT. The Schiőtz tonometer was superseded by GAT. Not because they agreed, but because they did not. Schiőtz demonstrated poor repeatability (Friedenwald 1937, Kronfeld 1945, Jackson 1955, Schottenstein 1996) and GAT was more accurate and repeatable.

If fundamental principles vary, or the reference instrument demonstrates poor repeatability (Bland and Altman 1986), comparison will be unproductive. Bland and Altman (1986) stress their technique simply determines if a new instrument can be considered interchangeable with another; accuracy of either instrument is not a consideration.

Reporting the understanding a 10% reduction in visual field progression risk and 10% improvement in outcome for patients with OHT with a reduction in IOP of only 1mmHg Smedowski *et al.* (2014) supports the quest for improving the accuracy of IOP measurement.

As with any modelled system, the model parameters and associated rationales are set initially. Deviations from these parameters, virtually by design definition, eliminate the model's predictive value. The variability in corneal biomechanics and the insignificance of tear forces to compensate for this would suggest elimination of both variables to be a positive goal if improved accuracy is to be realised.

Assessed via DTA (Chapter 2), Tonopen was the only instrument unaffected by the biomechanical markers measurable *in vivo*. The non-sensitive base plate supports the bending and boundary forces on the cornea while eliminating any tear artefact. A significant deficiency in this research was not incorporating the Dynamic Contour Tonometer (DCT), an instrument using very similar principles to Tonopen but with 21st century refinements. The DCT, described in section 1.7.4.2, is evidenced to approximate intracameral pressure very well, but does read several mmHg higher than GAT (Kanngiesser *et al.* 2005, Boehm *et al.* 2008).

Like Schiőtz (1905) and Goldmann and Schmidt (1957, 1961), the fundamentally different theoretical premise of the DCT, necessitated calibration against manometry (Kotecha *et al*. 2010, Kanngiesser *et al.* 2005). Based on the Law of Hydrostatic Pressure, rather than the Imbert-Fick principle, the instrument can be described as measuring pressure rather than force. Biomechanics are neutralised and tear artefacts eliminated. Kotecha *et al.* (2010) also suggests it demonstrates excellent precision and less intra and inter observer variability; precision potentially enhanced due to gathering 100 IOP readings per second over 5 to 8 seconds, thus neutralising effects of the cardiac cycle. A strong case has been made this should be the current 'Gold Standard'.

Leonardi *et al.* (2004) reporting a survey of Swiss ophthalmologists, indicate 99% maintain the conventional view GAT remains the most accurate and precise tonometer. However, Humphrey (2002) stresses as understanding of the characteristics of living

materials increases, concepts of mechanical modelling must adapt and entrenched postulates questioned; building on prior achievements and knowledge without being bound by past methods or concepts.

7.1.1.4 Alternative Arguments

Brandt (2009) suggests, regardless of instrument accuracy, the very way clinicians collect data is flawed; clinicians make management judgements of a complex and highly variable pathological process based on IOP snap shots. Ehrlich *et al.* (2012) also queries whether inconsistencies between IOP and glaucoma reflects shortcomings in office based IOP measurement.

Which instrument would demonstrate the most appropriate clinical utility, Brandt (2009) challenges, a static tonometer with proven accuracy of ±1mmHg or a tonometer able to record continuous IOP in real time with, perhaps, a precision of only ±3mmHg? Young (2007) certainly feels measurement of IOP alone not sufficient for identifying glaucoma in either OHT or NTG cases. This dilemma, Young suggests, will not be solved by the invention of new tonometers.

Mansouri *et al.* (2012a, 2012b) suggest GAT, while a worldwide standard, provides isolated readings not reflective of the dynamic nature of IOP. Clement *et al.* (2014) suggest IOP fluctuations are harmful, particularly in advanced disease. These authors report circadian variations in IOP in glaucomatous and normal subjects from 4.8 to 11mmHg and 3.17 to 5mmHg respectively. Snap shot, in office, measures of IOP cannot encapsulate the total IOP risk. Mansouri *et al.* (2012b) suggest this is the most significant shortcoming with GAT. GAT takes a 1 to 2 second snap shot of an individual's IOP, taken in the upright position (Mansouri and Weinreb 2012).

There is still some discussion as to what does constitute the highest risk for glaucoma progression. Gelatt and MacKay (2001), Kontas *et al.* (1999) and Zeimer, *et al.* (1990) suggest IOP peaks should be significant. Kontas and co-workers further suggest the timing of a patient's personal IOP peak, if it could be ascertained, could be an important factor in timing drug administration. The need for phasing is still strongly championed (Schiefer *et al.* 2011, Mansouri *et al.* 2011); with significant cost implications when conducted via a hospital. Conversely, Bengtsson *et al.* (2007) reporting the results of the Early Manifest Glaucoma Trial could not identify IOP fluctuations as an independent

variable in the progression of glaucoma. Caprioli and Coleman (2008) report this and the results of the Ocular Hypertensive Treatment Trial which also could not differentiate IOP fluctuations from mean IOP; patients with higher mean IOP also demonstrated greatest fluctuation. Caprioli and Coleman (2008) however, as part of the Advanced Glaucoma Intervention Study, found fluctuation associated with disease progression when the mean IOP was low but not when the mean IOP was high. Defining fluctuation could partially explain the discrepancies.

Hughes *et al.* (2003) reported 24 hour phasing identified IOP spikes 4.9 to 12mmHg higher than recorded with office based static tonometry, resulting in modified management in 79.3% of glaucoma patients. Discussing the Icare tonometer, van der Jagt and Jansonius (2005) consider instrument utility. The portability and ease of use makes the Icare ideal for self-monitoring. The authors challenge convention; is a single GAT reading in a consulting room more valid than the ability to monitor relative changes via home phasing? This concept is also mentioned by Draeger *et al.* (1989) suggesting the usefulness of a new instrument should not necessarily include comparison with traditional tonometry but should reflect the physical characteristics of the new machine.

Until recently phasing entailed either multiple IOP readings within office hours or hospitalisation in a sleep laboratory. The former only providing daytime readings, the latter cumbersome and expensive (Mansouri and Weinreb 2012). At best traditional phasing allows episodic, non-continuous measurement with 1 measure per hour (Mottet *et al.* 2013), equating to perhaps a minutes worth of data over 24 hours of disturbance. Further, these traditional phasing techniques do not reflect physiological conditions (Mottet *et al*. 2013). The subjects endure sleep disturbance, normal daily activities are necessarily curtailed and the measurements must still be taken in an upright, stationary position (Mansouri and Weinreb 2012).

Introduced by Leonardi *et al.* (2004), SENSIMED Triggerfish, Switzerland (Mansouri *et al.* 2012b) is an innovative concept of a micro fabricated platinum-titanium strain gauge (Laukhin *et al*. 2011) embedded in a soft contact lens (Chen *et al.* 2013). The machine does not attempt to record IOP but rather quantifies variation in corneal curvature induced by IOP. The instrument records in millivolts (Mansouri and Weinreb 2015) and the readout cannot be equated to specific magnitudes of pressure in either Pa or mmHg.

This totally innovative technology will test convention. Mansouri and Weinreb (2012) suggest the future of glaucoma diagnosis and management will require an entire paradigm shift. The same authors (2015) wonder how best to assimilate the ensuing data avalanche as well as the educational challenges this will pose for clinicians.

7.2 Final Statement.

Casson *et al.* (2012) adhere to the view it is prudent to be sceptical of any scientific paradigm.

The tonometer debate is driven by the goal to improve accuracy or utility but is tempered by the sheer magnitude of the task of overturning 60 years of convention. Convention not simply reflecting historical precedent directing expert opinion but the logistical and educational difficulties of redefining standards and statistical norms (De Moraes *et al.* 2008).

Regardless of guidelines and protocols advising the most appropriate tonometry strategy, a statement presented by NICE (2009b – page 31), but rarely quoted, deserves the final statement. 'While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills'.

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Appendix 1.0 – 'Grams Force': a lack of scientific accuracy.

The 'Imbert-Fick' equation as stated by Gloster and Perkins (1963) is: 'When a flat surface is pressed with a force, W, against a spherical container having an internal pressure, P, equilibrium is attained when:

$$PxA=W \text{ or } (P=W/A)$$

Imbert-Fick Construct
(Gloster & Perkins 1963)

Where:
W: Force acting on the cornea (units of measure stipulated – grams weight)
A: Area of the plunger acting on the cornea
P: Intraocular Pressure

Gloster and Perkins (1963), while using the descriptor 'Force' for the unit W, describe it in terms of grams-weight; there is no differentiation made between weight (W) and force (F). Goldmann and Schmidt (1961) initiated this misinformation by specifically using the term 'grams force' and present their interpretation as:

$$\text{Pressure} = \frac{\text{(Weight or Force applied)}}{\text{(Area of Applanation Contact)}}$$

Imbert-Fick Construct
(Goldmann and Schmidt 1957, 1961)

Weight and Force are not synonymous. The gram is a unit of mass not force (Kalenak 1991).

Kalenak (1991) suggests tonometry text books describe the GAT scale as indicating 'grams of force' which is meaningless. Force and mass are linked via Newton's Second Law, force created by a mass is calculated using acceleration due to the force of gravity (Kalenak 1991).

$$\text{Force}=\text{mass} \times \text{acceleration}$$

Newton's Second Law

Utilising CGS units (Centimetre-gram-second), a variant of the SI metric system, representing a more appropriate scale for the magnitudes of forces involved, a dyne is

the force required to accelerate a mass of 1gm at the rate of 1cm/s² (gravitation force in dynes: 981cm/s²)

Inserting this into Newton's Second Law:

$$F = 1g \times 981 dyn/cm^2.$$

1 gram of weight will apply 981 dynes of force to the corneal surface.

Pressure is exerted by a force acting normally on a unit area of a surface. Formulaically (Bird and Ross 2012):

$$P = F/A$$ Equation for Pressure

To calculate the pressure this force exerts on the cornea it must be divided by the area. The area of the applanated zone of radius 1.56mm equals 0.0735cm²: The resultant pressure of the force distributed over the area of applanation is:

$$P = F/A = \frac{981\text{dyn}}{0.0735cm^2} = 13334 \text{ dyn/cm}^2$$

Since there are 10000cm² in 1m² and 1dyn = 10^{-5}N this figure can be converted to Pascals. ISO8612 1 mmHg = 0.1333 kPa: .

$$P = F/A = \frac{13334\text{dyn}}{cm^2} = \frac{0.13334N}{cm^2} = \frac{1333.4N}{m^2} = 1.333 \text{ kPa} = 10 \text{ mmHg}.$$

ISO8612 states tonometry readings are expressed in millimetres of mercury (mmHg), where 1 mmHg = 0.1333 kPa (European Committee for Standardisation 2009). A scale reading of 1 translates to a pressure of 10 mmHg (Kalenak 1991). Thus 1gm of weight of the GAT probe equates to 1333 Pa (or 1.333 kPa) of GAT Pressure; 0.1gram will equate to 1mmHg on the GAT scale as stipulated by Goldmann and Schmidt (1957).

If force, rather than weight, is assumed to have been the intended principle to be included in the 'Imbert-Fick Law' and substituting 'W' (weight) with 'F' (force) it becomes the equation for pressure P=F/A (Bird and Ross 2012). In actuality neither author presented this equation.

Appendix 2.0 – Personal communication iso Central Secretariat and bsi Standards Group.

1.1 Communication with iso Central Secretariat.

From: **Peter Frampton**
Sent: **22 October 2015 08:46**
To: **'central@iso.org' <central@iso.org>**
Subject: **Data for ISO8612**

Hello

I am doing my Doctorate on tonometry and biomechanics and am looking at ISO8612.

As a member of the standards committee, the United Kingdom is bound to comply and implement European Standard ISO 8612. If an instrument reaches the UK market, it must be assumed to have passed stringent, controlled, standardised pre-release ISO processes (European Committee for Standardisation 2009).

My question therefore is: The ISO 8612 paper specifies the standards but is the actual data from each manufacturers ISO tests ever published? I have been unable to find these results for any commercially available machine, specifically Tonopen AVIA, Icare Rebound, Ocular Response Analyser and Diaton. Where do I find this data which should be the most publicised and most valid.

I am questioning the seemingly insatiable desire of other researchers to compare commercially available instruments to Goldmann Applanation Tonometry? Unless the standard itself is being questioned, which, as far as I am aware, is never the case, there is little benefit in further comparing instruments to GAT under disparate experimental conditions not compliant with the ISO 8612 protocol. The conclusions reached by the surfeit of other comparative papers, not procedurally compliant with the standard, should be questioned and could propagate misinformation.

Thank you for your help

Peter Frampton

From: **Customerservice <customerservice@iso.org>**
Sent: **Thursday, October 27, 2015 1:46 PM**
To: **Peter Frampton Peter@aaronoptometrists.com**
Subject: **FW: Data for ISO8612 - addendum**

Firstly, I would like to apologize for the delay in reply.

ISO standards are voluntary, and ISO itself does not carry out any testing or assessment of conformity. Therefore, we do not have a list of manufacturers which may have carried out any test to ISO 8612, nor do we know which company may be conforming to our standards.

Perhaps your national ISO member, the BSI, can advise you on any other available sources of information:

ISO member	British Standards Institution (BSI) 389 Chiswick High Road GB-LONDON W4 4AL Tel: + 44 208 996 90 00 Fax: + 44 208 996 74 00 E-mail: cservices@bsigroup.com Web: www.bsigroup.com
Sales service	As above Customer Services Tel: + 44 208 996 70 00 Fax: + 44 208 996 70 01 E-mail: cservices@bsigroup.com
Information service	As above Knowledge Centre Tel: + 44 208 996 70 04 Fax: + 44 208 996 70 05 E-mail: knowledgecentre@bsigroup.com

We note that the BSI is also a full participating member of the subcommittee (ISO/TC 172/SC 7) responsible for the development of ISO 8612.

Cordially,

Joseph Martinez
associate, product development | marketing and sales services |
marketing, communication & information | iso central secretariat |
phone: +41 22 749 03 17

1.2 Communication with bsi Knowledge Centre.

From: **Peter Frampton [mailto:peter@aaronoptometrists.com]**
Sent: **27 October 2015 17:36**
To: **Knowledge Centre**
Cc: **cservices**
Subject: **ISO 8612 (or equivalent)**

Hello

I am doing my Doctorate on tonometry and biomechanics and am looking at ISO8612. I initially targeted ISO (their response is copied into the bottom and they directed me to bsi.)

I thought, as a member of the standards committee, the United Kingdom was bound to comply and implement European Standard ISO 8612. If an instrument reaches the UK market, it must be assumed to have passed stringent, controlled, standardised pre-release ISO processes (European Committee for Standardisation 2009).

My question therefore is: The ISO 8612 paper specifies the standards but is the actual data from each manufacturers ISO tests ever published? I have been unable to find these results for any commercially available machine except the Icare, specifically Tonopen AVIA, Icare Rebound Ocular Response Analyser and Diaton. Where do I find this data which should be the most publicised and most valid.

ISO tell me, much to my surprise, it is not mandatory to stick to ISO and they do not ensure compliance. I am questioning the seemingly insatiable desire of other researchers to compare commercially available instruments to Goldmann Applanation Tonometry. Unless the standard itself is being questioned, which, as far as I am aware, is never the case, there is little benefit in further comparing instruments to GAT under disparate experimental conditions not compliant with the ISO 8612 protocol. The conclusions reached by the surfeit of other comparative papers, not procedurally compliant with the standard, should be questioned and could propagate misinformation.

So does BSI ensure standards are met before an instrument is released onto the market? If so where is this data published. I know Icare publish theirs in the hand book but none of the others appear to. Perhaps they are not even operating to these standards?

Can you help? And thanks regardless

Peter Frampton

From: Knowledge Centre <KnowledgeCentre@bsigroup.com>
Sent: 28 October 2015 7:46
To: Peter Frampton <Peter@aaronoptometrists.com>
Cc: cservices
Subject: ISO 8612 (or equivalent)

Dear Peter

Thank you for your enquiry. I have just forwarded on your enquiry to the committee secretary for this standard and will let you know as soon as I hear back from them. Unfortunately we are unable to give a timescale as to when they will get back to us. However, I will get back to you as soon as I hear anything.

Kind regards

Charlotte

Charlotte Elliott
Information Specialist
T: +44 20 8996 7004
charlotte.elliott@bsigroup.com

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BSI Group, 389 Chiswick High Road, London, W4 4AL, UK
bsigroup.com | Twitter | LinkedIn

From: BSI Standards <british.standards@bsigroup.com>
Sent: Fri 13/11/2015 12:57
To: Peter Frampton <Peter@aaronoptometrists.com>
Subject: Updates to BSI white paper, The proposed EU regulations for medical and in vitro diagnostic devices

Our white paper on 'The proposed EU regulations for medical and in vitro diagnostic devices' has been updated to reflect the current status of the legislation

Staying informed of changes that will impact the medical device sector can be a challenge. That's why BSI has published a series of free white papers covering a range of topic areas to help those working in the sector to stay up-to-date with the latest developments.

Our most recent white paper is a revision of a document originally published in March 2014. Titled *The proposed EU regulations for medical and in vitro diagnostic devices*, the revised document has been updated in line with the current debate surrounding the revised proposals for the new Medical Devices Regulations (MDR) and In Vitro Diagnostic Devices Regulations (IVDR) and reflects the status of the legislation as of October 2015.

Key changes to the white paper include:

- A revision to the wording in the section 'The changing role of notified bodies' with regard to special notified bodies
- Exemptions for distributors and importers as highlighted in the section 'The impact on own brand labelling'
- Changes in the section 'Where does this leave the clinical and regulatory environment?' relating to regulatory awareness in companies for which the proposals oblige companies to permanently and continuously have available at disposal in their organization at least one 'person responsible in charge for regulatory compliance activities'
- The requirement for manufacturers to prepare periodic safety update reports per device or per category / group of devices where relevant, as highlighted in the section 'The increasing requirement for vigilance and market surveillance'
- Changes to the 'Transitioning' section which explains more clearly how delegated and implementing acts can impact companies directly. As the new regulations will affect existing devices currently on the market as well as new devices, this section also explains when re-evaluation and certification under the new legislation will be required
- The paper also includes non-binding scientific advice

The regulations are due to come into force during the second half of 2016.
Download the revised white paper today to understand the impacts for your company.

Appendix 3.0 – Personal communication with David Taylor: Reichert.

----- Forwarded by Linda Hauser/NY-DEP/Ametek on 08/26/2015 08:22 AM -----

From: **Peter@aaronoptometrists.com**
To: reichert.information@ametek.com,
Date: 08/26/2015 02:56 AM

Name : Mr. Peter Frampton
Email : Peter@aaronoptometrists.com
Title : Doctoral Study.

Comments : I am doing my Doctorate on corneal biomechanics and tonometry. The Mackay- Marg principle eliminates 1) tear forces 2) boundary conditions 3) Biomechanics and measures pressure rather than force. Considering tonometry *de novo* tonopen makes sense and should be superior to Goldmann. Are there papers comparing tonopen to manometry rather than GAT? I expect to finish PhD next year and outcome will suggest tonopen should be reference standard rather than GAT. If you can help with manometric papers please let me know. I didn't start the PhD expecting this outcome but if you are interested please let me know.

Thanks Peter Frampton

From: **Dave Taylor [mailto:Dave.Taylor@ametek.com]**
Sent: 27 August 2015 15:37
To: Peter Frampton

Dear Peter

Thanks for your email.
Tonometry and biomechanics are exciting subjects - and ones that I have a keen interest in as I have spent the last 13 years of my life as the product manager and champion of our Ocular Response Analyzer device.
I assume your statements regarding the contention that Mackay-marg eliminates tear forces, boundary conditions, and biomechanics comes from the original 1963 mackay marg paper?
In any case, I do not believe these claims are totally true, and there are dozens of peer-reviewed papers that demonstrate that Tono-Pen has shortcoming similar to GAT. Tono-Pen (which is also my responsibility) is a great product and has many advantages due to its portability and ease of use. But it is not totally devoid of corneal

influence. It may be a tad bit better than GAT, but it is still influenced by corneal biomechanics and thickness.
May I suggest that you look into our ORA / 7CR, which I believe are the most accurate tonometers available.
I have attached some papers that you may find interesting and useful.

Best regards,

Dave
David A. Taylor
Senior Product Manager, Advanced Diagnostics and Tonometry
Reichert Technologies

From: **Peter Frampton <peter@aaronoptometrists.com>**
To: Dave Taylor <Dave.Taylor@ametek.com>
Date: 08/28/2015 10:33 AM

Thanks very much for this. We are using the ORA as well. Icare, ORA, GAT, Tonopen as they all use slightly different theory. I am fundamentally disputing the dogma GAT should be a reference. The paradigm in rubbish. But to change perception machines have to be calibrated against manometry rather than GAT. While the theory on Tonopen makes immense sense (pressure rather than force for a start) anything to support this as well as the ORA would be great but I suspect all comparisons are against GAT.

I am in the last 12/12 of the PhD and things have morphed. If you are interested – since both instruments are yours – I will keep in contact.

Peter

From: **Dave Taylor [mailto:Dave.Taylor@ametek.com]**
Sent: 02 September 2015 01:52
To: Peter Frampton

Peter

I totally agree with your comment about the Goldmann paradigm being rubbish. However, I don't fully agree with the need to calibrate tonometric devices against manometry. At the end of the day it's just a number and we use that number to decide how to diagnose and manage disease. The problem with Goldmann isn't the number we call IOP, it's that the number is contaminated by corneal (and other) artefact.
The Pascal DCT is supposedly closer to manometry, and there is pretty good evidence that this is the case. Yet the instrument has been a total failure. Why? One of the reasons is because the numbers the device provides are different than Goldmann

numbers. Average IOP with the DCT is a few mmHg higher than GAT. So when there is a difference between the DCT and GAT on the same eye is it because of this offset or is it because of corneal properties? Or both? These unresolvable questions make it difficult to use the DCT numbers clinically with any confidence.
That's why we spent a lot of time making our IOPcc measurement Goldmann correlated. It's like a Goldmann number that lacks the Goldmann corneal contamination. And studies have shown that our number is more strongly associated with actual glaucoma and glaucoma damage than GAT. So clinically, it's superior. Even if we don't know if the number represents the manometric pressure.

Measuring manometric IOP accurately is very difficult and presents a lot of technical and ethical challenges. Getting useful data out of a penetrating manometry study is impossible, in my mind anyway.
This is fun stuff! Of course I am interested and would be happy to keep in touch. I'm off to the ESCRS meeting in Barcelona tomorrow in case you are going. Stop by and say hello.
Hope to meet you out there somewhere someday.

Best Regards

Dave
David A. Taylor
Senior Product Manager, Advanced Diagnostics and Tonometry
Reichert Technologies

From: **Peter Frampton <peter@aaronoptometrists.com>**
To: **Dave Taylor <Dave.Taylor@ametek.com>**
Date: 09/14/2015 12:57 PM
Subject: RE: Fw: Reichert Technologies - General Contact Form Inquiry

I fully appreciate the stance taken and the fact we are so entrenched with GAT. From the very earliest days of Maklakoff the idea an absolute measure is not essential as long as the measure is standardised and repeatable (a primary fault with Schiőtz). However, M' and N' in the Goldmann-Imbert-Fick simple biomechanical model cannot be considered constant or equal; as with any modelled system, the model parameters and associated rationales are set initially, deviations from these parameters, virtually by design definition, eliminate the model's predictive value. Familiarity and cost ensured it took several decades for GAT to truly supplant Schiőtz as tonometer of choice, regardless of the latter's fully recognised poor repeatability. The repeatability of GAT is now highly questionable. If a reference machine has poor repeatability then, regardless how accurate an innovative machine may be, agreement with the reference is unlikely. Regardless of the entrenched views of clinicians, and how difficult it is to organise manometric studies, it is the only way to truly change opinion – as slow as that might be, it is as essential now (in my opinion) as it was for Goldmann to compare to manometry rather than Schiőtz in 1955.

Anyway I enjoy a good debate. I will certainly keep you in the loop. You may be interested. Finally I guess the answer to my initial enquiry is there are no papers calibrating tonopen to manometry?

Peter

From: **Dave Taylor [mailto:Dave.Taylor@ametek.com]**
Sent: 16 September 2015 02:42
To: **Peter Frampton**

Peter

How's this one?
Keep in touch. Fun discussing IOP with you

Best Regards,

Dave
David A. Taylor
Senior Product Manager, Advanced Diagnostics and Tonometry
Reichert Technologies

Appendix 4.0 – Consent Form Phase 1. Normals 2013

Patient Information Sheet

Study Title: Corneal biomechanics and its relationship with central corneal thickness, corneal curvature and tonometry in normal eyes

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

- Part 1 tells you the purpose of this study and what will happen if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

PART 1

What is the purpose of the study?
The cornea is the front structural part of your eyes. It has structural and physical properties that enable its unique function as the window of human vision. The cornea has several physical properties that have significant influence on the measurement of the pressure inside the eye (intraocular pressure). These physical properties include: corneal movement behaviour (biomechanics), corneal curvature and corneal thickness.

The accurate measurement of the intraocular pressure is very important in the management of a variety of eye conditions including glaucoma and corneal diseases. Currently the standard method of eye pressure measurement in hospital eye clinics is by using a Goldmann tonometer. It is not entirely clear how much the physical properties of the cornea affect the pressure measurement in normal eyes and how the different properties relate to each other. This study will investigate the effect of the physical properties of the cornea on the measurement of intraocular pressure. It will also investigate differences in corneal physical properties in participants from different ethnic backgrounds.

We will be measuring the eye pressure in **individuals not affected by any ocular diseases and have no history of corneal/eye surgery or laser treatment.**

Do I have to take part?
No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
First of all, we will ask information regarding your personal details, medical and surgical background and allergic history.

You will then have measurements taken of your cornea by a series of instruments. Some of the instruments will have no contact at all with your cornea (non-contact instruments) and some will touch your cornea (contact instruments) but you will not feel the contact as we will instil a drop of topical anaesthesia. The order in which the tests are done will be determined by a computer by a process called randomisation (like the tossing of a coin).

The instruments will examine your eye by either using flashes of light or mild touch on the front part of your eyes. In some tests you will see flashes of light in front of your eyes and in some you will feel puffs of air onto the surface of your eyes. This will not cause any pain or discomfort.

Each measurement will take less than 15 seconds to be performed. All the tests will take approximately 40 minutes.

At the end of the examination, you will be given a token of £10, after you provide your full name, contact number/email address and signature to acknowledge the receipt of the money. Your name and address is not required for the study but is required for our finance team.

You do not have to make any extra visits afterwards based on this study.

What is being tested?
We will assess the corneal behaviour (biomechanics), corneal thickness, corneal curvature and lastly the pressure inside your eyes using different techniques and instruments. Some of the instruments take several measurements at one time. We will compare the measurement from people of different ethnic backgrounds.

What are the potential side effects of the procedure?
Your eyes will be examined by an experienced ophthalmologist. You should not feel any pain or discomfort because your eyes will be numb from the eyedrop instilled prior to the investigations.

Some of the examinations do require gentle eye contact. In very rare situations, minor abrasion can happen and will typically heal within 24 hours.
Rarely, an allergic reaction to the eyedrop or the cover tip (containing latex) of the instruments may develop. The possible allergic symptoms are eye redness, itchiness and tearing.
We will examine your eyes at the end of the tests to identify any possible side effects. Appropriate action will be taken for any side effects and will be managed accordingly by our clinical team of experts.

What are the possible benefits of taking part?
Whilst there will be no direct benefit to you from taking part in the study the research will show how different corneal properties influence the measurement of intraocular pressure measurement. We will use this information to help us accurately measure eye pressure and improve patient eye care. The research may also lead to the development of new instruments that may not require eye contact to measure the eye pressure which would be more convenient for patients and clinicians.

What happens when the research study stops?
Your direct involvement in this study only lasts for the time taken to measure the corneal behaviour, corneal thickness, corneal curvature and pressure inside your eyes. The measurements will be kept until the research is completed. The data will be kept anonymised and then be destroyed.

Will my taking part in the study be kept confidential?
Yes. All the information about your participation in this study will be kept confidential.

Contact Details:
For further information about the study please contact:

Investigator:
Dr Shehzad Naroo School of Life and Health Sciences Aston University Birmingham, B4 7ET
Tel: 0121 2044132
Email: s.a.naroo@aston.ac.uk wanabdwb@aston.ac.uk

This completes Part 1 of the Information Sheet.

PART 2

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any point. However, we may still use the information collected up to your withdrawal unless you inform us not to.

What if there is a problem?

If you have a concern about any aspect of this study, you should in the first instance speak with the principal investigator who will do his best to answer your questions.

Dr Shehzad Naroo School of Life and Health Sciences Aston University Birmingham, B4 7ET
Tel: 0121 2044132
Email: s.a.naroo@aston.ac.uk

Who do I contact if I wish to make a complaint about the way in which the research is conducted?

If you have any concerns about the way in which the study has been conducted, then you should contact the Secretary of the University Ethics Committee on j.g.walter@aston.ac.uk or telephone 0121 204 4869.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. This information will be gathered by one of the clinical members of staff either directly from you at the time you enrol in the study or from your clinical notes at a later date. This information is anonymised, and only clinical members of staff involved directly with this research will have access to any identifiable data. Our procedures for handling, processing, storage and destruction of your data are compliant with the *Data Protection Act 1998*. You have the right to view the data we have on record about you and to correct any errors.

What will happen to the results of the research study?

It is intended that the results of the research will be presented at scientific meetings, and published in relevant clinical and academic journals. We also feed these results back to participants through patient support groups and information in clinic. You will not be identified in any report or publication.

Who is organising and funding the research?

The Ophthalmic Research Group, Aston University is organising this study. You will receive £10 as a token of appreciation for participating in the study.

Who has reviewed the study?

This study was reviewed by the Aston University Research Ethics Committee.

CONSENT FORM:

Corneal biomechanics and its relationship with central corneal thickness, corneal curvature and tonometry in normal eyes

Study Number: _____

Subject Identification Number: _____

	Please initial box
1. I confirm that I have read and understand the information sheet dated 05/08/13 (version 1.2) for the above study. I have had the opportunity to consider the information provided, ask questions and have had these answered to my satisfaction.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. I understand that my medical care or legal rights will not be affected.	☐
3. I understand that and data collected during the study may be looked at by individuals from Ophthalmic Research Group of Aston University, where it is relevant to my taking part in this research. I give permission for these individuals to have access to this information.	☐
4. I agree with my optometrist being informed of my participation in the study (if relevant).	☐
5. I agree to take part in the above study.	☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

1 copy for the patient, 1 for researcher site file

Appendix 5.0 – Ethics Approval Phase 1: Normals 2013

Aston University Ethics Committee
Aston University
Aston Triangle
Birmingham
B4 7ET
Telephone +44 (0)121 204 3000
Fax +44 (0)121 204 3696

Chairperson: Ms Nichola Seare

Secretary: Mr John Walter

5th September 2013

Dr Shehzad Naroo,

Life & Health Sciences

Dear Shehzad

Study Title: 'Corneal Biomechanics and its Relationship with Central Corneal Thickness, Corneal Curvature and Tonometry in Normal Eyes'

REC Reference: Ethics Application 542

Protocol Number:

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

The project is approved until the completion date specified on the form (April 9 2014) provided it is commenced within two years of the date of this letter and you are required to notify the Committee when the project is completed.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	EC Review Date
University Ethics Application Form	One	23/04/2013
Risk Assessment & Control Form	One	23/04/2013
Supporting Document: *Identification of Biomechanical Properties of the Cornea: The Ocular Response Analyzer*	One	23/04/2013
Supporting Document: *Human Corneal Thickness and Its Impact on Intraocular Pressure Measures: A Review*	One	23/04/2013

and Meta-analysis Approach		
Supporting Document: *Assessment of True Intraocular Pressure: The Gap Between Theory and Practical Data*	One	23/04/2013
Patient Information Sheet and Consent Form	Version 1.0 26/03/2013	23/04/2013
Cover letter of reply	One	21/05/2013
Patient Information Sheet and Consent Form	Version 1.1 20/05/2013	21/05/2013
Research Protocol	One	21/05/2013
Patient Information Sheet and Consent Form	Version 1.2 05/08/2013	05/08/2013
Patient Information Sheet and Consent Form	Version 1.5 05/08/2013	22/08/2013

Statement of compliance

The Committee operates in accordance with the Aston University Ethics policy and procedures:

http://www1.aston.ac.uk/registry/for-staff/regsandpolicies/ethics-policy-and-procedures/

Reporting Requirements

The details of the investigation will be placed on file. You should notify the Secretary of the University Ethics Committee of any adverse events which occur in connection with this study and/or which may alter its ethical consideration, and/or any difficulties experienced by the volunteer subjects.

If you intend to make any future protocol amendments these must be approved by the Ethics Committee prior to implementation. You should also seek approval for any extension of the approved completion date.

Membership

The members of the University Ethics Committee present at the meeting are listed below:

- Dr Robert Morse, Lecturer on the B.Sc. Audiology programme
- Ms Nichola Seare, AHRIC Director, Aston University
- Mr John Walter, Director of Governance, Aston University

REC reference: **Ethics Application 542**
Please quote this number on all correspondence

With the Committee's best wishes for the success of the project

Yours sincerely

J.G. Walter

Secretary of the Ethics Committee

Email: j.g.walter@aston.ac.uk

Appendix 6.0 – Experimental Synopsis for potential Orthokeratology Subjects

What does the final phase entail?

PhD Working Title:

Tonometry: A Study in Biomechanical Modelling. Specifically a Reappraisal of the Relative Impact of Corneal Shape, Corneal Hysteresis and Central Corneal Thickness on the Accurate Measurement of Intraocular Pressure with Conventional Tonometers.

Purpose of the study:

The fluid inside the eye exerts a pressure (intraocular pressure- IOP). If the pressure is too high it can cause glaucoma which damages the optic nerve carrying visual images to the brain. Accurate measurement of IOP is considered essential for the correct management of glaucoma.
Unfortunately the primary machines used to measure IOP do so indirectly by indenting the cornea (clear front surface of the eye) a little. This means this measurement is affected not only by IOP but also on how rigid the cornea is, how thick the cornea is and also by the curved shape of the cornea. It is now becoming very apparent most tonometers (machines measuring IOP) are prone to too many errors when dealing with the variations between individual patients. An area not previously investigated is the effect corneal shape may have on IOP readings. This experiment is aimed at trying to modify, temporarily, the shape of the participant's cornea by fitting an orthokeratology lenses which flatten the cornea - temporarily.

Orthokeratology and Short Sightedness:

If an eye is short sighted (Myopic) the focussing system of cornea and lens is too strong for the optical length of the eye. Light will be focussed in front of the retina (Fig 1) and only a blurred image will be projected onto the retina.
By modifying the optical system the focus of light can be pushed back onto the retina so giving a clear image.
This adjustment of focal power can be achieved by Spectacle (Fig 2) or Contact Lenses but also by remodelling the optical structures of the eye itself as in Orthokeratology.

Fig 1.

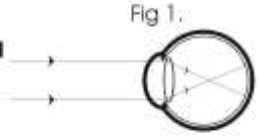
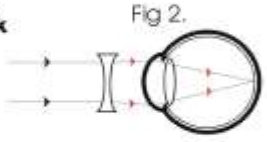
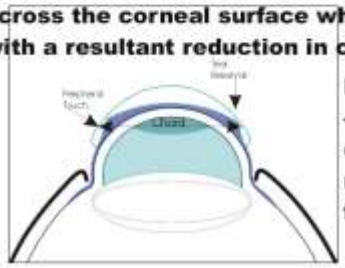


Fig 2.

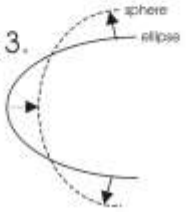


Specially designed rigid contact lenses worn while sleeping generate pressure differentials across the corneal surface which gently mould the corneal shape (Fig 3), with a resultant reduction in corneal power and myopia.



Best results are achieved up to -2.00 short sightedness. Most people could take part if wanted but others may experience slight blurriness for some hours post wear.

Fig 3.



Appendix 7.0 – Consent Form Phase 2. Orthokeratology

Email: peter@aaronoptometrists.com

Study Title:
Tonometry: A Study in Biomechanical Modelling.
Specifically a Reappraisal of the Relative Impact of Corneal Shape, Corneal Hysteresis and Central Corneal Thickness on the Accurate Measurement of Intraocular Pressure with Conventional Tonometers

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

- Part 1 tells you the purpose of this study and what will happen if you take part.
- Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

PART 1

What is the purpose of the study?
The cornea is the front structural part of your eyes. It has structural and physical properties that enable its unique function as the window of human vision. The cornea has several physical properties that have significant influence on the measurement of the pressure inside the eye (intraocular pressure). These physical properties include: corneal movement behaviour (biomechanics), corneal curvature and corneal thickness.

The accurate measurement of the intraocular pressure is very important in the management of a variety of eye conditions including glaucoma and corneal diseases. Currently the standard method of eye pressure measurement in hospital eye clinics is by using a Goldmann tonometer. It is not entirely clear how much the physical properties of the cornea affect the pressure measurement in normal eyes and how the different properties relate to each

other. This study will investigate the effect of the physical properties of the cornea on the measurement of intraocular pressure. It will also investigate differences in corneal physical properties in participants from different ethnic backgrounds.

We will be measuring the eye pressure in **individuals not affected by any ocular diseases and have no history of corneal/eye surgery or laser treatment.**

Do I have to take part?
No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
If you accept the invitation to take part, further examination techniques will be required involving three visits to the practice.

1. At the initial check :
    a. A full eye examination will be completed (there will be no charges for this).
        i. This will include asking information regarding your personal details, medical and surgical background and allergic history.
    b. We will re-discuss briefly the procedure and you can ask any further questions before we commence. Remember, you have every right to withdraw at any time without any question.
    c. The shape of the front of the eye will be measured and mapped with two instruments. These do not touch the eye.
    d. Intraocular pressure will be measured in four ways, rather than just one as is usual. One will be an air-puff type (but a much more advanced machine than the one you may be used to). Two will require drops to be instilled – these numb the eye for a very short while and we can assess pressure by applying a small probe to the front of the eye- this is a routine procedure at this practice and you may well have had it before. The third machine is very popular with patients who prefer it to the puffer air test. A tiny probe touches the front of the eye but is so gentle that we do not need to give drops.
    e. The thickness of the cornea will also be measured. This test also requires an eye drop to numb the eye before it lightly touches the front.
    f. Once all initial information about your eyes is gathered we will order the specific Orthokeratology lens to suit your eye.
2. At the second visit the procedures listed will be repeated.
    a. Why is it necessary to do them all again? We need to assess the repeatability of the tests used, how close will the second measurement be to the first.
3. At this second visit your lens will be ready. We can insert it for you (with more drops so you do not feel the lens at all). This must be a day when you are available to return to the clinic the following morning.
4. At the final visit, early the next day we will check the lens fit, remove it for you and then measure the same things as at the baseline check. Eye pressure with the four tonometers, corneal shape and corneal thickness. We will ensure the front of your eye

has not been affected. The blurriness will disappear over the day and while we do not necessarily need you back a fourth time you are more than welcome if you would feel more comfortable with another check the next day.

Each measurement will take less than 15 seconds to be performed. All the tests will take approximately 40 minutes.

At the end of the final examination, you will be given £100. Funded by Aaron optometrists and tax exempt,

You do not have to make any extra visits afterwards based on this study.

What is being tested?
We will assess the corneal behaviour (biomechanics), corneal thickness, corneal curvature and lastly the pressure inside your eyes using different techniques and instruments. Some of the instruments take several measurements at one time.

What are the potential side effects of the procedure?
Your eyes will be examined by an experienced Clinical Optometrist. You should not feel any pain or discomfort because your eyes will be numb from the eyedrop instilled prior to the investigations.

Some of the examinations do require gentle eye contact. In very rare situations, minor abrasion can happen and will typically heal within 24 hours.
Rarely, an allergic reaction to the eyedrop or the cover tip (containing latex) of the instruments may develop. The possible allergic symptoms are eye redness, itchiness and tearing.
We will examine your eyes at the end of the tests to identify any possible side effects. Appropriate action will be taken for any side effects and will be managed accordingly by our clinical team of experts.

What are the possible benefits of taking part?
Whilst there will be no direct benefit to you from taking part in the study the research will show how different corneal properties influence the measurement of intraocular pressure measurement. We will use this information to help us accurately measure eye pressure and improve patient eye care. The research may also lead to the development of new instruments that may not require eye contact to measure the eye pressure which would be more convenient for patients and clinicians.

What happens when the research study stops?
Your direct involvement in this study only lasts for the time taken to measure the corneal behaviour, corneal thickness, corneal curvature and pressure inside your eyes. The measurements will be kept until the research is completed. The data will be kept anonymised and then be destroyed.

Will my taking part in the study be kept confidential?
Yes. All the information about your participation in this study will be kept confidential.

Contact Details:
For further information about the study please contact:

Investigator:
Dr Shehzad Naroo School of Life and Health Sciences Aston University Birmingham, B4 7ET
Tel: 0121 2044132
Email: s.a.naroo@aston.ac.uk Peter@aaronoptometrists .com

This completes Part 1 of the Information Sheet.

PART 2

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any point. However, we may still use the information collected up to your withdrawal unless you inform us not to.

What if there is a problem?

If you have a concern about any aspect of this study, you should in the first instance speak with the principal investigator who will do his best to answer your questions.

Dr Shehzad Naroo School of Life and Health Sciences Aston University Birmingham, B4 7ET
Tel: 0121 2044132
Email: s.a.naroo@aston.ac.uk

Who do I contact if I wish to make a complaint about the way in which the research is conducted?

If you have any concerns about the way in which the study has been conducted, then you should contact the Secretary of the University Ethics Committee on j.g.walter@aston.ac.uk or telephone 0121 204 4869.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. This information will be gathered by one of the clinical members of staff either directly from you at the time you enrol in the study or from your clinical notes at a later date. This information is anonymised, and only clinical members of staff involved directly with this research will have access to any identifiable data. Our procedures for handling, processing, storage and destruction of your data are compliant with the *Data Protection Act 1998*. You have the right to view the data we have on record about you and to correct any errors.

What will happen to the results of the research study?

It is intended that the results of the research will be presented at scientific meetings, and published in relevant clinical and academic journals. We also feed these results back to participants through patient support groups and information in clinic. You will not be identified in any report or publication.

Who is organising and funding the research?

The Ophthalmic Research Group, Aston University is organising this study. Aarons is funding the £100 as a token of appreciation for participating in the study.

Who has reviewed the study?

This study was reviewed by the Aston University Research Ethics Committee.

CONSENT FORM:

Corneal biomechanics and its relationship with central corneal thickness, corneal curvature and tonometry in normal eyes

Study Number: _____

Subject Identification Number: _____

	Please initial box
6. I confirm that I have read and understand the information sheet dated September 2015 for the above study. I have had the opportunity to consider the information provided, ask questions and have had these answered to my satisfaction.	☐
7. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. I understand that my medical care or legal rights will not be affected.	☐
8. I understand that and data collected during the study may be looked at by individuals from Ophthalmic Research Group of Aston University, where it is relevant to my taking part in this research. I give permission for these individuals to have access to this information.	☐
9. I agree with my optometrist being informed of my participation in the study (if relevant).	☐
10. I agree to take part in the above study.	☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

1 copy for the patient, 1 for researcher site file

CONSENT FORM:

Corneal biomechanics and its relationship with central corneal thickness, corneal curvature and tonometry in normal eyes

Study Number: _____

Subject Identification Number: _____

	Please initial box
11. I confirm that I have read and understand the information sheet dated September 2015 for the above study. I have had the opportunity to consider the information provided, ask questions and have had these answered to my satisfaction.	☐
12. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. I understand that my medical care or legal rights will not be affected.	☐
13. I understand that and data collected during the study may be looked at by individuals from Ophthalmic Research Group of Aston University, where it is relevant to my taking part in this research. I give permission for these individuals to have access to this information.	☐
14. I agree with my optometrist being informed of my participation in the study (if relevant).	☐
15. I agree to take part in the above study.	☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

1 copy for the patient, 1 for researcher site file

Appendix 8.0 – Amended Ethics Approval for Orthokeratology Subjects

Aston University

2nd July 2015

Dr Shehzad Naroo,
Life & Health Sciences

Dear Shehzad

Study Title: Corneal Biomechanics and its Relationship with Central Corneal Thickness, Corneal Curvature and Tonometry in Normal Eyes

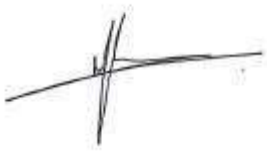
Reference Number: Project 542

Protocol Number:

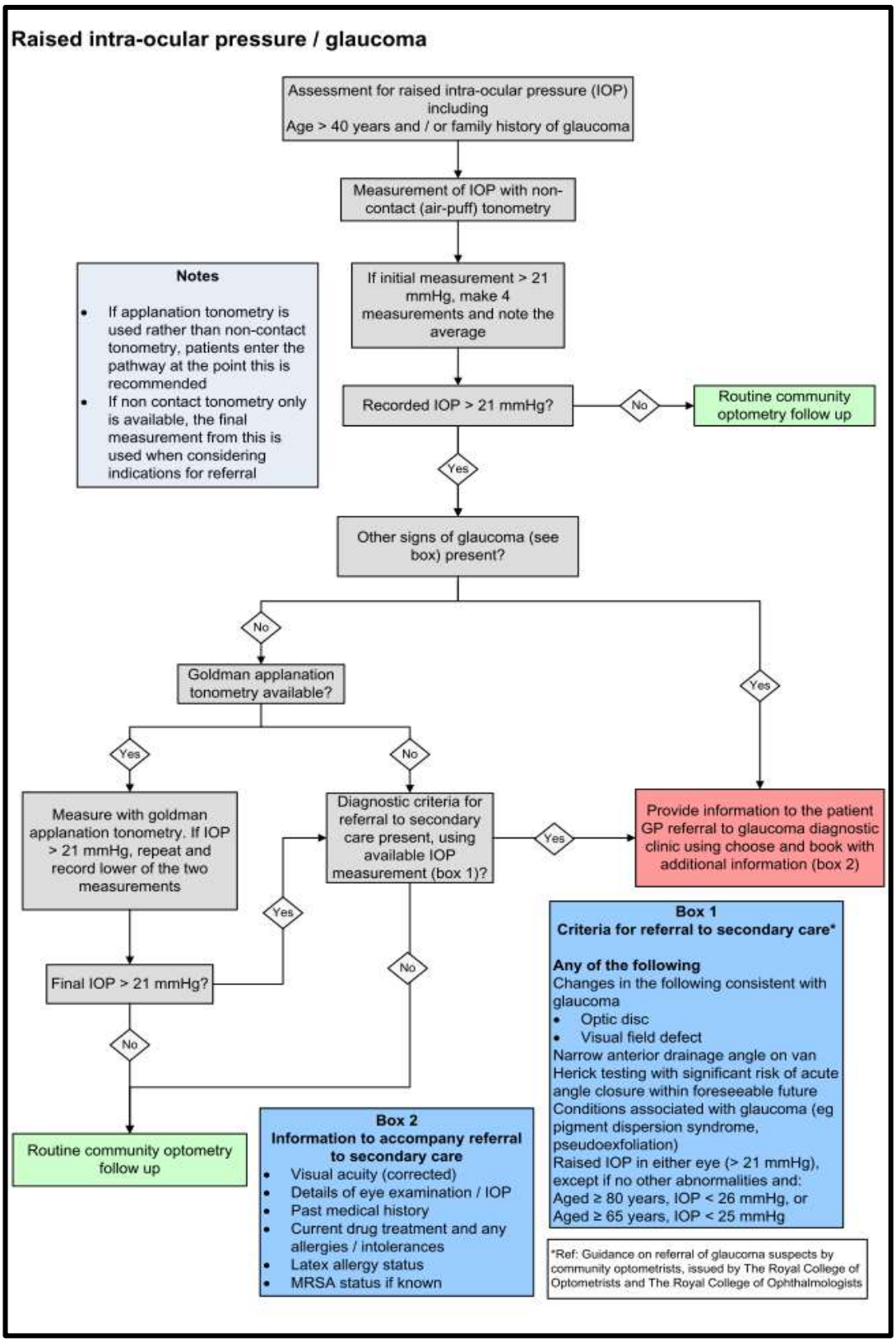
I am writing to inform you that I in my role as Chair of the University's Ethics Committee have approved on behalf of the Committee, the minor proposed amendment to the above project as described in your email of 16th June 2015, namely:

That as the project will continue with an ophthalmic doctoral student (Peter Frampton) in his practice in Northumberland on 35 contact lens (orthokeratology) patients, the previous ethics be amended to cover the extra 35 patients.

Yours sincerely



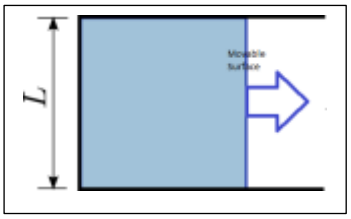
Appendix 9.0 – Referral Guidelines for Ocular Hypertension Accessed: http://www.newcastle-hospitals.org.uk/Ophthalmology_Referral_Guidelines_updated_April_2014



Appendix 10.0 – Force and Surface Tension

Force and Surface Tension:

Surface tension can be described either as a force (Force per Unit Length F/L) or as energy (Energy per Unit Area) (Trefethen 1969). Using SI notation surface tension is measured in Newton/metre (N/m) (Force) or Joules/metre² (J/m²) (Energy). However, a variant of the metric system, the CGS (Centimetre-Gram-Second) notation is often used (Force – Dyn/cm and Energy erg/cm²). The CGS units possibly represent a more appropriate scale for the magnitudes of the forces involved.



As a force: consider a thin surface film held within a rectangle (left); only the right hand side is moveable. The surface tension of the film will try to draw the moveable edge to the left; the force required to hold the side in place is proportional to the length (L) (F/L).

Considering a curved surface of a fluid meniscus, energy units are more intuitive.

Surface Tension (γ) is the property of a liquid surface ensuring it adopts a form minimising its outer surface area (van Honschoten et al. 2010).

$$\gamma = 1\frac{dyn}{cm} = 1\frac{mN}{m} = 1\frac{erg}{cm^2} = 1\frac{mJ}{m^2}$$

Dynes and Newtons are both measurements of Force.

A Dyne is the force required to accelerate a mass of 1gm at the rate of 1cm/s².
A Newton is the force required to accelerate a mass of 1 kg at the rate of 1m/s².
Since there are 1000gms in a kilogram and 100cm in a metre, dynes can be converted to Newtons:

$1dyn = 10^{-5}N \qquad 1N = 10^{5}\,dyn$

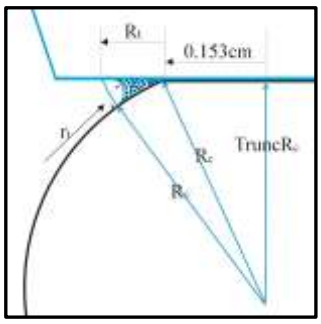
Appendix 11a - Excel Spread Sheet for Calculating Tear Bridge Forces. Step 1 estimation of tear meniscus radius

	A	B	C	D	E	F	G
1	Information	Corneal Radius (cm)	Truncated R (cm)	Tear Wedge Radius (cm)	Rt (0.1.53+C2)	Calculate Rc+2rt	Calculate rt
2							
3	Rc 8.0mm	0.8	0.785233086	0.039	0.192	0.808365635	0.004182818
4	Rc 7.8mm	0.78	0.764847044	0.039	0.192	0.788577834	0.004288917
5	Rc 6.9mm	0.69	0.672823157	0.039	0.192	0.699682071	0.004841035
6	Rc 9.0mm	0.9	0.886899656	0.039	0.192	0.907444213	0.003722107
7	Rc 11.0mm	1.1	1.089307578	0.039	0.192	1.106099001	0.0030495

r_t – Radius of Tear Mensicus
=(F3-B3)/2

=SQRT((C3*C3)+(E3*E3))

Pythagoras: calculation of hypotenuse: Radius of cornea + Diameter (2xr_t) of meniscus



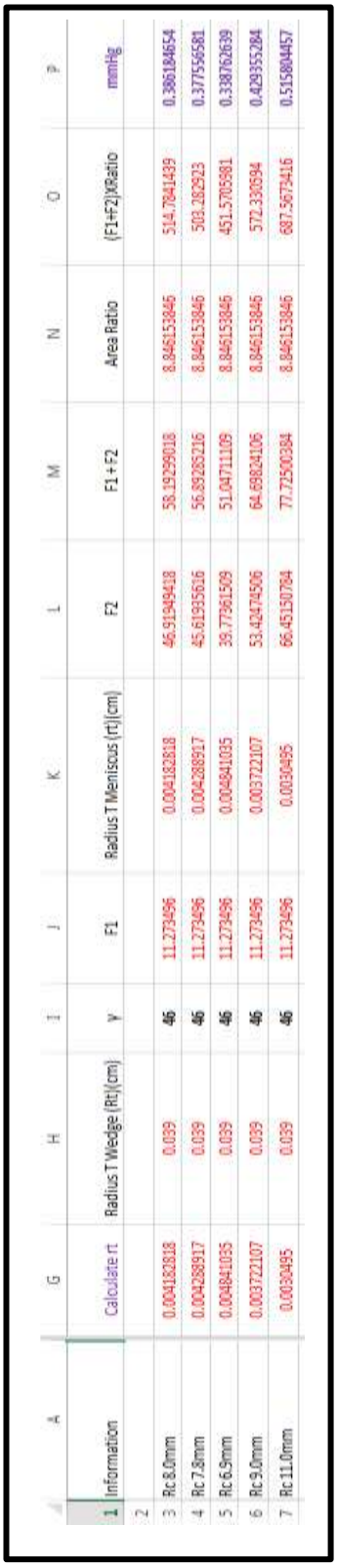
=D3+0.153 Smallest side of the triangle

=SQRT(((B3*B3) - (0.153*0.153)))

Step 1 from Figure 7.6:

$TruncR_c = \sqrt{(R_c^2 - (0.153)^2)}$

Appendix 11b - Excel Spread Sheet for Calculating Tear Bridge Forces. Step 2 estimation of tear bridge force P_c



	A	G	H	I	J	K	L	M	N	O	P
1	Information	Calculate rt	Radius T Wedge (Rt)(cm)	γ	F1	Radius T Meniscus (rt)(cm)	F2	F1+F2	Area Ratio	(F1+F2)XRatio	mmHg
2											
3	Rc 8.0mm	0.004182818	0.039	46	11.27496	0.004182818	45.91949418	58.19299018	8.846153846	514.7641439	0.386184654
4	Rc 7.8mm	0.004288917	0.039	46	11.27496	0.004288917	45.61935616	56.89285216	8.846153846	503.282923	0.377556581
5	Rc 6.9mm	0.004841035	0.039	46	11.27496	0.004841035	39.77961509	51.04711109	8.846153846	451.5705981	0.338762639
6	Rc 9.0mm	0.003722107	0.039	46	11.27496	0.003722107	53.42474506	64.69824106	8.846153846	572.330394	0.429355284
7	Rc 11.0mm	0.0030495	0.039	46	11.27496	0.0030495	66.45150764	77.72500364	8.846153846	687.5673416	0.515804457

=O3/1333

Tear Bridge Force converted to mmHg

(F1+F2) x proportional increase to full GAT tear annulus

Prportioning (F1+F2) to full GAT tear meniscus

=((3.142*(0.153+H3)*(0.153+H3))-(3.142*0.153*0.153))/(3.142*H3*H3)

Ratio

$$\frac{\text{GAT/Tear Bridge Area (Fig 7.3)}}{\textit{Point Contact Bridge Area (Fig 7.2)}} = \frac{(\pi(0.153+R_t)^2)-(\pi(0.153)^2)}{\pi(R_t)^2}$$

F1 + F2

Calculation of F2 =3.142*H3*H3*I3*(1/K3-1/H3)

$$F_2: \quad \pi R_t^2 \gamma \left(\frac{1}{r_t} - \frac{1}{R_t}\right)$$

From 10a Calculation (G3)

Calculation of F1 =(2*3.142*H3*I3)

$$F_1: \quad 2\pi(R_t)\gamma$$

Rt is width of cross section of tear annulus only. Does not include radius nof GAT probe.