Tonometry and Biomechanics of the Cornea in Contact Lens Wear

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Doctor of Optometry (by Research)

Aston University

May 2016

Thesis Summary

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Aims
Research on use of contact lenses as drug delivery systems continues. Disposable lenses are often used to treat corneal injuries. Accurate intraocular pressure (IOP) measurements with lenses *in situ* will enhance patient care and save valuable chair time.

Inter- and intraobserver reliability of rebound tonometer (RBT) and intraobserver reliability of ocular response analyser (ORA) with and without contact lenses of 50 (15 male, 35 female) healthy well adapted contact lens wearers between 18 – 55 years (M = 38.90, SD = 9.23) were examined. Clinical comparisons of IOP measurements with ORA and RBT were done. Accuracy of IOP measurements with four commonly prescribed disposable contact lenses (Acuvue Oasys, Frequency XC, Acuvue 1-Day Moist, and Pure Vision with powers -6.00 – +6.00 D) *in situ* was evaluated. Physiological and physical factors influencing IOP measurements with both instruments were determined.

Findings
Intraobserver reliability of RBT without and with lenses was excellent (ICC > 0.88; > 0.92 respectively). Interobserver reliability of RBT was excellent without or with lenses (ICC 0.81; 0.88 respectively). Intraobserver reliability of ORA was good for all metrics measured except for corneal hysteresis (CH) (ICC: CH 0.63; corneal resistance factor (CRF) 0.79; corneal compensated IOP (IOPcc) 0.77; IOPg 0.87).
RBT and ORA IOPg (Goldmann equivalent IOP) measurements were clinically and statistically comparable without or with lenses (differences < 0.6 mmHg). ORA IOPcc and RBT were less comparable (differences < 1.45 mmHg).
Accurate RBT and ORA tonometry (within 2 mmHg) was possible with low minus power (range -0.50 to -6.00 D); moderate modulus of elasticity (< 0.75 MPa); thin silicone hydrogel (Acuvue Oasys) and hydrogel (Frequency XC; Acuvue 1-Day Moist) contact lenses *in situ*.
Multiple regression analyses showed biomechanical metrics CRF and CH affected RBT and ORA (IOPcc and IOPg) measurements strongly ($p < 0.0001$). Therefore, cornea's biomechanical properties had greater influence on accuracy of IOP measurements with these two instruments than other variables examined.

Key words
Intraocular pressure, disposable contact lenses, modulus of elasticity, rebound tonometry, and ocular response analyser.

Dedication

This work is dedicated to the memory of Jan George Booysen and Dr John Leslie Eidelman.

Acknowledgements

I would like to thank my supervisor Dr's Amy Sheppard and Leon Davies for their guidance, support and encouragement over the past five years. In addition I would also like to thank Suzette Swart for the editing of this manuscript as well as my colleagues Gerrie Kruger, Magda Le Grange, and Marolize Botha for their help with the data collection and recording. Many thanks to Stephen Hugo and Lawrence Abrahamson from General Optical Pty. Ltd (SA) for the loan of the Reichert ocular response analyser used in the study. Thank you also to the 50 subjects (my patients) who volunteered to be part of the study. Finally, I must thank my family Sarah Leigh, Meagan, John Leslie, Angela, and Hester for their love understanding and encouragement to complete this work.

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Glossary of abbreviations

ACG – Angle closure glaucoma
CC – Correlation coefficient
CCC – Concordance correlation
CCT – Central corneal thickness
CH – Corneal hysteresis
CI – Confidence interval
CL – Confidence level
C/L – Contact lens
COR – Coefficient of repeatability
CoV – Coefficient of variation
CRF – Corneal resistance factor
CT – Centre thickness (contact lens)
CV – Coefficient of variation or correlation of variation
DCT – Dynamic contour tonometry
df – Degrees of freedom
DJB – Dirk Johan Booysen
ECM – Extracellular matrix
f – Fixation index
GAGs - Glycosaminoglycans
GAT – Goldmann applanation tonometry
GRRAS – Guidelines for reporting reliability and agreement studies
GHK – Gerrit Hendrik Kruger
H_0 – Null hypothesis
H_1 – Alternate hypothesis
HTG – High tension glaucoma
ICC – Intraclass correlation coefficient
IOP – Intraocular pressure
IOPcc – Corneal compensated IOP
IOPg – Goldmann equivalent IOP
K- Keratometry readings (corneal curvature)
KZN – KwaZulu Natal
LASIK – Laser assisted keratomeulesis
LC – Lamina cribrosa
M - Mean
MLG – Magda Le Grange
MPa – Mega Pascal
NCT – Noncontact tonometry
NTG – Normal tension glaucoma

OHT – Ocular hypertension
ONH – Optic nerve head
OHTS – Ocular hypertension treatment study
OPA – Ocular pulse amplitude
ORA – Ocular response analyser
p – Calculated probability
PACG – Primary angle closure glaucoma
PGs - Proteoglycans
POAG – Primary open angle glaucoma
PoF – Point of focus
QS – Quality score
RBT – Rebound tonometry
RC – Reliability coefficient
RR – Relative risk and or relative repeatability
R^2 - Coefficient of determination
R.L.L.R – Right left left right
Rx – Refractive error or contact lens prescription
SD – Standard deviation
SWAP – Short wavelength automated perimetry
t – Ratio of the coefficient against its standard error
UP – Ultrasound pachymetry
VARMID – Variance of difference between middle reading and the average of the first and last readings
wsSD – Within subject standard deviation
X^2 – Chi squared
Z -Standard score
≈ – Approximately equal

Chapter 1

Intraocular pressure measurements and factors influencing its accuracy

1.1 General introduction

Tonometry refers to the measurement of intraocular pressure (IOP) with various instruments (tonometers) with each tonometer employing at least one or combinations of the following four physical principles: indentation, applanation, contour matching, and rebound tonometry (Kniestedt et al., 2008). The accuracy of all tonometers is affected by specific characteristics of the eye being measured. These characteristics include, but are not limited to, central corneal thickness (CCT), corneal curvature, corneal and scleral elasticity and viscoelasticity, biomechanics of the eye, ocular pulse amplitude (OPA), and tear film surface tension (Kniestedt et al., 2008).

It has been suggested that measurements of the CCT should be a mandatory investigation in patients with glaucoma and ocular hypertension (Brandt, 2004) and several correction formulae have been produced to account for the variation in corneal thickness and its influence on IOP measurements (Ehlers et al., 1975; Whitacre et al., 1993; Stodtmeister, 1998; Doughty and Zaman, 2000; Shimmyo et al., 2003). Significant among these formulae are the Ehlers model which corrects IOP for errors induced by corneal thickness and the mathematical or theoretical model of Orssengo & Pye which corrects IOP for errors induced by corneal thickness as well as corneal curvature (Ehlers et al., 1975; Orssengo and Pye, 1999). Gunvant et al. (2005), investigated the efficacy of the Ehlers and the Orssengo & Pye formulae to correct IOP measured by the Goldman applanation tonometer (GAT) for CCT and found that both these models overestimated the effect of corneal parameters on GAT IOP measurements (Gunvant et al., 2005). This effect of CCT on measured IOP reported by Gunvant et al. (2005) was found to be consistent with other studies in literature (Herndon et al., 1997; Wolfs et al., 1997; Singh et al., 2001; Bhan et al., 2002) thereby indicating other intrinsic and extrinsic factors may also influence the accuracy of IOP measurements. Corneal characteristics such as CCT, corneal curvature, and biomechanics can be altered by using soft contact lenses on the eye when measuring IOP. This makes it possible to clinically evaluate the effects of these changes on the accuracy of the IOP measurements with different instruments, techniques and contact lens materials. Recent research posits that contact lenses will be used as drug delivery systems to the eye (Maddox and

Bernstein, 1972; Peng et al., 2010; Jung et al., 2013) and that accurate measurements of IOP with these lenses *in situ* would greatly benefit clinicians treating patients with glaucoma, corneal trauma, and other eye disease.

The literature review covered the following topics: intraocular pressure (IOP); the importance of IOP in the diagnosis and management of the glaucomas; measurements of IOP; prevalence of glaucoma worldwide as well as in South Africa; the Goldmann applanation tonometer (GAT); noncontact tonometry (NCT) and the ocular response analyser (ORA); rebound tonometry or ICare tonometry (RBT); Scheimpflug or Pentacam corneal tomography; and the impact of soft contact lenses on the accuracy of IOP measurements.

1.2 Intraocular pressure

The vertebrate eye is a fluid-filled sphere with flexible and partially elastic walls. Intraocular pressure (IOP) maintains a stable shape necessary for the important optical properties of the eye (Hart, 1992). IOP is maintained within a fairly narrow range by a complex, dynamic equilibrium in which aqueous production is matched by a constant rate of aqueous escape from the eye through the drainage pathways. Flow rates vary between 2 µl/min and 3 µl/min with higher flow rates during waking hours than during sleep (Lawrenson, 2007). Although small variations in either the production or rate of outflow from the eye can result in large changes in IOP, a remarkably stable homeostasis is maintained in the healthy eye (Hart, 1992). Aqueous is produced in the ciliary body epithelia by a complex, energy-dependent metabolic pump. The pump operates at a constant rate which is not sensitive to IOP. A semipermeable membrane blocks all macromolecules (ensuring high optical quality), resulting in a blood aqueous barrier similar to the blood-brain barrier (Hart, 1992). The metabolic needs (mainly oxygen and glucose) of the lens epithelium, corneal endothelium, and other structures in the anterior chamber are provided by the aqueous humour (Hart, 1992).

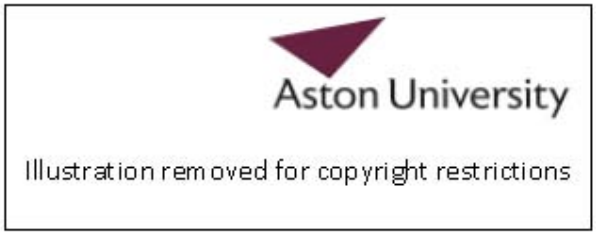


Figure 1.1 Aqueous flows from the posterior chamber, between the lens and the posterior surface of the iris, through the pupil into the anterior chamber of the eye to drain mainly through the trabecular meshwork into Schelmm's canal. Note the iris-lens channel. (Drawing courtesy of Gerrie Kruger)

From the ciliary body the aqueous moves from the posterior chamber, across the anterior surface of the lens, past the narrow space between the posterior surface of the iris and the anterior surface of the lens (iris-lens channel), through the pupil and into the anterior chamber of the eye. From the anterior chamber the vast majority of the aqueous then exits the eye via the trabecular meshwork into Schelmm's canal as well as the collector channels into the network of episcleral veins (Hart, 1992) (Figure 1.1). A secondary, non-pressure dependent, drainage passage exists via the uveoscleral outflow. At normal IOP levels, the aqueous slowly weeps through the face of the ciliary body (just posterior to the scleral spur in the apex of the anterior chamber) into the supraciliary and suprachoroidal spaces and surrounding periocular tissues to be absorbed into the blood vessels draining the uvea (Hart, 1992; Lawrenson, 2007). It is estimated that 15% – 20% of total aqueous outflow is via this route (Freddo, 1993; Lawrenson, 2007). Although uveoscleral outflow is not

pressure dependent, contraction of the ciliary muscle − while beneficial for trabecular outflow − can significantly alter the amount of uveoscleral outflow by compressing the intracellular spaces within the muscle that constitutes the drainage pathway (Freddo, 1993).

Resistance to aqueous flow occurs between the iris and the lens due to the close approximation between the posterior surface of the iris and the anterior capsule of the lens (iris-lens channel); additionally, a pressure gradient is also present from the cornea to the cerebrospinal fluid. This leads to a small but significant difference in pressure between the posterior and anterior chambers of the eye (Hart, 1992; Robert, 2007). Normally the anterior-posterior chamber pressure differential is around 1 mmHg (higher pressure in the posterior chamber) but this can be significantly affected by variations in the iris-lens channel dimensions and viscous forces within the aqueous resulting in clinically significant pressure differences (Silver and Quigley, 2004). Tonometry on the cornea measures the anterior chamber pressure and does not estimate the true pressure in the posterior chamber and vitreous cavity. Hence, the pressure at the optic nerve head may be significantly different in some eyes from the pressure measured at the cornea obscuring an additional risk factor in glaucoma damage (Silver and Quigley, 2004). However, the principal resistance to aqueous flow in the eye is encountered in the trabecular meshwork. Resistance to flow rises gradually through the progressively smaller spaces of the mesh with the juxtacanalicular tissue being responsible for the highest resistance to aqueous outflow and the generation and fluctuation of the IOP in the normal eye (Hart, 1992; Lawrenson, 2007; Robert, 2007). IOP is dependent on the vascular and respiratory properties of the body and the eye. Therefore, the pulse also affects the eye pressure (more specifically the ocular pulse amplitude); hence, IOP is only correctly measured when this effect on the measurements is considered (Robert, 2007).

Although IOP is relatively constant, long-term variations associated with age, blood pressure, and calendar seasons as well as short-term variations associated with body posture, exercise, eye movement, and drug effects can occur (Hart, 1992; Spry and Harper, 2010). For example, IOP is usually measured during office hours which are generally from between 08h00 to 17h00 in South Africa. The normal diurnal variation (short-term fluctuation) during this timeframe is about 5mmHg (Harper and Henson, 2007; Spry and Harper, 2010). Conversely, the nocturnal IOP can be significantly higher in part due to the supine body position, and can consequently lead the clinician to underestimate peak IOP (Harper and Henson, 2007; Spry and Harper, 2010). The measurements of IOPs during routine office hours can miss up to 62% of IOP peaks found if testing is done outside

office hours and up to 88% of IOP troughs (Hughes et al., 2003; Mosaed et al., 2005; Barkana et al., 2006). Yet, supine IOP measurements can be used to estimate nocturnal peak IOPs better than sitting IOP measurements thereby providing valuable information to the clinician when evaluating ocular hypertension (OHT) patients (Mosaed et al., 2005). The relative importance of IOP peaks remain unclear even though several studies have demonstrated that IOP peaks tend to be associated with visual field loss as well as short-term fluctuation in IOP of more than 5 mmHg (Sultan et al., 2009). Long-term IOP fluctuation (between office visits on separate days) is also associated with a greater risk of progression of visual field loss but is not considered an independent risk factor (Sultan et al., 2009).

1.3 The importance of IOP in the diagnosis and management of the glaucomas

Although historically there has been a great deal of emphasis on intraocular pressure, IOP is no longer included in the definition of glaucoma but is rather seen as a primary risk factor for the development of glaucoma (Rudnicka and Owen, 2007). Glaucomatous optic nerve head and/or visual field changes can occur in the presence of "low, normal or elevated" IOP (Anderson et al., 2001). More recently glaucoma has been defined as "a group of diseases of the optic nerve which result in a loss of retinal ganglion cells in a characteristic pattern of optic neuropathy or an optic neuropathy which causes characteristic optic nerve head cupping and visual field loss"(Coleman, 1999). Nowadays, glaucoma is recognised as a chronic non-curable condition which is often symptom free. Unfortunately, if left untreated it eventually leads to severe loss of vision and quality of life (Rudnicka and Owen, 2007; Heijl et al., 2008; Spry and Harper, 2010). Treatment, which consist mainly of drugs or surgical procedures to lower IOP, attempt to avoid significant vision loss during the patient's lifetime (Heijl et al., 2008; Heijl et al., 2013).

The classification of glaucoma includes primary (mechanism of the disease is unknown) and secondary (secondary to another ocular or systemic disease) glaucoma. Primary glaucoma is further subdivided into primary open angle glaucoma and primary closed angle glaucoma. Primary open angle glaucoma (POAG) is subdivided into normal tension glaucoma (NTG), high tension glaucoma (HTG), and ocular hypertension (OHT) (Rudnicka and Owen, 2007).

OHT can be defined as IOP above 21 mmHg with no evidence of optic nerve damage, visual field loss and/or symptoms (Rudnicka and Owen, 2007). Normal IOP is considered as 15 to 16 mmHg with a standard deviation of 2.5 mmHg. The upper limit is given as 2 standard deviations higher at 21 mmHg

(Harper and Henson, 2007; Rudnicka and Owen, 2007). The distribution is not strictly Gaussian (positively skewed) thus resulting in considerable overlapping of IOP between normal and glaucomatous patients (Harper and Reeves, 1999). Approximately 6.6% of the normal population will have an IOP > 21 mmHg (Harper and Reeves, 1999).

The prevalence of OHT is estimated to be between 4 and 7% in the over 40-year-old population in the United States of America (USA) (Kass et al., 2010). The Roscommon study examined an Irish population over 50 years of age and found the prevalence of OHT at 4.2% and POAG at 1.87% (Coffey et al., 1993) while the Blue Mountains eye study in Australia looked at Caucasian males and females over the age of 49 and found the prevalence of OHT at 3.7% and POAG at 2.4% (Mitchell et al., 1996). Bonomi et al. (1998) also evaluated Caucasian males and females between 40 and 70 years of age in a closed population in Egna-Neumarkt, Northern Italy and found the prevalence of OHT at 2.1% and POAG at 1.4% (Bonomi et al., 1998). Wormald et al. (1994) determined the prevalence of OHT among a Black African Caribbeans (35 – 60+ years old) to be 2.18%. The prevalence of POAG in African Americans, Hispanics, and Latinos over the age of 40 years was around 4 to 5 times that of the Caucasian population therefore indicating a higher prevalence of OHT as well (Sommer, Tielsch, Katz, Quigley, et al., 1991; Tielsch, Sommer, et al., 1991).

Elevated intraocular pressure remains the leading risk factor for developing glaucoma and glaucomatous visual field loss. Davanger et al. (1991) did an investigation to determine the probability of glaucoma in a large population-based study of older Norwegians. Their data show at an IOP of 18 mmHg or lower the probability of having POAG was near zero; at 28 mmHg the probability was 60%; and at 35 mmHg the probability approached 100% (Davanger et al., 1991). A further cross-sectional study in Europeans with IOPs ranging from 25 to 29 mmHg and 30 to 34 mmHg estimated the prevalence of glaucoma at 7% and 14% respectively (Pohjanpelto and Palva, 1974). Sommer et al. (1991) found in a multiracial population the risk of optic nerve damage increased nonlinearly when the IOP was higher than 22 mmHg. They calculated at IOPs of 22 to 29 mmHg and 30 mmHg or more, patients were 12.8 times and 39 times more likely to develop glaucoma respectively. Finally, the overall risk of glaucomatous field loss is 5 times higher in patients with an IOP higher than 21 mmHg than in patients with an IOP lower than 21 mmHg (Leske, 1983). Table 1.1 summarises the prevalence of POAG at different screening IOP levels and the relative risk at specific IOP levels from the population-based Baltimore Eye Survey data (Sommer, Tielsch, Katz and et al., 1991; Tielsch, Katz, et al., 1991).

IOP (mmHg)	Cumulative % with POAG	Prevalence of eyes with POAG (%)	Relative Risk (RR)
<15	13	0.65	1.0
16-18	37	1.31	2.0
19-21	59	1.82	2.8
22-24	78	8.30	12.8
25-29	88	8.33	12.8
30-34	97	25.37	39.0
≥ 35	100	26.09	40.1

Table 1.1 Data from the Baltimore Eye Survey indicating the prevalence and relative risk of POAG at different IOP screening levels and specific IOP levels respectively (Sommer, Tielsch, Katz and et al., 1991; Tielsch, Katz, et al., 1991)

Lowering IOP has been shown to slow or halt the onset of primary open angle glaucoma in patients with OHT by 50 to 60% (Kass et al., 2002). This seems to firstly confirm that the pathophysiological basis for glaucoma is an elevated IOP and, secondly, it supports the mechanical theory of the pathogenesis of optic nerve neuropathy in glaucoma (Quigley and Addicks, 1981; Lusky et al., 1993; Cartwright and Anderson, 1998; Quigley, 2001; Maier et al., 2005).

It is estimated that 3 to 6 million people in the USA alone have elevated IOP (OHT) without detectible glaucomatous damage on standard clinical tests (Kass et al., 2010). In fact, in 2006 Quigley and Broman estimated the number of people with glaucoma (POAG and PACG) in 2010 would be about 60.5 million which would increase to 79.6 million by 2020. Although these authors do not provide separate estimates for OHT, their estimates for people suffering from POAG worldwide were 44.7 million in 2010 increasing to 58.6 million by 2020 (Quigley and Broman, 2006). At this point it is important to reiterate that population-based prevalence studies such as the Roscommon, Blue Mountains and Egna-Neumarkt studies affirm that the prevalence of OHT is known to be nearly double that of POAG. Therefore, it can be argued that in 2010 about 50% of the estimated 110 million people with OHT worldwide would probably go undiagnosed. Of further significance is the conclusion of Quigley and Broman (2006) that glaucoma is the second leading cause of blindness worldwide (Quigley and Broman, 2006). Table 1.2 summarises their 2010 worldwide estimates for POAG according to geographic locations.

In a systematic review and meta-analysis entitled *Global Prevalence of Glaucoma and Projections of Glaucoma Burden Through 2040: A Systematic Review and Meta-analysis*, Tham et al. (2014) addressed, estimated and evaluated the worldwide burden of glaucoma. According to these authors'

evaluation, their review projected the worldwide prevalence of glaucoma burden up until 2040 for populations aged 40 to 80 years is 3.54% (95% CI [2.09 to 5.82]). The prevalence of POAG is higher in Africa at 4.20% (95% CI [2.08 to 7.35]), and the prevalence of PACG is higher in Asia at 1.09% (95% CI [0.43 to 2.32]). According to the review, in 2013 the number of people between 40- and 80-years old with glaucoma (both POAG and PACG) was 64.3 million worldwide. The projected increase in numbers is 76 million by 2020 and 111.8 million by 2040. Of further note is that after adjusting for age, gender, habitation type, response rate, and year of study, people of African ancestry are more likely to have glaucoma than people of European ancestry (OR, 2.80: 95% CI [1.83 to 4.06]). The review further indicated that people living in urban areas are more likely to have POAG than those living in rural areas (OR, 1.58; 95% CI [1.19 to 2.04]) (Tham et al., 2014).

	Total POAG	95% Confidence levels	% Worldwide
Europe	10,693,335	7,599,188 to 14,040,703	23.9%
China	8,309,001	6,695,433 to 10,423,439	18.6%
India	8,211,276	6,812,711 to 9,937,413	18.4%
Africa	6,212,179	4,992,103 to 7,722,626	13.9%
Latin America	5,354,354	2,943,534 to 9,697,792	12.0%
Japan	2,383,802	2,106,534 to 2,697,623	5.3%
SE Asia	2,116,036	1,744,523 to 2,580,354	4.7%
Middle East	1,440,849	1,001,315 to 2,082,944	3.2%
World	44,720,832	33,895,340 to 60,182,894	

Table 1.2 Number of people with POAG 2010 (POAG – Primary open angle Glaucoma)(Quigley and Broman, 2006)

1.4 Glaucoma in South Africa

Kyari et al. (2009) suggests that the differences between the prevalence of blindness in different countries in Africa and Asia could be due to a number of factors and the criteria used for the definition and collection of the data. These include the causes of blindness, access to eye care services, or even differences in life expectancy of the various populations. They found a national

prevalence of 4.19% for the blind or visually impaired in Nigeria (Kyari et al., 2009). Ntim-Amponsah et al. (2004) also found that West African and people of African descent also had a high prevalence of glaucoma (Ntim-Amponsah et al., 2004).

In 2004 Resinkoff et al. (2004) observed that in sub-Saharan Africa 27 million people were visually impaired of which 6.8 million were blind (Resnikoff et al., 2004). According to the World Health Organization (WHO), the main causes of preventable blindness in Africa are cataract (50%); glaucoma (12%); corneal opacity (5%); diabetes (5%); trachoma (4%); vitamin A deficiency, measles and neonatal conjunctivitis (4%); and onchocerciasis (0.8%). Other causes include low vision and refractive errors (14%) (WHO, 2007). The major causes of blindness in children in Africa vary widely from region to region as it is largely determined by socioeconomic development and the availability of primary health care and eye care services. Furthermore, corneal scarring from measles, vitamin A deficiency, using harmful traditional eye remedies, ophthalmia neonatorum, and rubella cataract are the leading causes in low-income countries whereas in high-income countries lesions of the optic nerve and higher visual pathways predominate as the cause of blindness (WHO, 2007). Retinopathy of prematurity is an important cause in middle-income countries. Other significant causes in all countries are congenital abnormalities such as cataract, glaucoma, and hereditary retinal dystrophies (WHO, 2007).

However, the WHO (2007) also points out that the majority of the causes of childhood blindness are preventable or treatable; indeed, 75% of all cases of blindness in Africa are preventable (WHO, 2007). As part of the strategy for reducing these statistics, the WHO emphasises the urgency for early diagnosis and treatment and recommends strengthening of the capabilities of eye care providers (WHO, 2007). It was also concluded by Bastawrous et al. (2014) that posterior segment eye diseases "are likely to grow in importance as causes of visual impairment and blindness in sub-Saharan Africa in the coming years as populations grow, age and become more urban in lifestyle" (Bastawrous et al., 2014). While children (less than 16 years of age) contribute to a minority in the glaucoma epidemiology estimates, in the late nineties it was found that glaucoma (6.7%) was the major cause of blindness in pupils in the majority (16 out of 17) schools for the blind in South Africa (O'Sullivan et al., 1997). Of further importance is the fact that the proportion of previously undiagnosed glaucoma was found to be as high as 87% in South Africa (Table 1.3) (Shaarawy et al., 2009). In South Africa, ±5% of the Black population over 40 years have primary open angle glaucoma while the prevalence in the white populations is around 1.5%. (Salmon et al., 1993; Rotchford and Johnson, 2002; Rotchford

et al., 2003). Similar numbers are reported for Black Cameroonians (Ellong et al., 2006) but the prevalence is lower than the estimate of ±7% for Blacks in Ghana and in Barbados (Ntim-Amponsah et al., 2004; Kyari et al., 2013). According to South African Government statistics (2014), 43,333,700 Blacks reside in South Africa, 10.5 million of them are older than 40 years. Considering a POAG prevalence of ±5% (over 40 year old group) the number of Black citizens in South Africa with diagnosed glaucoma is therefore ±525 000

A review of publications in PubMed on glaucoma specifically in sub-Saharan Africa was done by Cook (2009) to investigate the priority need for inclusion into Vision 20/20 planning. Cook's conclusion reads: "Glaucoma should be included as a priority disease in Vision 2020 programs" (Cook, 2009). Further suggestions included "cases could be followed up after surgery by mid-level eye care workers, using the intraocular pressure as the indicator for adequacy of control, and using a glaucoma register to identify and trace defaulters" because follow-up requirements for treatment were often disregarded (Cook, 2009).

Additionally, in the 2003 Temba glaucoma study (Rotchford et al., 2003) it was determined that a large number of the African Black population in an urban South African population had blindness due to glaucoma (Table 1.3) and the majority was undiagnosed and untreated. Blindness also occurred at a young age. The prevalence in the urban African Black population was much higher than in the urban white population (Rotchford et al., 2003). In a previous population-based study conducted by Rotchford and Johnson (2002) with a Zulu ethnic population in a rural region in South Africa, the blindness prevalence was found to be relatively high: 4.7% with POAG contributing 2.7%. While this study attempted to only include data relevant to the Zulu ethnicity in a rural region, some other ethnicities were included by default, possibly due to the impact of migrant working conditions and multiple partners. Nevertheless, the finding that the prevalence of glaucoma was found to be high carries significant implications for the already struggling rural health care districts in KwaZulu-Natal (KZN), (one of the nine provinces in South Africa). The findings of researchers like Rotchford and Johnson (2002) and Cook (2009) confirm the varied prevalence of glaucoma in African Black populations in sub-Saharan Africa as well as in South Africa (Rotchford and Johnson, 2002; Cook, 2009).

Investigating the possible differences due to glaucoma variations in different ethnic races, a study was conducted in a community of mixed ethnic backgrounds in the Western Cape, another province in South Africa (Salmon et al., 1993). The findings were idiosyncratic and indicated that across all

ages, females were affected four times more frequently than males. Bilateral blindness occurred with a prevalence of 0.5% for both primary glaucomas in this community. The implications for the rural health care districts of both KZN (Rotchford and Johnson, 2002) and the study done in the Western Cape (Salmon et al., 1993) are of significance. Due to the different ethnic backgrounds of populations, Salmon et al. (1993) are of the opinion that similar findings may result in the populations of Southeast Asia (Salmon et al., 1993).

Population Studied	**Percentage of cases previously undiagnosed (POAG)**
South Africa (Temba)	87%
Chennai – Southern India	98.5%
Los Angeles Latinos (LALES)	75%
Australia – Blue Mountains Eye Study	51%
Melbourne (Visual Impairment Project)	50%
Rotterdam	53%

Table 1.3 Proportion of people with glaucoma cases detected in population-based surveys that were previously undiagnosed(Shaarawy et al., 2009)

1.5 Summary

Given the hypothesis that elevated IOP causes glaucoma one can postulate that the only way to treat glaucoma effectively is to lower IOP. But, not all patients with elevated IOP do develop glaucomatous optic nerve head and visual field changes; conversely, other patients with low or normal IOP can develop these changes. Risk factors for the development of primary open angle glaucoma include: elevated IOP; myopia > 3.00D; older age; male gender; African American/Hispanic/Latino ethnicity; low socioeconomic status; alcohol drinking and smoking; positive family history; genetic factors; systemic hypertension; type 2 diabetes; cholesterol and coronary heart disease; and vasospastic disease (Rudnicka and Owen, 2007). However, multicentre trials have shown the most important predictive risk factors for the development of POAG in individuals with OHT may be higher baseline IOP; thinner central corneal thickness; older age; higher vertical cup to disc ratios; and higher pattern standard deviation values with standard automated perimetry (Gordon et al., 2002; Coleman and Miglior, 2008).

The Ocular Hypertension Treatment Study (OHTS) conclusively demonstrated a 20% reduction in IOP reduced the incidence of POAG between 50 and 60% (Kass et al., 2002). Consequently, the prevalence and severity of POAG can be significantly reduced by treating OHT individuals before they develop glaucoma. However, the treatment of all OHT individuals is neither medically indicated nor economically justified because of the high prevalence of the condition, the low conversion rate to POAG, and the cost, inconvenience as well as possible adverse effects of treatment (Heijl et al., 2008). By carefully evaluating specific baseline risk factors, OHT individuals at high risk for developing POAG can be identified and appropriately treated or observed depending on their specific risk profiles (Heijl et al., 2008).

Ultimately, clinicians are faced with the difficult decision of who to treat and who not to treat. As our understanding of glaucoma improves, technology to evaluate the structural and functional changes earlier in the disease process becomes available while medical treatment (neuroprotective or conventional IOP lowering) is also refined to further reduce unwanted side effects. Subsequently, the management and the prevention of the progression of OHT will be simplified. In the meantime it makes sense that younger patients with several high risk factors should receive prophylaxis while elderly patients with few risk factors should not (Heijl et al., 2008; Sommer, 2010).

Global and regional epidemiological studies are required to support community ocular health care to subsequently reduce the risk of preventable blindness. Research is progressing on various aspects of the aetiology and management of glaucoma, particularly with the development of newer technologies. Clinically useful measurements of intraocular pressure, besides contributing to better patient management, may contribute to bringing epidemiology studies up to date and current; a desideratum that is long overdue. Accuracy and reliability of intraocular pressure measurements as well as an understanding of the factors influencing the accuracy of the measurements with the different techniques is imperative in the treatment and diagnosis of glaucoma. With the predicted increase in the prevalence of glaucoma worldwide and the already high prevalence and proportion of undiagnosed glaucoma in South Africa, more streamlined screening, treatment and public health strategies (including the use of mid-level eye care workers) will be needed in future (Cook, 2009; Shaarawy et al., 2009; Tham et al., 2014). The measurement of IOP forms an integral part of an effective screening and treatment strategy for glaucoma. A simple, safe, non-invasive, accurate, and cost-effective instrument to measure IOP would benefit these health care initiatives.

1.6 Measurement of intraocular pressure

IOP can be measured in three ways: palpation, manometry, and tonometry. Palpation of the eye is the oldest, least expensive, simplest, and least accurate method of estimating IOP (Baum et al., 1995). This technique involves the patient closing their eyes in a downward gaze while the redundant skin of the upper lid is displaced and the central area of the eye ball is palpated with the tips of each index finger. By comparing palpation estimates of IOP with actual measured pressures, the clinician can "calibrate" his/her sense of touch to a limited extent (Baum et al., 1995). Palpation correlates poorly with Goldmann applanation tonometry (GAT) and should be avoided in eyes with significant trauma (Feldman et al., 1987; Baum et al., 1995; Kniestedt et al., 2008).

Manometry is an invasive technique which accurately measures the pressure in the eye; it is used as the reference pressure whereby all tonometers are judged and calibrated (Kniestedt et al., 2004; Kniestedt et al., 2005; Kniestedt et al., 2008). Manometry is used most commonly as a laboratory technique to measure IOP measurements over time as well as to study aqueous humour dynamics in post-mortem eyes (Ellingsen and Grant, 1971; Blumenthal et al., 1992). Ethically, the use of manometry in living human eyes is restricted to eyes undergoing enucleation or intraocular surgery (Blumenthal et al., 1992).

Tonometers are instruments used for performing IOP measurements with the least disturbance to the eye. In clinical practice the following four physical principles apply: indentation, applanation, contour matching, and rebound tonometry (Kniestedt et al., 2008). Indentation and applanation tonometry use force to deform the eye, more specifically the cornea, in order to measure the IOP (Robert, 2007; Kniestedt et al., 2008). Contour matching tonometers use an external piezo-electric pressure sensor to measure the pressure in the eye when the tangential forces on the cornea are cancelled by the concave tip of the instrument without applanation of the cornea (Robert, 2007; Kniestedt et al., 2008). The rebound tonometer probe has a small footprint (1.7 mm diameter plastic end-tip) and there is no applanating of the cornea (contact time approximately 0.2 m/s) (Beasley et al., 2013). Therefore the rules applying to applanation tonometry cannot be applied to this tonometer. It has an induction coil to magnetize a metal probe with a polymer tip. The probe contacts the cornea and bounces back resulting in an induction current being generated. IOP is then calculated from the generated induction current (Lim et al., 2012). The rebound response of the probe may be affected by the viscoelastic properties of the cornea as well as the central corneal thickness (Chihara, 2008).

Although many tonometers are used in clinical practice today, this review will only elaborate on the theories, principles, and factors influencing the accuracy of the most commonly used tonometers in South African optometric practices. This includes applanation tonometry − specifically Goldmann applanation tonometry (GAT), and noncontact tonometry (NCT) as used in the ocular response analyser (ORA), and rebound or ICare tonometry (RBT).

1.6.1 Goldmann applanation tonometry – GAT

The Goldmann applanation tonometer (GAT) is a fixed area tonometer measuring the force necessary to flatten a fixed area of the cornea (Goldmann and Schmidt, 1957; Kniestedt et al., 2008). The applanating surface has a diameter of 3.06 mm and an applanating an area of 7.354 mm^2 displacing a volume of 0.44 mm^3. The area and volume are always the same regardless of the IOP or the force necessary for its measurement (Robert, 2007).

Applanation tonometry is based on the Imbert-Fick law which, when applied to the eye, states the IOP is equal to the weight (grams) applied to the cornea divided by the applanated area (mm^2) (Goldmann and Schmidt, 1957; Liu and Roberts, 2005; Harper and Henson, 2007; Kniestedt et al., 2008). In other words, pressure is defined as force per unit area (pressure = force/area) providing a nearly direct method of IOP measurement (Schmidt, 1960; Hart, 1992; Kniestedt et al., 2008). However, the law is correct only for a spherical container with an infinitely thin, flexible, elastic and dry membrane which will create no resistance to flattening and will allow for expansion elsewhere so that the pressure will not increase/decrease with applanation (Liu and Roberts, 2005; Harper and Henson, 2007). In the living eye the anterior corneal curvature is not equal to that of the posterior corneal curvature, the cornea is not sufficiently soft, has a thickness of ±520 µm, and resists a force that applanates the cornea. Furthermore, the corneal modulus of elasticity can differ among individuals, and different amounts and characteristics of the tear film can affect surface tension, intermolecular force of the tear film and, therefore, the IOP readings (Chihara, 2008).

Goldmann and Schmidt (1965) expected an empirical balance between the surface tension and a force to deform the cornea. The surface tension of the tears creates a capillary attraction that pulls the tonometer towards the cornea, lowering the force required to applanate the cornea (Chihara, 2008). However, Goldmann found that with an applanation diameter of 3.06 mm and an assumed corneal thickness of 500 µm (measured optically), the forces of tear surface tension and corneal rigidity cancelled out so that the force of $1/10^{th}$ gram on an area of 7.354 mm^2 is equivalent to 1 mmHg (Schmidt, 1960; Goldmann and Schmidt, 1965; Kniestedt et al., 2008) (Figure 1.2). Although

the surface tension may be nearly constant among individuals, the force needed to deform the cornea varies with the corneal thickness and modulus of elasticity of the cornea thereby causing a cornea-dependent error in the IOP reading (Chihara, 2008).

Although Goldmann used a value of 500 µm to calibrate the applanation tonometer (Schmidt, 1960; Goldmann and Schmidt, 1965), a major review on corneal thickness and IOP by Dougthy and Zaman (2000) describes a chronological shift in the average central corneal thickness (CCT) values as a result of changes in pachymeter use. Optical pachymetry measured consistently lower CCT values (20-30 µm) compared to ultrasound pachymetry; therefore, the average reported CCT across all 300 included data sets in their review was 534 µm (Doughty and Zaman, 2000). More recent population-based studies using ultrasound pachymetry give a range of 537 - 567µm in healthy eyes (Argus, 1995; Bron et al., 1999; Shah et al., 1999; La Rosa et al., 2001; Nemesure et al., 2003). Other methodologies to measure CCT such as specular microscopy, optical coherence tomography, slit-scanning systems, and Scheimpflug camera systems added to the confusion and possibly obscured the relationship between CCT and IOP (Chihara, 2008).

It has been suggested that pachymetry should be a mandatory investigation in patients with glaucoma or ocular hypertension (Brandt, 2004). Several nomograms or correction formulae have been produced to account for the variation in corneal thickness and its influence on IOP measurements (Ehlers et al., 1975; Whitacre et al., 1993; Stodtmeister, 1998; Doughty and Zaman, 2000; Shimmyo et al., 2003). Among these formulae is the Ehlers model which states the correction value is equal to the measured corneal thickness in microns minus a mean corneal thickness of 578 microns (from their measurement series) times a factor of 5/70. Also, included in these models is the mathematical or theoretical model of Orssengo & Pye which corrects IOP for errors induced by corneal thickness as well as corneal curvature (Ehlers et al., 1975; Orssengo and Pye, 1999).

Gunvant et al. (2005) investigated the efficacy of the Ehlers and the Orssengo & Pye models to correct IOP measured by GAT for CCT. They found that both these models overestimated the effect of corneal parameters on GAT IOP measurements (Gunvant et al., 2005). The effect of CCT on measured IOP reported by Gunvant et al. (2005) was consistent with other studies in literature (Herndon et al., 1997; Wolfs et al., 1997; Singh et al., 2001; Bhan et al., 2002). If correction factors overestimate the effect of CCT on IOP, then the reclassification of subjects with ocular hypertension with thicker than average corneas as “normal”, and individuals with normal tension glaucoma and

thinner CCT as “primary open angle glaucoma” may, in fact, be questionable as it may result in the inappropriate management of these subjects (Gunvant et al., 2005).

Liu and Roberts (2005) developed a model whereby the influence of individual corneal variables influencing corneal biomechanical properties (Young’s modulus, corneal thickness, and corneal curvature) as well as true IOP can be adjusted one at a time while the other variables were kept constant. Keeping Young’s modulus constant at 0.19 MPa, and corneal curvature at 7.8 mm and true IOP at 10, 15, and 20 mmHg respectively, the difference in predicted IOP readings in a normal population with CCT M = 536, SD = 0.031 µm would be 2.87 mmHg lower for thinner corneas but higher for thicker corneas (Liu and Roberts, 2005). The influence of CCT on predicted IOP in normal eyes is nearly linear (Liu and Roberts, 2005). In their review Douhty and Zaman (2000) found for normal eyes any differences in CCT between individuals are unlikely to have a clinically significant effect on measured IOP due to the fact that a tonometer will generally measure to the nearest 1 mmHg. This generalisation is applicable over a wide range of CCT values (model generated from data sets with average CCTs ranging from 488 µm to 584 µm) (Doughty and Zaman, 2000). However, for eyes with chronic disease even moderate changes in CCT can have a measurable impact on tonometry measures (Doughty and Zaman, 2000).

Although GAT demonstrated poor agreement with dynamic contour tonometry (DCT), adjustment with published correction formulae did not improve agreement. This suggests that correction formulae for GAT IOP are unsuitable to clinically approximate “true IOP” in Caucasian glaucoma and glaucoma suspect patients (Ang et al., 2011). This suggestion was confirmed in a later study by Park et al. (2012) who found that adjusted IOP using CCT-based formulae resulted in poorer agreement between DCT and GAT if compared with unadjusted GAT IOP. This suggests that although CCT may be useful in population-based analysis, CCT-based formulae should not be applied to individuals (Park et al., 2012). The question thus arising is: ‘Is it therefore justified to routinely correct tonometry measures for differences or changes in CCT?’ According to Brubaker (1997) “it is doubtful that such an adjustment, except in rare cases, will alter the weight of evidence that leads a clinician to treat or not to treat a given case” (Brubaker, 1997).

In addition to CCT and scleral rigidity there are other ocular sources of error that may influence the accuracy of applanation tonometry (Whitacre and Stein, 1993; Kniestedt et al., 2008). Corneal curvature can affect the accuracy of IOP measurements possibly due to volume changes with changes in corneal curvature after a given area has been applanated (Liu and Roberts, 2005). Using

Liu and Roberts' model and varying only the corneal radius of curvature, the difference in predicted IOP readings in a normal population with a radius of curvature M = 7.8, SD = 0.27 mm is 1.76 mmHg lower in flatter corneas and higher in steeper corneas (Liu and Roberts, 2005).

Figure 1.2 Goldmann applanation tonometer.(Drawing Gerrie Kruger)

Corneal elasticity and viscoelasticity can also affect the accuracy of IOP measurements. It is important to differentiate viscoelastic properties from the elastic modulus (Young's modulus). Elasticity refers to how a material deforms in response to an external force. Elastic materials regain its original form when the stress is removed (Kotecha, 2007). Young's modulus or the modulus of elasticity, calculated from the stress-strain relationship, is a function of the applied force and is not rate- and time-dependent (Roberts, 2012). The elastic modulus of the cornea varies directionally and regionally: a high modulus is exhibited meridionally at the centre and para-central areas as well as circumferentially at the limbus due to the specific arrangement of the corneal collagen fibrils. A high modulus indicates a stiffer material (Hjortdal, 1996; Kotecha, 2007). Young's modulus varies with IOP in that a stiffer cornea is manifested at higher levels of true IOP (Kotecha, 2007). Young's modulus can currently only be measured *ex vivo* (Kerautret et al., 2008). Viscous materials flow when an external force is applied and, unlike materials with elastic properties, do not regain their original shape when stress is removed.

The cornea is viscoelastic, having elements of both elasticity and viscosity. When stress is applied to a viscoelastic material energy is dissipated (Kotecha, 2007; Chen et al., 2008; Fontes et al., 2010; Terai

et al., 2012). Liu and Roberts' model predicts that varying Young's modulus between 0.1-0.9 MPa [normal human cornea range 0.01-10 MPa (Jue and Maurice, 1986; Liu and Roberts, 2005)] while keeping corneal curvature and CCT constant at 7.8 mm and 536 µm respectively, the difference in the predicted IOP readings between the low and high modulus can be 17.26 mmHg (Liu and Roberts, 2005). Combining changes in CCT with different values for Young's modulus substantially influenced the predicted IOP values. A 10% change in the value of Young's modulus from an assumed population mean of 0.19 MPa leads to an error in IOP readings of ±0.41 mmHg (Liu and Roberts, 2005). However, Young's modulus can vary from 0.01 – 10 MPa in human corneas; differences in biomechanical properties may have a significant impact on IOP measurement error (Liu and Roberts, 2005).

Data from the Ocular Hypertension Treatment Study (OHTS) revealed that central corneal thickness is an important and powerful independent risk factor for progression from OHT to POAG. Thinner corneas have consistently been associated with a higher risk of developing POAG. It seems that this effect in the OHTS is independent of the effect of CCT on the measurement of IOP (Gordon et al., 2002). Other studies by Medeiros et al. (2003) and Medeiros and Weinreb (2008) indicated that thin central corneas are associated with more frequency-doubling technology perimetry field defects, are risk factors for pre-perimetric glaucoma progression to field loss, and are also risk factors for the development of short wavelength automated perimetry (SWAP) test defects in ocular hypertension (Medeiros, Sample and Weinreb, 2003; Medeiros and Weinreb, 2008). According to the OHTS, the risk of progression to POAG is statistically higher among African Americans (16%) despite similar baseline and follow-up IOPs. The increased risk seems to be largely related to other baseline risk factors including vertical cup to disc ratio and, importantly, central corneal thickness which were respectively larger and thinner in the African American participants taking part in the OHTS (Kass et al., 2010). Adjusting for these factors in a multivariate analysis, race is no longer a statistically significant predictor of progression to POAG (Gordon et al., 2002).

Non-ocular sources that may influence the accuracy of GAT include: the quantity and concentration of fluorescein which may produce wider mires and lead to underestimation of the IOP (Grant, 1963; Kniestedt et al., 2008); incorrect alignment of the semicircles can also result in erroneous measurements (Harper and Henson, 2007); pressure on the globe by the eye lids or clinician can lead to overestimation of the IOP (Harper and Henson, 2007); prolonged contact between the probe and the cornea can cause an apparent decrease in IOP due to the effect of aqueous massage (Harper and

Henson, 2007); the ocular pulse amplitude (OPA) can also affect the time dependent IOP measurement (Robert, 2007); and corneal astigmatism or an irregular cornea can also lead to erroneous measurements (Harper and Henson, 2007). Dielemans et al. (1994) found a mean intraobserver variation of 1.64 mmHg and interobserver variation of 1.79 mmHg with GAT (Dielemans et al., 1994). Thorburn (1978) found a difference of 2 mmHg or more in 40% of eyes and 3 mmHg in 17% of eyes measured using GAT by two experienced ophthalmologists (Thorburn, 1978). Phelps and Phelps (1976) reported differences between GAT measurements between two examiners of at least 2 mmHg in 50% of eyes and 3 mmHg in 30% of eyes (Phelps and Phelps, 1976). Kotecha et al. (2005) reported high intraobserver reliability (within 1.7 mmHg) and interobserver variability (equal to 0.4 mmHg) with GAT (Kotecha et al., 2005).

Considering the above information it is difficult to understand what a single IOP measurement actually means and how it should be interpreted. While research into the measurement of true IOP continues, it still remains a vital measurement in clinical practice and the only modifiable risk factor in the management of glaucoma. According to the International Standards Organization (ISO) (2001), GAT corrected for CCT remains the reference instrument for clinical measurements of IOP; in other words, the gold standard for tonometry (ISO, 2001). However, tonometric correction factors attempt to give GAT a degree of precision that is not warranted and should therefore be used with caution (Brubaker, 1997; Herndon et al., 1997; Wolfs et al., 1997; Singh et al., 2001; Bhan et al., 2002; Gunvant et al., 2005; Ang et al., 2011; Park et al., 2012).

1.6.2 Noncontact air puff tonometry and the ocular response analyser

The noncontact air puff tonometer (NCT) works on the same basic principle as the GAT (Forbes et al., 1973; Harper and Henson, 2007; Kniestedt et al., 2008). A puff of air is directed at the cornea with the force of the air stream rising linearly over several milliseconds (Forbes et al., 1973; Kniestedt et al., 2008). The air puff is designed so that it hits the cornea within a known and reproducible area, much like the GAT. The air puff then progressively flattens/applanates the cornea over the predetermined area (Forbes et al., 1973; Harper and Henson, 2007; Kniestedt et al., 2008). The area of the column of air is known and the force of the air puff increases linearly over a period of ±8 ms. An illumination and detection system identifies the point at which the cornea is in its flattened state and acts like a mirror to reflect the illumination maximally to the detector. The force of the air puff is monitored by a microcomputer and recorded at the moment of applanation. The IOP is calculated either from the force of the air puff and the known predetermined area of applanation or time to

applanation and then displayed digitally (Forbes et al., 1973; Harper and Henson, 2007; Kniestedt et al., 2008). Although noncontact tonometry is affected by the same ocular sources of error including CCT, scleral rigidity, corneal curvature, and corneal biomechanics (Kniestedt et al., 2008), data have been presented that show that noncontact tonometry is influenced more than conventional applanation tonometry by the corneal thickness. Starting from a central thickness of 0.51 mm, the NCT is assumed to underestimate the actual intraocular pressure in eyes with thinner and to overestimate it in eyes with thicker cornea by 1 mmHg per 0.01 mm difference of corneal thickness. This value changes with individual corneal tissue qualities and is not valid especially in presence of corneal oedema (Graf, 1991). Compared to GAT, NCT is the tonometer with the least amount of variability in IOP. Sixty-six per cent (66%) of measurements with NCT were estimated to be within 2 mmHg of the GAT measurement (Cook et al., 2012).

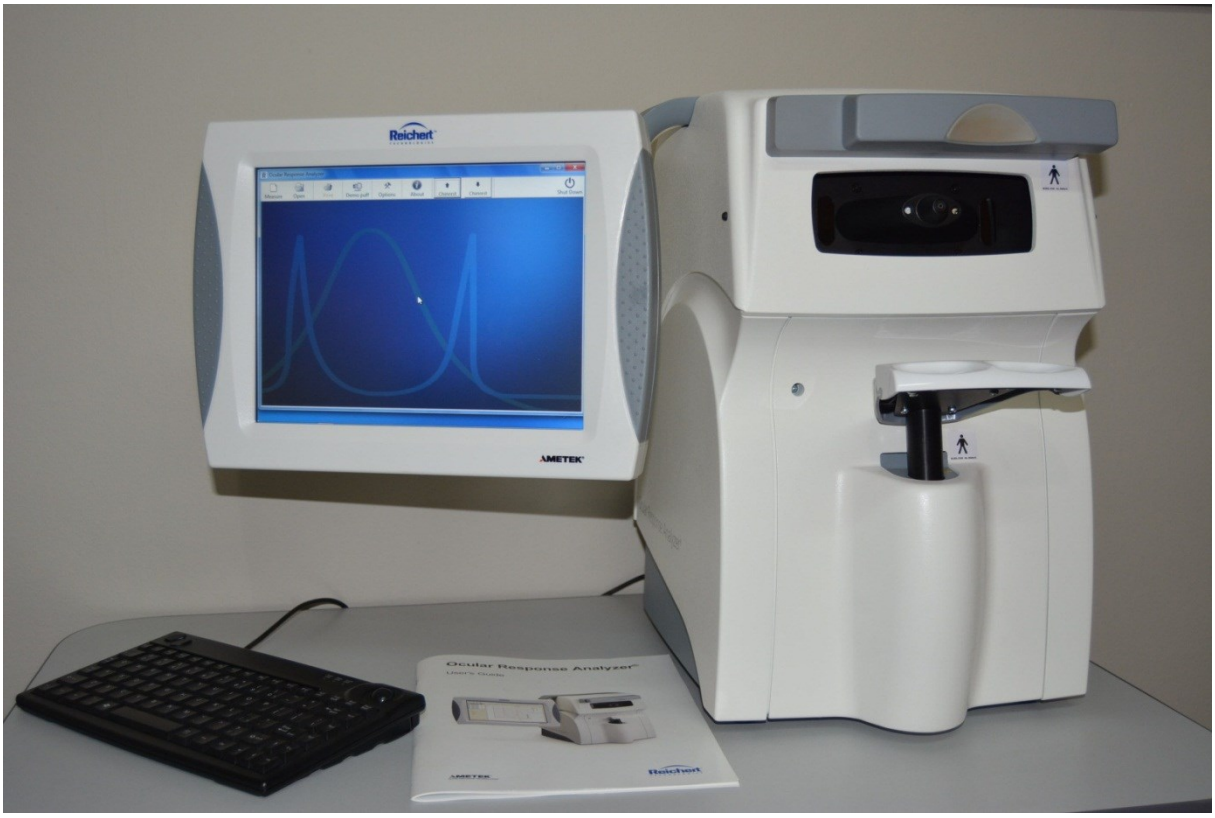


Figure 1.3 The Reichert Ocular Response Analyser used in this study.(Photo D Booysen)

The ocular response analyser (ORA) was developed by Reichert, Inc. in Depew, New York (NY), USA. It measures the response of the cornea to indentation by a rapid air pulse (Reichert, 2013) using the delay of corneal response after the applanation process to estimate the amount of energy absorbed and to derive the viscous as well as viscoelastic properties of the cornea (Jorge, Gonzales-Meijome,

et al., 2008). The principles of the ORA are based on those of the noncontact tonometer (Luce, 2005; Kotecha, 2007; Kniestedt et al., 2008) (Figure 1.3). A controlled amount of air pulse lasting 20 ms deforms the central 3 mm of the cornea inward, past the applanation point (P1), and into a concave shape. The air pulse is then reduced in an inverse time-symmetrical profile, and the corneal shape returns back to normal, through the applanation point (P2) (Figure 1.6) (Luce, 2005; Kotecha, 2007; Kniestedt et al., 2008; Lau and Pye, 2011; Wolffsohn et al., 2012). According to Reichert, P2 occurs at a lower pressure than P1 due to the viscoelastic dampening effects of the cornea. The average of these two pressure values provides the Goldmann-correlated IOP value (IOPg):

Equation 1.1 IOPg

$$\boldsymbol{IOPg = (P1 + P2)/2}$$ *(Kniestedt et al., 2008; Lau and Pye, 2011)*

The difference between the two pressures is termed corneal hysteresis (CH):

Equation 1.2 CH

$$\boldsymbol{CH = P1 - P2}$$ *(Luce, 2005; Kotecha, 2007; Kniestedt et al., 2008; Lau and Pye, 2011)*

Equation 1.3 IOPCC

Corneal compensated IOP (IOPcc) utilises information of individual corneal elasticity and viscosity and is less affected by corneal properties such as CCT which does affect IOPg significantly:

$$\boldsymbol{IOPcc = 1.51(P1 - 0.43xP1) + 13.82}$$

(Luce, 2005; Kniestedt et al., 2008; Lau and Pye, 2011)

In addition to CH, the ORA also measures the corneal resistance factor (CRF) which is derived from the formula (P1-kP2) where 'k' is a constant derived from an empirical analysis of the relationship between P1, P2 and the central corneal thickness (CCT):

Equation 1.4 CRF

$$\boldsymbol{CRF = (P1 - 0.70xP2) - 3.08}$$ *(Lau and Pye, 2011)*

CRF is therefore more closely associated with CCT than CH and offers a measurement of the corneal viscoelastic resistance (Luce, 2005; Kotecha, 2007; Kniestedt et al., 2008; Lau and Pye, 2011). Unlike CH, CRF is unaffected by changes in the IOP (Luce, 2005; Kotecha, 2007). It has been shown that CH and CRF are reduced in patients with keratoconus; Fuchs endothelial dystrophy; glaucoma; high myopia; and in conditions which may cause changes in the CCT (Luce, 2005; Kotecha, 2007; Ortiz et al., 2007; Shen et al., 2008).

The morphological signal or waveform produced by the Ocular Response Analyser is a unique "signature" for the eye being measured. The waveform signal is complex and stores considerably more information than just the interrelation of the inward and outward applanation pressure conveyed by CH and CRF (Galletti et al., 2015). The ORA software provides 37 additional descriptors that further describe each signal (Mikielewicz et al., 2011). The prospect of improved diagnosis by multivariate waveform analysis is attractive and have been explored by researchers (Mikielewicz et al., 2011; Wolffsohn et al., 2012; Galletti et al., 2015). In terms of diagnosing keratoconus characteristics of the waveform profile (Wolffsohn et al., 2012) and indices describing the second peak in the ORA waveform signal had excellent performance (Mikielewicz et al., 2011).

In glaucoma patients with low hysteresis there is greater backward bowing of the lamina cribrosa in response to transient IOP elevation (Wells et al., 2008). The low CH and CRF in keratoconic corneas (Figures 1.4 and 1.5) are due to the reduced ability of the cornea to dissipate energy which, in turn, is a function of both viscosity and elasticity (Roberts, 2012). Although the low CH and CRF may be partially caused by a decrease in corneal thickness, it is primarily due to the altered structure of keratoconic PGs (proteoglycans) and GAGs (glycosaminoglycans) which leads to lower lamellar adhesion and a lower shear modulus (Terai et al., 2012). It is important to consider that the ORA screens only the central 3 to 4 mm of the cornea which could result in an incorrect analysis of the corneal biomechanics in the early stages of off-centre corneal ectasia (Touboul et al., 2011). Furthermore, it has been observed that CH and CRF were markedly reduced following Laser assisted keratomeulesis (LASIK); this was possibly due to the creation of the LASIK flap and the subsequent alteration of the anterior stromal lamellae (Luce, 2005; Kotecha, 2007; Ortiz et al., 2007; Chen et al., 2008). (Figures 1.4 and 1.5).

Figure 1.4 Comparison of the CH distribution in normal, post LASIK, and keratoconic eyes(Note the lower CH values in post LASIK and keratoconus eyes. Reproduced from the original paper with written permission, [Appendix 2.1]) (Ortiz et al., 2007)

Figure 1.5 Comparison of the CRF distribution in normal, post LASIK, and keratoconic eyes(Note the lower CHF values in post LASIK and keratoconus eyes. Reproduced from the original paper with written permission [Appendix 2.1]) (Ortiz et al., 2007)

Factors influencing the CH and CRF include diurnal variation; tear film (a dry cornea leads to false CH values); IOP (the higher the IOP the lower the CH and higher the CRF); age (CH and CRF decrease on average by 0.24 to 0.28 mmHg and 0.31 mmHg per decade of life respectively); corneal curvature (flatter corneas have lower CH and CRF values); and corneal swelling (corneal thickness increases but CH decreases due to the modified matrix viscosity and reduced dampening capacity of the cornea) (Moreno-Montanes et al., 2008; Sullivan-Mee et al., 2009; Kotecha et al., 2010; Terai et al., 2012; Wang et al., 2013).

As mentioned, CH is dependent on IOP and measured IOP is dependent on CH. Interestingly, lowering IOP with topical prostaglandin therapy [and trabeculectomy (Sun et al., 2009)] increased the CH, but the magnitude of IOP reduction seems to be associated with the baseline CH. In other words, lower CH values prior to therapy tend to be associated with larger treatment effects. CH may therefore be a useful measure to predict IOP change and treatment effect in clinical settings (Agarwal et al., 2012). Hence, CH can be seen as a dynamic corneal property indicating how much energy the cornea can absorb under stress. Studies suggest that along with IOP, CH and age are good indicators of glaucoma progression manifested in visual field changes as well as ONH damage (Medeiros et al., 2013). Xu et al. (2008) found that long-term soft contact lens wear leads to changes in corneal viscoelastic properties. Lower CH and CRF were apparent the first day after contact lens removal as well as two weeks after discontinuing contact lens wear while CCT remained constant (Xu et al., 2008).

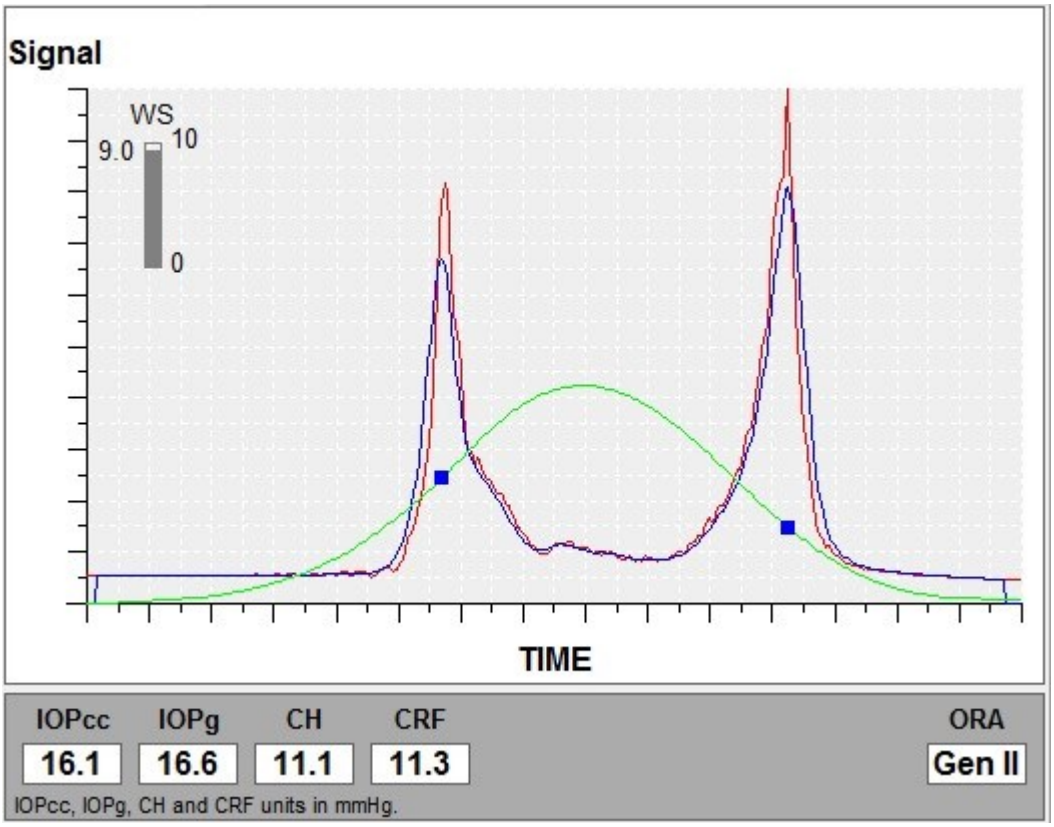


Figure 1.6 Typical ORA display showing the wave score, IOPcc, IOPg, CH, and CRF values recorded in this study.(The green curve represents the pressure of air on the cornea; the red curve indicates the raw signal of the applanation detection system. The blue curve is a filtered version of the red curve designed to identify the optimum point of applanation. The blue squares indicate the inward (P1) and outward (P2) applanation pressures on the green pressure curve. Ideally the peak-amplitude of the applanation signals (blue and red spikes) should be above the green pressure curve, similar in height, free of noise and the pressure curve should be fairly symmetrical) (Photo D. Booysen)

According to Kerautret et al. (2008), normal CH is considered to be between 8 and 12 mmHg (Kerautret et al., 2008). In a study conducted by Luce (2005) it was found that the CH in a normal population (339 eyes; average age was 28 years) was 9.6 mmHg and in keratoconic eyes (60 eyes; average age was 31 years) it was 8.1 mmHg (Luce, 2005). However, in different studies on normal eyes the CH ranged between 9.6 and 12.7 mmHg and the CRF between 9.5 and 11 mmHg (Ortiz et al., 2007; Shehadeh-Mashor et al., 2012). In other studies involving at least 100 normal eyes, the mean CH and CRF ranged between 10.0 and 11.0 mmHg with the standard deviation (SD) lying between 1.3 and 2.0 and 1.5 and 2.0 mmHg respectively (Lau and Pye, 2011). It was observed that ORA measurements during a single test series were highly reproducible with interclass correlation coefficients (ICC) for a CH and CRF of 0.73 and 0.881 respectively. Moreover, the reproducibility of measurements between two examinations showed an ICC of 0.799 indicating highly consistent measurements during a series of repeated tests (Terai et al., 2012).

The ORA allows an *in vivo* measurement of the viscoelastic and corneal resistance properties in addition to corneal compensated (IOPcc) and Goldmann-correlated IOP (IOPg). According to Reichert (2013), CH represents ocular resistance due to the combined effects of CCT, ocular rigidity, and the cornea's elastic properties. CRF is dominated by the viscous and elastic properties of the cornea and appears to be an indicator of the overall resistance of the cornea (Reichert, 2013). However, unlike true corneal properties such as CCT and Young's modulus which are invariant to the measurement technique, CH and CRF are specific responses to the ORA measurement process and can therefore not be considered corneal properties (Lau and Pye, 2011).

Although GAT IOP has a significant association with CCT, IOPcc produced by the ORA was found to have no significant association with ocular variables such as CCT, corneal curvature, and axial length (Medeiros and Weinreb, 2006; ElMallah and Asrani, 2008). Studies of the ORA have produced conflicting results; two studies with untreated patients show promising results with the ORA, IOPcc seeming to compensate for corneal factors (Kotecha et al., 2006; Medeiros and Weinreb, 2006). In another study of glaucoma patients undergoing therapy with topical medication, the ORA IOPcc and IOPg consistently overestimated GAT IOP by 8.3 mmHg and 7.2 mmHg respectively. In this group of patients the ORA IOP measurements were not independent of CCT (Martinez-de-la-Casa, Garcia-Feijoo, Fernandez-Vidal, et al., 2006). Medeiros and Weinreb (2006) reported a difference of M = 0.068, SD = 2.77 mmHg between ORA IOPcc and GAT IOP. The difference was significantly influenced by CCT. Thicker CCT resulted in higher GAT compared to ORA IOPcc and thinner CCT resulted in lower GAT compared to ORA IOPcc (Medeiros and Weinreb, 2006). Kotecha et al. (2006) reported that ORA IOPcc overestimates GAT by 1.7 mmHg (Kotecha et al., 2006). In a study by Lam et al. (2007), 80% (100 of 125 eyes) in IOPg and 79% (99 of 125 eyes) in IOPcc could achieve this ±3 mmHg agreement with GAT. The 95% limits of agreement with GAT are similar from IOPg and IOPcc respectively. Lam et al. (2007) found good agreement between GAT and ORA and the mean difference was just 0.33 mmHg between IOPg and GAT, and 0.24 mmHg between IOPcc and GAT respectively. The conclusion of the study was that in general, ORA is comparable with GAT findings in normal subjects when IOP is in the teens (Lam et al., 2007).

Vandewalle et al. (2009) found that although the ORA overestimated IOP compared to GAT, 41.8% of ORA IOPg and 35.2% of IOPcc measurements were within 3 mmHg of GAT (Vandewalle et al., 2009). Studies conducted by Carbonaro et al. (2010) and Kotecha et al. (2010) also found that the ORA IOPg and IOPcc overestimated GAT by ±2 mmHg and that the differences were independent of CCT

(Carbonaro et al., 2010; Kotecha et al., 2010). Ehrlich et al. (2010) reported that ORA IOPg overestimated GAT by 0.1 mmHg. Of the ORA IOPg measurements 53.9% were within 2 mmHg and 92.3% within 5 mmHg of GAT (Ehrlich et al., 2010).

Lau and Pye (2011) observed that the IOPg and IOPcc overestimate GAT IOP by 3.2 to 3.7 mmHg (Lau and Pye, 2011). In a more recent systematic review of agreement between different tonometers and GAT, 42 % of the measurements with the ORA were estimated to be within 2 mmHg of the GAT measurement (Cook et al., 2012). However, it is not clear from the review of Cook et al. (2012) whether the ORA's corneal corrected IOP (IOPcc) or Goldmann IOP (IOPg) was used in the comparison.

It is clear from the literature that the ORA (IOPg and IOPcc) tend to overestimate GAT IOP (Table 1.4). The exact magnitude of this difference is not clear and depends on the biomechanical properties of the cornea. However, differences of more than 3 mmHg are rare. The suitability of the NCT process used by the ORA for determining corneal biomechanics and the "true" IOP have not been demonstrated with traditional biomechanical testing and manometry in human subjects. Validation of the ORA IOP measurements using manometric data needs to be performed (Lau and Pye, 2011).

Study	**Subjects**	**IOP: ORA compared to GAT. Mean(M), Standard deviation(SD)**
Marinez-de-la-Casa et al.(2006)	48 eyes of 48 patients with glaucoma.	IOPcc overestimated GAT by 8.3 mmHg IOPg overestimated GAT by 7.2 mmHg ORA IOP measurements were not independent of CCT
Medeiros and Weinreb, (2006)	153 eyes of 78 subjects without prior intraocular or refractive surgery, secondary causes of high intraocular pressure, or other intraocular disease	ORA IOPcc and GAT measurement difference was M = 0.068, SD = 2.77 mmHg. The difference was significantly influenced by CCT. Thicker CCT resulted in higher GAT compared to IOPcc and thinner CCT resulted in lower GAT compared to IOPcc
Kotecha et al. (2006)	ORA and GAT IOP and CCT were measured in 144 eyes of 144	ORA overestimated GAT by 1.7mmHg

	untreated subjects.	
Lam et al. (2007)	125 subjects free of glaucoma and any ocular symptoms not taking any medication. Subjects had no history of ocular surgery. Subjects with a family history of glaucoma were excluded.	IOPg 0.33 mmHg higher and IOPcc 0.24 mmHg higher than GAT. ORA IOP is comparable with GAT findings in normal subjects when IOP is in the teens.
Study	**Subjects**	**IOP: ORA compared to GAT. Mean(M), Standard deviation(SD)**
Vandewalle et al. (2009)	92 patients, 72 with primary open angle glaucoma, 6 secondary glaucoma, 5 chronic angle closure glaucoma, and 2 ocular hypertension	ORA IOPg overestimated GAT by > 3.1 mmHg and ORA IOPcc overestimated GAT by > 3.6 mmHg 41.8% of ORA IOPg and 35.2% of IOPcc measurements were within 3mmHg of GAT.
Carbonaro et al. (2010)	694 individuals were recruited from the TwinsUK (UK Adult Twin Registry), based at St Thomas' Hospital, London. The subjects were twin volunteers from the general population, and were part of a twin study on glaucoma heritability.	ORA IOP measurements significantly higher than GAT independent of CCT. GAT – M = 14.1, SD = 2.8 mmHg, IOPcc - M = 15.9, SD = 3.2 mmHg, IOPg – M = 16.6, SD = 3.2 mmHg
Kotecha et al. (2010)	100 patients comprising a mixture of normal volunteers, glaucoma suspects, and glaucoma patients attending the Glaucoma Research Unit at Moorfields Eye Hospital.	ORA IOPcc overestimated GAT by 2 mmHg. IOP differences were predicted better by CRF than CCT. IOP measurements with each device are not interchangeable.
Ehrlich et al. (2010)	260 consecutive patients over the age of 18 years undergoing glaucoma evaluation at the Weill Cornell Medical College.	ORA IOPg overestimated GAT by 0.1 mmHg. 53.9% of ORA IOPg measurements were within 2mmHg and 92.3% within 5 mmHg of GAT
Lau and Pye, (2011)	99 subjects (age, 21 ± 2 years) who were free of ocular and systemic disease.	IOPg overestimated GAT by 3.2 mmHg IOPcc overestimated GAT by 3.7 mmHg
Cook et al. (2012)	Variety of individuals: both patient and non-diseased cases, some with treatment and others untreated	Systematic review of 12 studies. 42% of the IOP measurements with the ORA were estimated to be within 2 mmHg of

	cases of ocular hypertension and glaucoma.	the GAT. Mean difference 1.5 mmHg Not clear if this refers to IOPcc or IOPg.

Table 1.4 Comparison of ORA IOPg and IOPcc with GAT. Both ORA IOPg and IOPcc overestimate GAT IOP. (Differences of more than 3.5 mmHg are rare. In a systematic review 42% of the overestimation was within 2 mmHg and the mean difference was 1.5 mmHg) (Cook et al., 2012)

1.6.3 Rebound tonometry or ICare tonometry

The ICare tonometer (TA01, Tiolat Oy, Helsinki, Finland) was developed, validated and successfully used on animal eyes before use on human eyes (Goldblum et al., 2002; Danias et al., 2003; Wang et al., 2005). It showed good correlation with the IOP measurements manometrically obtained on the eyes of mice and rats but so far no manometric comparison on human eyes has been done (Kontiola et al., 2001; Danias et al., 2003).

The ICare rebound tonometer uses a probe of stainless steel with one end covered by a small plastic cap with a radius of 0.90 mm, total length of 50 mm, and total weight of 26.5 mg (Chihara, 2008; Kniestedt et al., 2008). A magnetic field holds the one end of the probe in place in the tonometer. The tonometer is held 4 - 8 mm from the cornea before pressing a button that releases an extension spring shooting the probe toward the cornea. A microprocessor analyses the deceleration or bounce of the probe after it has impacted the cornea and a digital reading displays the IOP (Chihara, 2008; Kniestedt et al., 2008). Deceleration is less at low than high IOPs and therefore the higher the IOP the shorter the duration of the corneal impact (Kniestedt et al., 2008). No topical anaesthetics are used and the probes are exchanged after every patient (Chihara, 2008).

The ICare tonometer is pre-programmed for six measurements. The IOPs measured are displayed for each measurement and the software discards the highest and lowest value to calculate the average IOP from the remaining measurements (Kontiola and Puska, 2004). The software can also detect erroneous measurements that may occur when the probe speed was too high or too low, if the probe did not move, if the probe hit the lid, or if the probe did not hit the central cornea. In these cases the tonometer displays an error message and does not accept the measurement as correct (Kontiola and Puska, 2004). Furthermore, the software considers the relationship between all the measures taken by estimating the standard deviation to ensure a coherent final result. If the instrument detects a discrepancy an error sign ('-') is displayed. If the standard deviation of the measurements is higher than normal the 'P' blinks:

- 'P_' (P bottom) indicates a slightly higher than normal standard deviation but the effect will most likely not affect the final result;

- ‘P-’ (P middle) indicates the standard deviation is clearly higher than normal, but a new measurement is only recommended if the IOP is higher than 19 mmHg;
- ‘P¯’(P top) indicates the standard deviation of the measurements is large and a new set of measurements is recommended (Fernandes et al., 2005). (Figure 1.7)

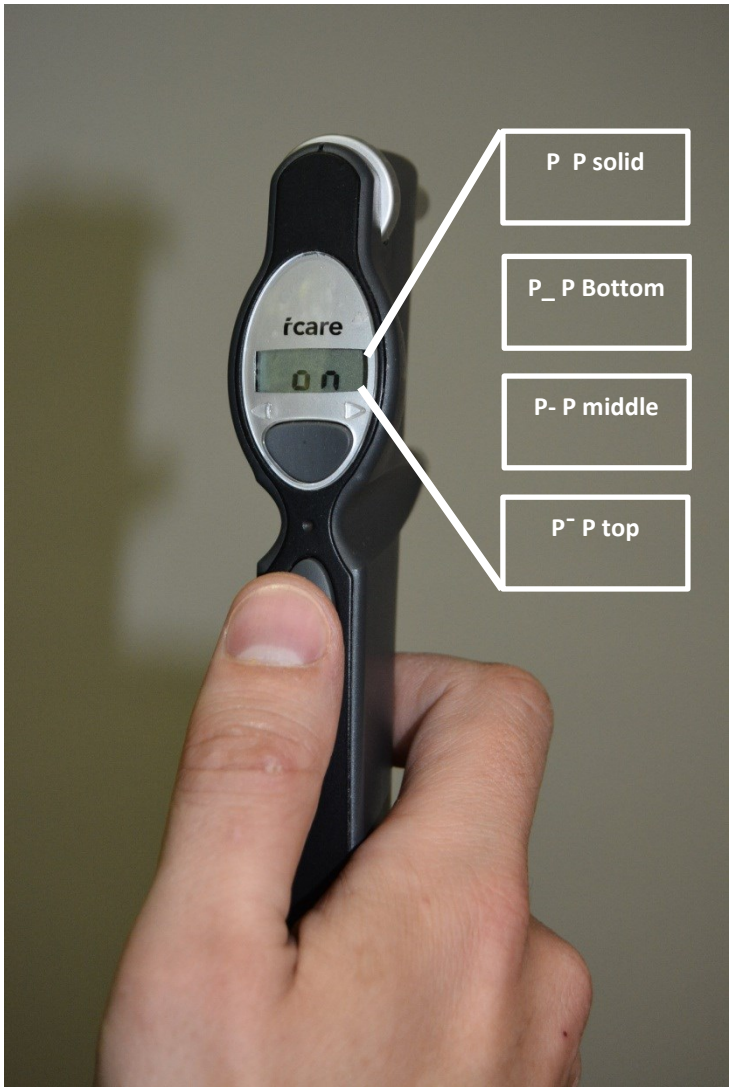


Figure 1.7 ICare rebound tonometer.If the instrument detects a discrepancy an error sign [‘-‘]is displayed. The most reliable measurement is indicated by P solid and the least reliable measurement by ¯P top. (Photo D. Booysen) (Fernandes et al., 2005).

IOPs measured at the central cornea as well as 3 mm from the periphery have been shown to be similar (Chui et al., 2008). IOP measurements with the ICare tonometer are reproducible when used in humans. Furthermore, intra- and interobserver correlation coefficients are high and close to those of GAT as long as the device is correctly positioned (Martinez-de-la-Casa et al., 2005; Detry-Morel et

al., 2006; Sahin, Basmak, et al., 2007). With the rebound tonometer (RBT) the small tip of the probe impacts the cornea and energy is absorbed due to the biomechanical properties of the cornea which may influence the measurements (Jorge, Gonzales-Meijome, et al., 2008). From the researcher's personal experience, when measuring IOP over a rigid gas permeable (RGP) lens, RBT shows a zero value (reproducible). Therefore, the effects of biomechanics on this measurement should not be underestimated. ICare or RBT is thus affected by the same physical properties of the eye that affects GAT. These properties include CCT, corneal curvature, corneal biomechanics as well as refractive error with RBT overestimating GAT IOP in myopic eyes, but it is not influenced by the ocular pulse amplitude (OPA) (Detry-Morel et al., 2006; Lopez-Caballero et al., 2007; Avitabile et al., 2010; Hohmann et al., 2012; Rao et al., 2012). In the higher IOP range (> 18 mmHg) the ICare tonometer tends to significantly overestimate IOP when compared to GAT (Lopez-Caballero et al., 2007; Munkwitz et al., 2008; Avitabile et al., 2010). It has also been shown that RBT may be more sensitive to CCT than GAT and that a CCT change of 10 µm can result in a measurement deviation of 0.7 mmHg (Brusini et al., 2006; Nakamura et al., 2006; Sahin, Niyaz, et al., 2007; Avitabile et al., 2010). Salvetat et al. (2011) also found that CCT in subjects with normal corneas significantly affected IOP measurements with GAT and RBT, an increase of 0.41 mmHg and 0.50 mmHg respectively for a 10 µm increase in CCT was observed. These authors further found that although corneal curvature did not seem to influence GAT, it significantly affected RBT. RBT tends to underestimate IOP in healthy steep corneas and overestimate IOP in healthy flat corneas by 0.76 mmHg per 1.00 D change in corneal curvature. Steep corneas may therefore hypothetically decrease the probe velocity leading to the underestimation of the IOP (Salvetat et al., 2011).

Chui et al. (2008) found that other biomechanical "corneal" (ORA − specific) properties such as CH and CRF were more important than CCT in influencing IOP measurements with the RBT (Chui et al., 2008). Although their study considered the influence of CCT, CH and CRF on IOP measured with the RBT, it did not report or comment on the correlation between the RBT IOP, GAT IOP (IOPg), and the corneal corrected IOP (IOPcc) measured with the ORA (Chui et al., 2008). In a 2008 a study by Jorge et al. the influence of CCT and corneal biomechanical properties of the cornea (measured by the ORA) on ICare tonometry was evaluated. In the study ICare tonometry and ultrasound pachymetry were measured centrally, nasally and peripherally and the ICare IOP measurements were correlated with corneal thickness as well as ORA CH, CRF, IOPg, and IOPcc (Jorge, Gonzales-Meijome, et al., 2008). The findings showed that, although CCT plays a role in the accuracy of RBT measurements, the elastic and viscous properties of the cornea seem to play a more significant role in the interaction of

the tonometer probe with the ocular surface. CRF showed a higher correlation with ICare RBT than CCT or CH (Jorge, Gonzales-Meijome, et al., 2008). They also found a high correlation between ICare RBT and IOPg but a lower correlation with IOPcc which suggests that ICare RBT measurements are affected by corneal properties including viscosity and viscoelasticity, and not only by the actual IOP of the eye (Jorge, Gonzales-Meijome, et al., 2008). Currently studies comparing the IOP measured with GAT and RBT have somewhat divergent results (Table 1.5). ICare tonometry measurements were similar to GAT measures in pathologic corneas, and in some cases could obtain measurements where GAT could not (Moreno-Montanes et al., 2007).

It seems as if the ICare RBT is able to estimate IOP within a range of ±3.00 mmHg in more than 80% of the population (Fernandes et al., 2005; Iliev et al., 2006; Munkwitz et al., 2008). It is influenced by CCT, corneal curvature, and corneal biomechanics (Brusini et al., 2006; Nakamura et al., 2006; Sahin, Niyaz, et al., 2007; Chui et al., 2008; Jorge, Gonzales-Meijome, et al., 2008; Salvetat et al., 2011) and although RBT measurements are highly correlated with GAT measurements, they are not interchangeable (Salvetat et al., 2011).

Not many studies compare ICare RBT with ORA IOP measurements (Table 1.6). Jorge et al. 2008 found that the ICare RBT overestimated ORA IOPg and IOPcc while Vandewalle et al. (2009) found the opposite (Jorge, Gonzales-Meijome, et al., 2008; Vandewalle et al., 2009). Theoretically, due to the dependence of the RBT on the cornea's biomechanics, IOP measurements with this instrument should correlate well with ORA IOPg while poorly with IOPcc (Chui et al., 2008; Jorge, Gonzales-Meijome, et al., 2008).

Study/Subjects	**IOP: RBT compared to GAT. Mean(M), Standard deviation (SD)**
Kontiola and Vesti, (2003) 114 subjects	Of all the IOP readings 55% were between ± 2 mmHg and 75% were between ±3 mmHg from the mean GAT readings
Fernandes et al. (2005) 46 subjects, left eye only	Higher than GAT by M = 1.34, SD = 2.03 mmHg
Van der Jagt and Jansonius (2005) 103 subjects	Higher than GAT by +0.6 (95% CI -0.0 to +1.2) mmHg
Martinez-de-la-Casa et al. (2005) 85 subjects, 147 eyes	Higher than GAT by M = 1.8, SD = 2.8 mmHg
Kumar et al. (2006) 107 subjects, 213 eyes	Higher than GAT by ±2.2mmHg
Martinez-de-la-Casa et al. (2006) 90 subjects, 146 eyes	Higher than GAT by M = 1.4, SD = 2.7 mmHg
Garcia-Resua et al. (2006) 65 young subjects	Higher by M = 3.35, SD = 2.28 mmHg than Perkins applanation tonometry
Brusini et al. (2006) 178 subjects, 89 eyes	RBT highly correlated with corrected GAT, M = 18.4, SD = 5.2 mmHg and M = 18.5, SD = 5.7 mmHg respectively
Davies et al. (2006) 42 eyes	Higher by M = 0.5, SD = 2.33 mmHg and M = 0.52, SD = 1.92 mmHg than GAT
Detry-Morel et al. (2006) 138 subjects	Higher on average by 1.5 mmHg than GAT
Nakamura et al. (2006) 45 subjects	Higher by M = 1.4, SD = 2.9 mmHg than GAT
Iliev et al. (2006) 28 subjects, 52 eyes	Higher by M = 1.0, SD = 2.7 mmHg than GAT
Moreno-Montanes et al. (2007) 258 corneas	Higher by ±2 mmHg in 73-77.4% of normal and abnormal corneas than GAT
Lopez-Caballero et al. (2007) 68 subjects,132 eyes	Higher by M = 3.4, SD = 3.6mmHg than GAT
Ruokonen et al. (2007) 243 subjects, 445 eyes	Higher by M = 2.5, SD = 1.1 mmHg than GAT
Sahin et al. (2007) 61 subjects, 61 eyes	Higher by M = 0.43, SD = 2.33 mmHg than GAT
Schreiber et al. (2007) 102 eyes	Comparable to GAT. GAT M = 13.2, SD = 3.1 mmHg & RBT M = 13.4, SD = 3.1 mmHg
Abraham et al. (2008) 100 subjects – experienced clinician	In experienced hands, higher than GAT by M = 0.2, SD = 2.15 mmHg

58 subjects – inexperienced technician	In inexperienced hands, lower by M =-0.5, SD = 2.8 mmHg
Study/Subjects	**IOP: RBT compared to GAT. Mean(M), Standard deviation(SD)**
Rehnman and Martin (2008) 45 subjects	Higher by M = 1.5, SD = 3 mmHg than GAT
Johannesson et al.(2008) 150 eyes	Higher by 2 mmHg than GAT
Chui et al.(2008) 125 normal subjects	Higher by M = 1.94, SD = 2.75 mmHg than GAT
Munkwitz et al. (2008) 75 subjects, 75 eyes	Higher by M = 0.79, SD = 4.73 mmHg than GAT, in 62.7% the measurement was within ±3 mmHg of the GAT
Vandewalle et al. (2009) 93 subjects, 93 eyes	No significant difference between the mean IOP with RBT and GAT. GAT M = 15.1, SD = 4.8 mmHg & RBT M = 15.7, SD = 5.7 mmHg
Avitabile et al. (2010) 78 emmetropes 83 hyperopes 87 myopes 79 astigmats	Higher than GAT by: Emmetropic M = 0.6, SD = 1.5 mmHg Hyperopic M = 0.7, SD = 1.5 mmHg Myopic M = 1.6, SD = 1.8 mmHg Astigmatic M = 0.6, SD = 1.2 mmHg
Flemmons et al. (2010) 71 subjects, 71 eyes	Higher by M = 2.9, SD = 3.6 mmHg than GAT. 67% of RBT measurements were within 3 mmHg of GAT
Scuderi et al. (2011) 97 subjects	Higher by M = 0.78, SD = 3.55 mmHg than GAT. Not clinically relevant
Flemmons et al. (2011) 71 eyes of 71 subjects	Higher by M = 2.3, SD = 3.7 mmHg than GAT
Salvetat et al. (2011) 58 normal, 43 glaucoma, 90 post keratoplasty, 34 penetrating keratoplasty, 20 ALK, 19 DASEK, and 17 corneal graft subjects one eye only	Lower in all groups by M = 3.5, SD = 3.5 mmHg than GAT
Hohmann et al. (2012) 150 subjects, 150 eyes	Higher by M = 0.84, SD =2.63mmHg than GAT
Rao et al. (2012) 102 subjects	Higher by 1 mmHg than GAT
Cook et al., 2012 Meta-analysis, 11582 subjects, 15525 eyes	Approximately 52% of measurements with RBT were estimated to be within 2 mmHg of GAT measurements
Gandhi et al. (2012)	Higher by M = 3.3, SD = 4.0 mmHg than GAT

60 subjects, 60 eyes	
Study/Subjects	**IOP: RBT compared to GAT. Mean(M), Standard deviation(SD)**
Kim et al. (2013) 86 subjects, 72 eyes	Higher by M = 1.92, SD = 3.29mmhg than GAT
Beasly et al. (2013) 36 subjects, right eye only	Higher by M = 2.7, SD = 2.8mmHg than GAT
Suman et al. (2013) 71 subjects, 142 eyes	Higher by 2-3 mmHg than GAT
Rosentreter et al. (2013) 99 subjects	Significantly underestimates IOP in pathologic corneas in relation to GAT by 1-3 mmHg

Table 1.5 Comparison of RBT with GAT.(ICare RBT overestimates GAT IOP, however some studies [indicated by shaded cells] found that ICare RBT underestimated GAT IOP. From the studies listed ICare RBT is able to estimate IOP within a range of ±3.00 mmHg in more than 80% of the population)

Study/Subjects	**ICare RBT compared to ORA IOPg and IOPcc. Mean(M), Standard deviation (SD)**
Jorge et al. (2008) 76 subjects, right eye only	ICare RBT measured higher more variable IOP than ORA IOPg and IOPcc ICare central M = 17.17, SD = 4.04 mmHg ICare nasal M = 16.83, SD = 3.89 mmHg ICare temporal M = 18.57, SD = 4.28 mmHg ORA IOPg M = 15.61, SD = 3.06 mmHg ORA IOPcc M = 15.47, SD = 3.43 mmHg
Vandewalle et al. (2009) 93 subjects, 93 eyes	ORA IOPg M = 18.30, SD = 6.60 mmHg ORA IOPcc M = 18.70, SD = 6.30 mmHg ICare RBT M = 15.7, SD = 5.7 mmHg ORA overestimates ICare RBT by > 2.5mmhg

Table 1.6 Comparison of ICare RBT with ORA IOPcc and IOPg.(ICare RBT is dependent on the corneal biomechanics. IOP measurement with this instrument should correlate well with ORA IOPg and poorly with IOPcc. The results of the listed studies are not conclusive)

1.7 Scheimpflug or Pentacam corneal tomography

Theodor Scheimpflug (1865 − 1911) was a pioneer of aerial photography and mapping. He used land surveying instruments to create aerial photographs. The Scheimpflug rule describes the orientation of the plane of focus of an optical system, such as a camera, when the lens plane is not parallel to the image plane (Wegener and Laser-Junga, 2009). Normally in photography the image and film or sensor planes are parallel and the plane of focus (PoF) is parallel to the lens and image (film) planes. If the subject plane is not parallel to the image (film) plane, it will be in focus only along a line where it intersects the PoF (Figures 1.8, 1.9 and 1.10). By tilting the lens plane to lie parallel to the image plane the depth of field extends between the parallel planes on either side of the plane of focus resulting in distortion-free images (Figure 1.9 and figure 1.10) (Wegener and Laser-Junga, 2009; Erdkamp, 2012). Initially Scheimpflug took photos from kites and balloons, deskewing the oblique

views with his device to create “photo-perspectographs” or distortion-free images in order to create aerial maps (Figure 1.10 and figure 1.11) (Erdkamp, 2012). He published his work, *The making of maps and plans using photography,* in 1907 and to this day his geometric rule on camera position to enhance depth and focus when displaying oblique views without distortion is of major significance not only in architectural but also in diagnostic ophthalmology imaging. Recently this 100-year-old rule was used again by Google-Earth to produce undistorted images of landscapes and cities (Neuhann, 2007; Wegener and Laser-Junga, 2009).

Figure 1.8 Diagram illustrating the positions of the PoF, lens plane, and film plane where the film plane and lens planes are not parallel.(Drawing courtesy of Gerrie Kruger)

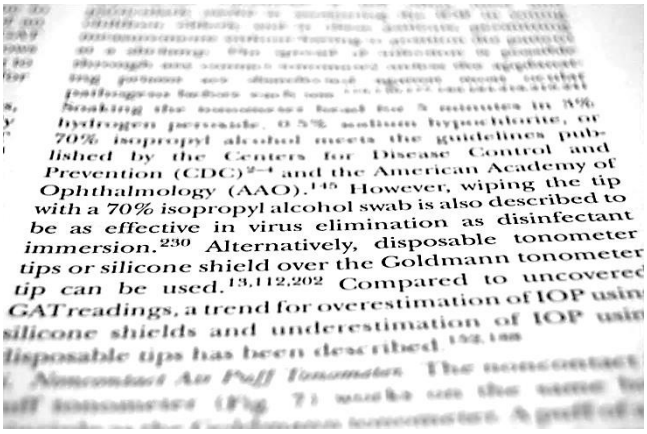


Figure 1.9 Image illustrating the PoF when the subject is not parallel to the lens plane.Only a small region of the image is in focus with elliptical blurred areas surrounding it (Photo D. Booysen) (Wegener and Laser-Junga, 2009; Erdkamp, 2012)

through any contact tonometry unless the applanating prisms are disinfected against most ocular pathogens before each use.[119,149,177,183,184,218,219,241] Soaking the tonometer head for 5 minutes in 3% hydrogen peroxide, 0.5% sodium hypochlorite, or 70% isopropyl alcohol meets the guidelines published by the Centers for Disease Control and Prevention (CDC)[2–4] and the American Academy of Ophthalmology (AAO).[145] However, wiping the tip with a 70% isopropyl alcohol swab is also described to be as effective in virus elimination as disinfectant immersion.[230] Alternatively, disposable tonometer tips or silicone shield over the Goldmann tonometer tip can be used.[13,112,202] Compared to uncovered GAT readings, a trend for overestimation of IOP using silicone shields and underestimation of IOP using disposable tips has been described.[152,188]

ii. Noncontact Air Puff Tonometer. The noncontact air puff tonometer (Fig. 7) works on the same basic

Figure 1.10 When the image (film) plane and the lens plane are parallel, the depth of field extends between parallel planes on either side of the PoF rendering the entire image in focus(Photo D. Booysen) (Wegener and Laser-Junga, 2009; Erdkamp, 2012)

Figure 1.11 Scheimpflug's original eight piece panoramic camera, rear view(Photo reproduced with written permission – Bundesampt –für Eich- und Verwessungwesen, Vienna [Appendix 2.2])

Figure 1.12 Eight images from the panoramic camera, perspective corrected and merged into a panorama with a recording angle of ± 140 degrees(Photo reproduced with written permission – Bundesampt –für Eich- und Verwessungwesen, Vienna [Appendix 2.2])

Corneal topography using a computer-aided system was developed in the 1980s and can be used to display an undistorted image of the curved corneal surface. However, the camera is placed at the centre of the imaging instrument (placido disc) resulting in a central 1 to 2 mm area of the cornea not being measured. Individual tear film characteristics can also influence the accuracy of the images. The rotating Scheimpflug camera overcomes these inadequacies by scanning the entire cornea with the same precision independent of the individual tear film (Neuhann, 2007). The Pentacam (Oculus, Wetzlar, Germany) generates real-time images of the actual eye segments, creating a precise three-dimensional view of the anterior segment including the central cornea. The instrument measures the anterior and posterior surface of the cornea by taking single slit images within one scan in less than two seconds while rotating from 0 - 180° to maximize the measured area of the cornea. Five hundred measurement points from each slit image is recorded, totalling twenty-five thousand (25000) true elevation points (HR model one hundred-and-thirty-eight-thousand [138000] real data measurements). The centre of the cornea is finely measured during the rotation while the pupil camera detects eye motion which is corrected for in the calculation process. An exact three-dimensional model of the anterior eye is then created. The topography and pachymetry of the entire anterior and posterior surface of the cornea, from limbus to limbus, are displayed and calculated.

Unlike placido curvature measurements systems, topography maps are generated by true elevation data. The analysis also includes a calculation of the anterior chamber angle; chamber volume; chamber height; lens densitometry; and manual measurements at any location in the anterior chamber of the eye. The Pentacam further calculates a quality specificity score (QS), which takes into account the analysed area of the cornea front and back curves, alignment, and ocular motion. This helps the clinician to assess the validity of the data in each examination (Neuhann, 2007; Wegener and Laser-Junga, 2009). (Figure 1.13 and figures 1.14, 1.15).

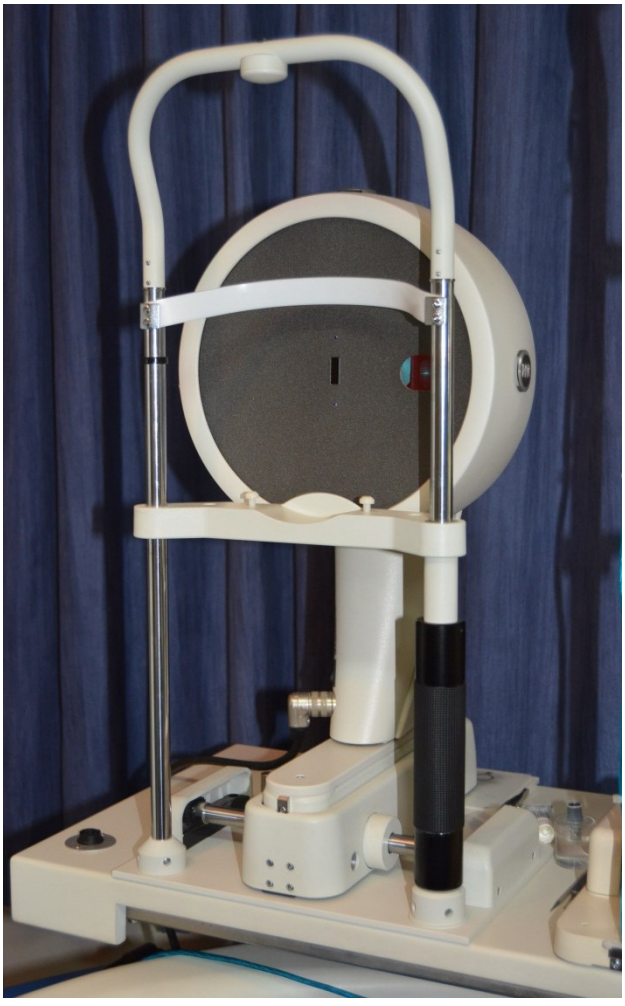


Figure 1.13 Pentacam HR.(Photo D. Booysen)

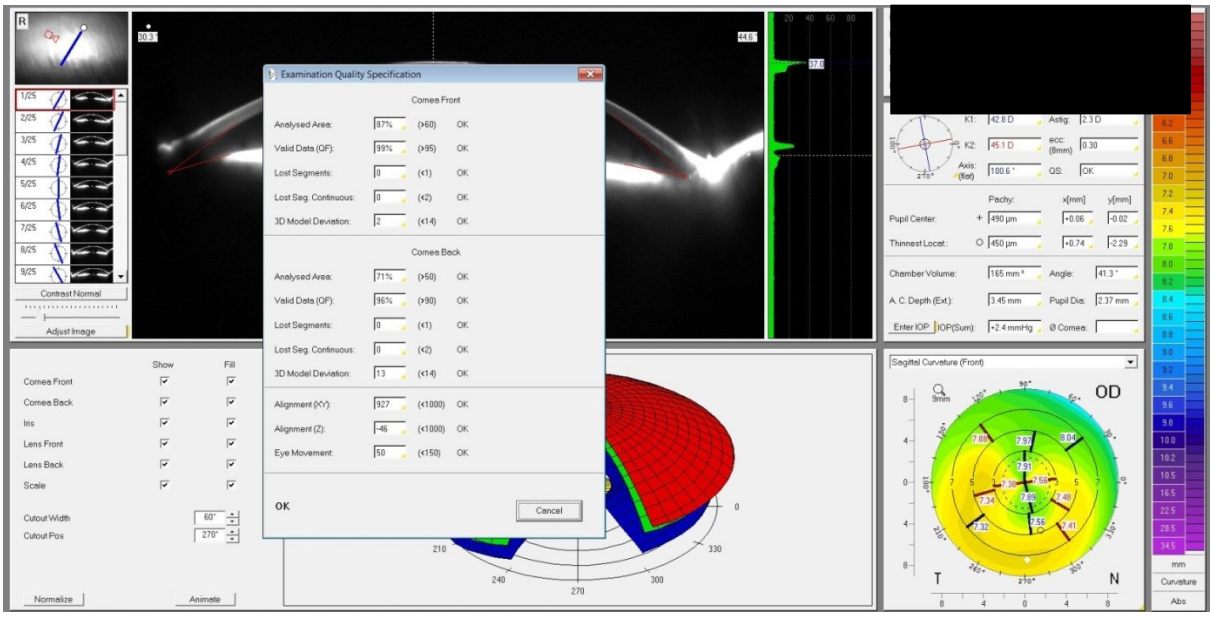


Figure 1.14 Pentacam Quality Score (QS)information indicating an acceptable measurement in this patient with Pellucid Marginal degeneration (not part of the study population) (Photo D Booysen)

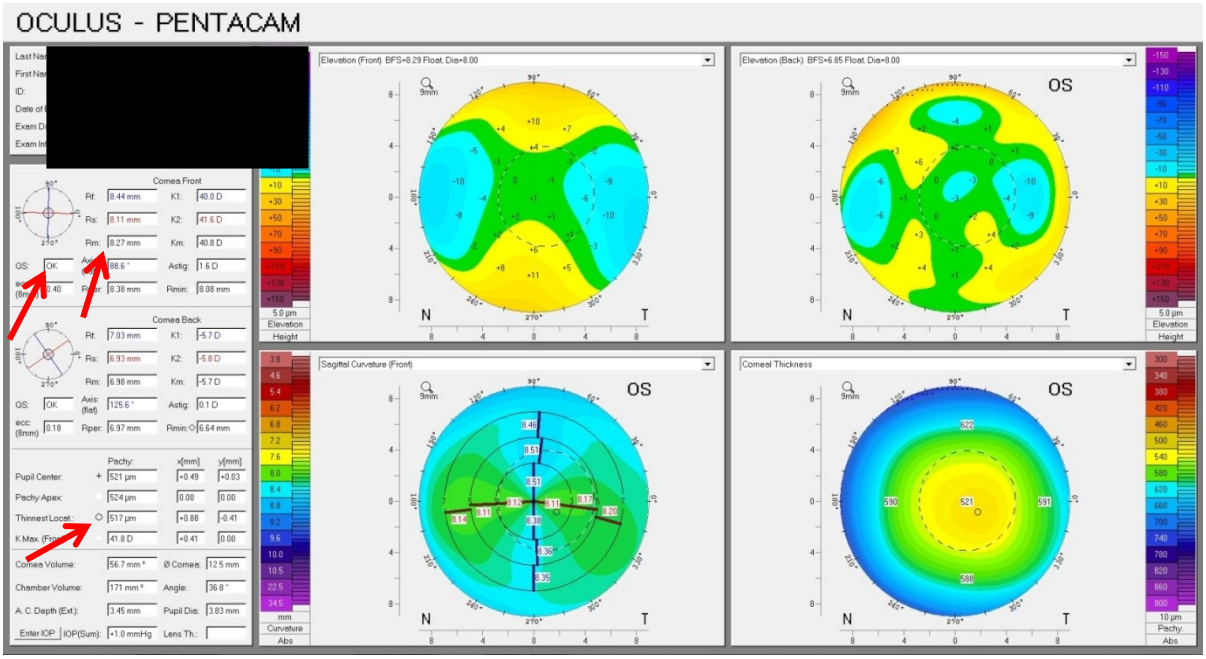


Figure 1.15 Pentacam display of the anterior float, posterior float, sagittal front curvature, and corneal thickness.The Arrows show the arithmetic mean corneal radius (RM 6.27 mm), quality score (QS OK), and thinnest corneal thickness (Thinnest local 517 µm) values recorded in this study. (Photo D Booysen)

Although Scheimpflug photography provides images of the anterior segment with minimal distortion, the distortion of the cornea and lens itself distort the image. Therefore biometrical measurements in the anterior segment such as corneal curvature, changes in lens curvature during accommodation,

depth of anterior chamber angle, always have to be corrected by specific algorithms. The amount of correction depends on the depth of the layer in question, meaning that each refractive zone adds a small amount of distortion to the path of the light rays (Wegener and Laser-Junga, 2009). Furthermore traditional anterior surface power maps, whether axial (sagittal) or meridional (tangential), are produced using the keratometric refractive index (n = 1.3375). Posterior corneal topography is calculated using the true refractive indices for the tissue-fluid interface (1.376 for the cornea and 1.336 for the aqueous) (Shankar et al., 2008).

In conclusion, for many anterior cornea measurements of normal healthy corneas, the Scheimpflug imaging system showed reasonable repeatability that was comparable to that of the Placido-based videokeratoscope. However, certain higher order aberrations (HOA's) derived from corneal elevation data from the Scheimpflug system such as trefoil and tetrafoil showed poor reliability compared to videokeratoscope results (Read et al., 2009).

Ultrasound pachymetry (UP) is widely regarded as the gold standard for measuring central corneal thickness (CCT) due to its superiority to older mechanical pachymeters (Thornton, 1984; Al-Mezaine et al., 2008). However, although UP has good intraobserver reproducibility it has a high degree of interobserver variability (Wheeler et al., 1992; O'Donnell and Maldonado-Codina, 2005). An ultrasound pachymeter uses the principles of A-scan ultrasonography to measure corneal thickness. The ultrasonic beam is aligned perpendicular to the central corneal surface and ultrasonic echoes are obtained from the anterior and posterior surfaces of the cornea. The time interval between the echoes can be used to determine the corneal thickness if the ultrasonic speed of propagation in the cornea is known. Ultrasound pachymetry (UP) could not be used in this study to measure corneal the thickness with contact lenses *in situ* as only the contact lens thickness would be measured due to the ultrasonic echo reflection from the lens surfaces.

Pentacam pachymetry yields high intraobserver reproducibility as well as low interobserver variability indicating that a reliable measurement of CCT can be obtained in a single reading and that the measurement is practically operator independent (Barkana et al., 2005). Pentacam pachymetry overestimates the CCT slightly (by 8.2 µm on average) compared with UP - probably due to the slight applanation force created when the UP probe displaces the 7 − 30 µm-thick tear film and compresses the epithelium (Al-Mezaine et al., 2008), thus agreeing with previous studies by Ucakhan et al. (2006) and Lam and Chen (2007) (Ucakhan et al., 2006; Lam and Chen, 2007). However, O'Donnell and Maldonado-Codina (2005) found the Pentacam slightly (by 2.4%) underestimated the CCT when

compared to UP (O'Donnell and Maldonado-Codina, 2005). The finding of Lackner et al (2005) agrees with that of O'Donnell and Maldonado-Codina (2005) in that, compared to UP, Pentacam pachymetry can be expected to err on the lower side of CCT by 11 – 15 µm on a 99% limit of agreement basis. In other words, as Lackner et al. (2005) observe, only one in 100 patients will have Pentacam CCT measurements > 11 − 15 µm lower than it would have been with UP (Lackner et al., 2005).

Pentacam corneal curvature measurements showed good repeatability, anteriorly (simulated keratometry mean (COR ±0.28 D; RR = 0.64%) and posteriorly (COR ±011 D; RR = 1.85%) as did anterior chamber parameters, but pupil measurements had poor repeatability (Shankar et al., 2008). According to McAlinden et al. (2011) the repeatability limits of the anterior keratometry readings with the fine scan were 0.04 D (*r* = 0.11 D) for both K1 and K2. Pachymetry maps, corneal maps, anterior chamber depth maps, corneal volume, topometric Q values and indices were also found to be precise. Poor precision was found for estimates of axis (astigmatic and progression index), pupil centre pachymetry, and single points on corneal maps, refractive power maps, and equivalent K-readings (McAlinden et al., 2011).

Scheimpflug or Pentacam corneal tomography was used in this study to measure the corneal curvature, central corneal thickness, and to determine whether the subject had any corneal disease such as keratoconus which would result in him or her being excluded from the study.

1.8 Measuring IOP over soft contact lenses

Although the diagnosis of glaucoma relies on many clinical tests, accurate IOP measurements form a pivotal part of the diagnosis and, more importantly, the treatment of glaucoma (Quigley and Addicks, 1981; Lusky et al., 1993; Cartwright and Anderson, 1998; Quigley, 2001; Maier et al., 2005; Heijl et al., 2008). In certain clinical situations it may be necessary to measure the IOP with a soft contact lens on the eye. Examples include patients wearing bandage contact lenses for the treatment of corneal injuries, after corneal surgery such as LASIK, PRK, and corneal crosslinking (Arora et al., 2004; Blackmore, 2010; Markoulli et al., 2012). Also, in situations where patients wear extended wear contact lenses, and it may not be possible to remove the lenses for the measurement of IOP.

More recent developments include the use of soft contact lenses for sustained drug delivery to the eye. The soft lenses are impregnated with the drug required for therapy which is then released into the eye over a period of time to treat the specific disease such as glaucoma, microbial keratitis, and

ocular inflammation (Braga et al., 2011; Peng and Chauhan, 2011; Gupta and Aqil, 2012; Peng et al., 2012; Tieppo, Pate, et al., 2012; Tieppo, White, et al., 2012). Several studies have demonstrated that contact lenses can be used as drug delivery systems for the treatment of chronic and acute eye disease (Morgan, 1971; Maddox and Bernstein, 1972; Maurice, 1972). Therapeutic contact lenses consist of pHEMA with or without silicone which are impregnated with drugs through various techniques such as soaking in a drug solution, colloidal particle laden lenses, molecular imprinting, and micro-emulsion gels (Carvalho et al., 2015). The drugs diffuse into the post-lens tear film and then into the cornea leading to increased retention of the drug on the surface of the cornea, increased bioavailability, increased therapeutic efficacy, and a reduction in the amount of drugs administered as well as preservatives used (Carvalho et al., 2015). Although commercially available contact lenses soaked in a drug solution is the most simplistic it has many limitations including poor uptake or release of the drug, poor retention of the drug within the lens and therefore lack of sustained delivery to the eye (Carvalho et al., 2015). Of concern is that these authors draw attention to the fact that no studies showed prolonged drug release exceeding two hours (Carvalho et al., 2015), however it is not clear if the studies were conducted in-vivo or in-vitro as the former may have more ideal slower release properties due to the drug being retained by the ocular surface barrier (Mahomed et al., 2016).

Modified medicated contact lenses use a barrier to prevent molecular diffusion of the drug from the lens matrix prolonging its action. Creation of these barriers can affect lens transparency as well as oxygen permeability. One way to create a barrier is to soak the lenses in vitamin E before drug incorporation (Peng et al., 2010). Lotrafilcon A (Focus Night & Day) contact lenses are especially suited for this type of drug delivery system (Peng et al., 2010). Depending on the concentration of the vitamin E, the release time can be manipulated from 5.5 to 192 hours for 16% and 74% vitamin E respectively (Carvalho et al., 2015). Imprinted medicated contact lenses involve the formation of macromolecular memory sites during the contact lenses polymerization process to accommodate the drug. The degree of polymer crosslinking plays an important role in the stability of the imprinted cavities; however, high polymer crosslinking affects the hydrogel's transparency, optical performance, flexibility, and water content making the lenses unsuitable for ocular use (Carvalho et al., 2015).

Additional strategies to overcome the limitations of eye drops as a dosage form involve the use of nanoparticles and their ability to include several drugs and control their release within the contact

lenses (Carvalho et al., 2015). The nanoparticles are incorporated during the production of the lens ensuring a high concentration in the lens matrix and therefore drug loading capacity (Jung et al., 2013). Drug release is affected by the specific nanoparticles used and in the case of polymeric nanoparticles the release of timolol can be sustained for two to four weeks in a temperature dependent manner (Jung and Chauhan, 2013).

It is important to evaluate the accuracy and repeatability of IOP measurements with the ICare tonometer and the Reichert ORA compared to measurements without contact lenses on the eye to validate clinical decisions based on IOP measurements with these instruments.

The following section gives an overview of the studies found in a recent literature search dealing with the measurements of IOP with contact lenses on the eye. Although comparative data are available for the ICare tonometer, only two studies, those of Lam and Tse (2014) and Sapkota et al. (2014), were found where the Reichert ORA was used to measure IOP with contact lenses on the eye (Lam and Tse, 2014; Sapkota et al., 2014). Both studies were published well after the commencement of the current study. The ORA also provides instrument specific measurements of corneal biomechanics (CH & CRF) which can be used to measure the effect of contact lenses on this corneal property (Luce, 2005; Kotecha, 2007; Reichert, 2013). The accuracy of IOP measured with different tonometers over various soft contact lens materials and powers has been extensively studied over the years (Table 1.7)

As early as 1976, Polse et al. used a Mackay-Marg and Schiotz tonometer to measure the IOP with and without a -8.00 D Softlens (Bausch & Lomb) on the eye, concluding that there appeared to be little, if any, significant difference in IOP caused by the lens as long as the lens remained fully hydrated and was approximately 0.16 mm thick (Polse et al., 1976). These researchers suggested that thicker or less pliable lenses would result in less accurate readings (Polse et al., 1976). In 1977, Janoff studied the effect of contact lens wear on IOP and found no significant difference between pre-fit IOP and those measured after six months of lens wear. The results provided the first evidence that continued contact lens wear does not adversely affect IOP (Janoff, 1977).

In 1986, McMonnies obtained reliable IOP measurements over soft contact lenses using a non-contact tonometer as long as the centre thickness of the lens was not more than 0.15 mm (McMonnies, 1986). The following year, Insler and Robbins (1987) compared the accuracy of IOP measurements over soft contact lenses using non-contact tonometry with positive and negative

power contact lenses and concluded that the difference in IOP was highly correlated with lens power (Insler and Robbins, 1987). The findings of the Insler and Robbins study indicated the difference in IOP was greater for positive power hyperopic lenses, with IOP measuring higher over these lenses (Insler and Robbins, 1987). Their results correlated well with the earlier findings of Draeger (1980) who performed Goldmann applanation tonometry over high water content contact lenses. He observed that the power of the lens had a highly significant effect on the IOP readings measured and produced a correction table for this effect when measuring IOP over high water content soft contact lenses (Draeger, 1980).

Panek et al. (1990) reported there was no significant difference in the TonoPen measurements of tonometry readings on cadaver eyes with plano-T bandage contact lenses *in situ* (Panek et al., 1990). These results were recently corroborated by Klein et al. (2011) who used the TonPen (Reichert instruments) and two other portable tonometers (the Phosphene tonometer [Bausch & Lomb] and TERT or Through Eyelid Russian Tonometer [Rjazan State Instrument Making] to measure IOP with and without soft contact lenses (Klein et al., 2011). Sugimoto-Takeuchi et al. (1991) found similar results with the plano-T and plano-B4 therapeutic lenses using a non-contact tonometer (NCT) (Sugimoto-Takeuchi et al., 1991).

Mark et al. (1992) measured IOP through bandage contact lenses on cadaver eyes with both NCT and TonoPen tonometry. They concluded that NCT could accurately measure IOP with and without a therapeutic contact lens, but that TonoPen was equally inaccurate with and without lenses, giving false low measurements (Mark et al., 1992). Scibilia et al. (1996) compared the IOP measurements with and without contact lenses using the TonPen and NCT. The lenses used were O4 (Bausch & Lomb), Acuvue (Johnson & Johnson), and Permalens (Cooper Vision). Although the lenses used in their study varied in water content and central thickness, no statistically significant differences were identified, suggesting that these variables did not affect the IOP measurements. However, the study did mention that the lenses used were relatively new and were all thinner than 0.45 mm (Scibilia et al., 1996).

Lim et al. (1997) compared the IOP measurements in 40 normal eyes with and without a low minus power daily disposable contact lens (-1.00 D SeeQuence [Bausch & Lomb]) using GAT and the TonoPen. The TonoPen consistently measured higher IOP than the GAT by ±4 mmHg, but the findings were not affected by the presence of a low minus power soft contact lens (Lim et al., 1997). GAT without fluorescein consistently underestimated the IOP by M = 2.15, SD = 1.97 mmHg. These were

similar to GAT measurements over low minus soft contact lenses which also underestimated IOP by M = 2.90, SD = 2.37 mmHg. The study suggested that practitioners who do not have access to topical anaesthesia may use a low minus power soft contact lens when performing GAT without fluorescein as long as a correction factor of +2.0 mmHg is applied (Lim et al., 1997). Aditionally, Schollmayer and Hawlina (2003) compared IOP measurements over different power soft silicone hydrogel contact lenses (Focus Night & Day [Ciba Vision]) with an NCT. The measurements over low minus lenses were accurate but measurements were considerably higher over positive power lenses with increased centre thickness. The conclusion was that IOP could be reliably measured with NCT in patients wearing minus power and low positive power soft contact lenses (Schollmayer and Hawlina, 2003).

Touboul (2008) also found that NCT over soft contact lenses was only accurate if the lenses had low minus power. It was his stance that this practice was only acceptable for glaucoma screening and that standard GAT should remain the gold standard for IOP measurements (Touboul, 2008). Allen et al. (2007) measured IOP using GAT with fluorescein and topical anaesthesia over low minus silicone hydrogel lenses (-0.50 D Pure Vision [Bausch & Lomb]) and found IOP could be accurately measured through the lenses (Allen et al., 2007). Zeri et al. (2007) measured IOP using GAT through a daily disposable contact lens (-1.50 D Softlens One Day [Bausch & Lomb]) and concluded that IOP measurements by GAT of over a thin, low minus power daily lens compared favourably with the standard GAT procedure within the normal IOP range in patients with low levels of astigmatism (Zeri et al., 2007). Nosch et al. (2010) found no statistically significant difference regarding the accuracy and repeatability of IOP measurements with or without a thin soft contact lens on the eye. A Pascal dynamic contour tonometer (DCT) and a -0.50 D Filcon IV hydrogel lens (Bioclear One Day [Sauflon]) was used in this study (Nosch et al., 2010).

With respect to high power myopic lenses, Patel and Illahi (2004) reported no significant change in IOP with or without lenses ranging from -15.00 to +3.00 D when measuring IOP with an NCT. The study concluded that as long as the lens thickness was not more than 0.30 mm and the power no more than +3.00 D, NCT could be performed accurately over a soft contact lens (Patel and Illahi, 2004). In another study by Liu et al. (2011) NCT was performed through three different types of minus power soft contact lenses. The powers selected were -3.00, -6.00, and -9.00 D and the lenses used were hilafilcon A (Softlens One Day [Bausch & Lomb]) in 8.60 base curve and etafilcon A (1- Day Acuvue [Johnson & Johnson]) in 8.5 and 9.0 base curves. IOP readings through higher power minus lenses decreased, especially with lens powers above -6.00 D. The reduction in the measured IOP may

be associated with the change in the front surface curvature of the lenses and not the centre thickness of the lenses, as the centre thickness of higher power minus lenses remains constant in contrast to the increased centre thickness of higher power plus lenses. The researchers concluded that low power minus lenses could be left on the eye when measuring IOP with an NCT, but caution should be exercised with lens powers over -6.00 D due to underestimation of IOP (Liu et al., 2011).

In another study Patel and Stevenson (2009) used an NCT to measure the IOP over a low water content silicone hydrogel lens of relatively high modulus (Focus Night & Day, modulus 1.20 MPa [Ciba Vision]) as well as a high water content daily disposable lens with low modulus (Focus Dailies, modulus 0.91 MPa [Ciba Vision]). The lens powers varied between -7.50 D and +6.00 D. The measured difference in IOP was related to both lens power, material modulus and, to a lesser extent, IOP (Patel and Stevenson, 2009).

Zeri et al. (2011) evaluated the effect of hydrogel and silicon hydrogel lenses on the accuracy of the rebound tonometer (RBT). An Acuvue 2 hydrogel and an Acuvue Oasys silicone hydrogel lens (both Johnson & Johnson) were used. IOP was measured with and without the lenses on the eye with the ICare RBT. The results were interesting in that they unexpectedly found the RBT tended to underestimate IOP measured through low (+2.00 D) hydrogel and silicone hydrogel contact lenses. The reasons for this “inversion” of previous studies results are not clear and the researchers posit that it may be due to biomechanical characteristics with the low plus lenses on the eye. The study concluded that RBT can be reliably performed over silicone hydrogel contact lenses, but that measurements with hydrogel lenses were lower than those without contact lenses. However, despite the fact that these differences were statistically significant, their clinical significance is negligible (Zeri et al., 2011).

Firat et al. (2012) evaluated the influence of silicone hydrogel contact lenses on IOP measurements with NCT and Pascal dynamic contour tonometry (DCT). A Focus Night & Day (Ciba Vision) contact lens with 24% water content, 1.1 MPa modulus of elasticity and plano refractive power was used. Results showed the mean IOP measured with NCT without and with the contact lens on the eye was respectively M = 14.5, SD = 2.95 mmHg and M = 13.92, SD = 2.58 mmHg (difference was not statistically significant). The mean IOP measured with DCT without and with the contact lens was respectively M = 16.26, SD = 2.33 mmHg and M = 15.19, SD = 2.40 mmHg (difference was statistically significant). The study concluded that silicone hydrogel contact lens use does not significantly affect IOP measured with the NCT, but it does affect IOP values measured with DCT (Firat et al., 2012).

The influence of a bandage contact lens on the IOP measured by NCT and RBT was evaluated by Anton et al. (2013). In their study a Pure Vision 2 HD (Bausch & Lomb) silicone hydrogel lens with a 36% water content, 1.5 MPa modulus of elasticity and plano prescription was used. NCT and RBT were performed with and without the lenses on the eye and the results compared. With the NCT IOP without and with the lens were respectively M = 15.6, SD = 2.6 mmHg and M = 15.3, SD = 2.6 mmHg (difference was not statistically significant), and with the RBT, the IOP without and with the lens was respectively M = 17.5, SD = 4.3 mmHg and M = 16.4, SD = 3.5 mmHg (difference was not statistically significant but correlated well with corneal thickness – 0.03 mmHg per µm corneal thickness change). It was concluded that the NCT and RBT tonometer appeared to measure the IOP with a silicone hydrogel lens on the eye with sufficient accuracy for routine clinical practice (Anton et al., 2013).

In a study by Lam and Tse (2014) IOP and OPA were measured using the DCT over silicone hydrogel lenses of different modulus. The lenses used were Focus Night and Day (Ciba Vision) with a modulus of 1.5 MPa and Acuvue Advance (Johnson & Johnson) with a modulus of 0.43 MPa. Corneal biomechanics were also measured with and without lenses using the ORA CH and CRF metrics. Results showed IOP was slightly higher when measured through the higher modulus lenses than without or through the low modulus lenses. OPA was also significantly lower when measured through the contact lenses, and the corneal biomechanical metrics CH and CRF clinically measured the same with and without lenses on the eye. In contrast to the findings of Firat et al. (2012) which showed that IOP measurements with silicone hydrogel lenses *in situ* was possible with an NCT but not an DCT, Lam and Tse concluded it was feasible to measure IOP with DCT over low modulus silicone hydrogel lenses (Lam and Tse, 2014).

Using a -3.00 D Silicone hydrogel one day lens (Acuvue True Eye [Johnson & Johnson]) and hydrogel one day lens (Daily Aqua Comfort Plus [Ciba Vision]), Sapkota et al. (2014) measured both ORA IOPg and IOPcc with and without the lenses on the eyes of 28 subjects with normal corneas. Both IOPg and IOPcc when measured with contact lenses *in situ* were statistically lower than without contact lenses ($p<0.05$). With Acuvue True Eye (Johnson & Johnson), the IOPg and IOPcc were lower by M = 0.88, SD = 2.04 and M = 1.55, SD = 2.16 mmHg respectively, and with Daily Aqua Comfort (Ciba Vision) the values were M = 1.03, SD = 1.93 mmHg and M = 1.62, SD = 3.12 mmHg respectively. The study concluded that to measure IOP accurately with the ORA, contact lenses should be removed (Sapkota et al., 2014).

Rimayati et al. (2014) studied the ocular surface displacement with and without contact lenses during noncontact tonometry and made two interesting findings. Firstly, they discovered that GAT IOP without lenses was similar to NCT IOP without lenses. The second finding was that with higher plus powered thicker lenses NCT overestimated IOP while with higher minus powered thinner lenses NCT underestimated IOP. The authors concluded that changes in NCT IOP depend on lens power and that the radius of ocular surface curvature affects the ocular surface displacement and IOP readings with lenses *in situ* (Rimayanti et al., 2014).

Kumar, et al. (2015) compared IOP measured with and without a daily disposable hydrogel contact lens on the eye with the Corvis ST Scheimpflug non-contact tonometer and found the measurements were similar, M = 13.80, SD = 2.70 mmHg and M = 13.79, SD = 2.54 mmHg with and without lenses respectively. The difference of M = 0.01, SD = 0.16 mmHg was not statistically significant (Kumar et al., 2015).

After the completion of this present study on tonometry and biomechanics of the cornea in contact lens wear, Zeri et al. (2015) studied the accuracy of ICare RBT through Acuvue 2 hydrogel (Johnson & Johnson) plus lenses. They measured the IOP with and without a +2.00 D and a +6.00 D lens on the eye and found that the ICare RBT significantly underestimated IOP with the lenses *in situ:* without lenses M = 19.0, SD = 4.1 mmHg; with +2.00 M = 17.6, SD = 4.6 mmHg, and with +6.00 D M = 17.8, SD = 4.1 mmHg) (Zeri et al., 2015). Surmising that the reasons for the lower IOP measurement with the lenses could be attributed to the lower resistance to deformation of the high water content etafilcon A material, the authors' conclusion was that the corneal thickness (combined lens and corneal thickness) does not affect the value of the IOP measured with the ICare RBT (Zeri et al., 2015).

In a study by Takenaka et al. (2015), using GAT measurements without lenses as a baseline, compared it to measurements through Acuvue 2 (Johnson & Johnson) lenses (-5.00D, -0.50D and +5.00D) with GAT, NCT, ICare RBT, and Tono-Pen XL. Although the authors found no significant differences in IOP measured with and without minus lenses using NCT, GAT, and ICare RBT, there was an exception with GAT through the -5.00 D lenses. IOP measurements with the Tono-Pen XL were significantly higher than baseline GAT IOP without lenses on the eye. The conclusion was that IOP obtained through contact lenses with the NCT exhibited the highest correlation with GAT without lenses. NCT and ICare RBT are more accurate than the other instruments used in the study to measure IOP through soft lenses (Takenaka et al., 2015).

Study	Methods/Subjects	Lenses used	Results
Polse et al. (1976)	Mackay-Marg & Schiotz tonometers 5 eyes of albino rabbits	-8.00 D Softlens (Bausch & Lomb), hydrogel	Fully hydrated, approximately 0.16 mm thick lenses = little or any effect on measurements
Draeger (1980)	GAT Not known	High water content hydrogel lenses	Measured IOP was highly correlated with lens power
Mc Monnies (1986)	NCT 20 eyes	Hydrogel lathe cut lenses, -5.00 and 38% water content; CT (0.057-0.219 mm) Spun cast U3 & B4 (Bausch & Lomb) hydrogel lenses; CT (0.071 & 0.152 mm)	No effect on IOP as long as the CT < 0.15 mm
Insler and Robbins (1987)	NCT 23 subjects and 43 eyes	Plus and minus powered hydrogel lenses	Measured IOP was highly correlated with lens power. Plus lenses = higher measured IOP
Panek et al. (1990)	TonoPen 20 subjects and 40 eyes	Plano-T bandage hydrogel lenses on cadaver eyes	No effect on IOP
Sugimoto-Takeuchi et al. (1991)	NCT 18 subjects and 29 eyes	Plano-T & Plano B4 therapeutic hydrogel lenses	No effect on IOP
Mark et al. (1992)	TonoPen and NCT 9 cadaver eyes	Bandage hydrogel lenses on cadaver eyes	NCT accurate with and without a therapeutic contact lens. TonoPen equally inaccurate with and without a therapeutic contact lens
Scibilia et al. (1996)	TonoPen and NCT 20 eyes	Hydrogel lenses, O4 (Bausch & Lomb); Acuvue (Johnson & Johnson); Permalens (Coopervision)	No statistically significant differences with or without the lenses
Lim et al. (1997)	GAT and TonoPen 20 subjects and 40 eyes	Daily disposable hydrogel low minus lens (-1.00 SeeQuence (Bausch & Lomb)	TonoPen consistently measured higher than GAT by ±4 mmHg but the findings were not affected by the contact lens

Schollmayer and Hawalina (2003)	NCT 80 subjects and 120 eyes	Silicone hydrogel lenses of different power (Focus Night & Day [Ciba Vision])	Lower measured IOP over low minus lenses but higher IOP measured with plus power lenses
Study	**Methods/Subjects**	**Lenses used**	**Results**
Patel and Illahi (2004)	NCT 8 subjects and 8 eyes	-15.00 to +3.00 D hydrogel lenses	With CT < 0.30 mm and power < +3.00 D, accurate measurements could be obtained with NCT
Allen et al. (2007)	GAT 10 subjects and 20 eyes	Low minus silicone hydrogel lenses (-0.50 Pure Vision [Bausch & Lomb])	Accurate measurements were possible
Zeri et al. (2007)	GAT 68 subjects and 136 eyes	Low minus hydrogel lens (-1.50 Softlens One Day [Bausch & Lomb])	Measurements compared favourably to standard GAT measurements
Touboul (2008)	NCT Not known	Hydrogel lenses	Measurements only accurate with low power minus lenses
Patel and Stevenson (2009)	NCT 25 subjects and 50 eyes	Low water content silicone hydrogel lenses (Focus Night & Day [Ciba Vision]) and high water content hydrogel lens (Focus Dailies [Ciba Vision]). Power varied between -7.50 to +6.00 D)	Lens power, modulus, and IOP affect the accuracy of the measurements
Nosch et al. (2010)	DCT 46 subjects and 46 eyes	Hydrogel low minus lens (-0.50 D Bioclear One Day [Saflon])	No statistically significant difference regarding the accuracy and repeatability with or without lenses
Liu et al. (2011)	NCT 32 subjects and 32 eyes	-3.00, -6.00, and -9.00 D, Soflens One Day [Bausch & Lomb]; 1 day Acuvue [Johnson & Johnson] in 8.5 and 9.0 base curves	Lower IOP measured through higher power minus lenses; low power minus lenses did not affect IOP measurements
Klein et al. (2011)	TonoPen, Phosphene, and TERT tonometers 66 eyes	Therapeutic soft contact lenses	The presence of a therapeutic contact lens does not affect the IOP measurements obtained by the three instruments.

Zeri et al. (2011)	RBT 68 subjects and 136 eyes	Hydrogel (Acuvue 2 [Johnson & Johnson]) and silicone hydrogel (Acuvue Oasys [Johnson & Johnson])	RBT can be accurately performed over silicone hydrogel lenses. However, measurements with low power plus and hydrogel lenses were lower than without them.
Study	**Methods/Subjects**	**Lenses used**	**Results**
Firat et al. (2012)	NCT and DCT 40 subjects and 40 eyes	Silicone hydrogel plano power lens (Focus Night & Day [Ciba Vision])	Statistically insignificant difference with NCT. Statistically significant difference with DCT.
Anton et al. (2013)	NCT and RBT NCT 16 subjects RBT 23 subjects	Silicone hydrogel plano powered lens (Pure Vision 2 HD [Bausch & Lomb])	Statistically insignificant difference with both NCT and RBT, but RBT correlated well with corneal thickness changes.
Lam and Tse (2014)	DCT and ORA CH and CRF 74 subjects and 148 eyes	Silicone hydrogel lenses' high (Focus Night and Day - Ciba Vision) and low (Acuvue Advance [Johnson & Johnson]) modulus.	No significant difference in CH and CRF measured through the lenses. High modulus silicone hydrogel lenses demonstrated greater effect on IOP (95% LoA 2.73 mmHg) than low modulus lenses (95 % LoA 1.0 mmHg). DCT can be performed reliably over low modulus silicone hydrogel lenses.
Sapkota et al. (2014)	ORA IOPcc and IOPg 28 subjects and 56 eyes	Silicone hydrogel one day lens (Acuvue True Eye [Johnson & Johnson]) and hydrogel one day (Daily Aqua Comfort Plus [Ciba Vision]). Power used was a -3.00 D lens on 28 subjects without ocular pathology	Both IOPg and IOPcc when measured with contact lenses were statistically lower than without contact lenses ($p < 0.05$). With True Eye IOPg and IOPcc was M = 0.88, SD = 2.04 and M = 1.55, SD = 2.16 mmHg lower respectively. With Aqua Comfort the values were M = 1.03, SD = 1.93 mmHg and

			M = 1.62, SD = 3.12 mmHg respectively. To measure IOP accurately with the ORA contact lenses should be removed.
Study	**Methods/Subjects**	**Lenses used**	**Results**
Rimayanti et al. (2014)	GAT and NCT 21 subjects and 21 eyes	Acuvue 2 (Johnson & Johnson), etafilcon A, 58% water content, 8.70 mm base curve, 14.00 mm diameter, 40 Dk/t, 0.084 mm CT, modulus 0.25 MPa, power -5.00, -0.50, and +5.00 D	GAT without lenses was similar to NCT. With higher plus powered thicker lenses NCT overestimated IOP; with higher minus powered thinner lenses NCT underestimated IOP. Changes in IOP depend on lens power and the radius of ocular surface curvature affects the ocular surface displacement and IOP readings.
Kumar et al. (2015)	Corvis ST 88 subjects and 88 eyes	Dailies-nelfilcon A (Ciba Vision), 69% water content, 8.70 mm base curve, 14.00 mm diameter, 0.10 mm centre thickness, hydrogel lenses	IOPs with and without the contact lenses were M = 13.80, SD = 2.70 and M = 13.79, SD = 2.54 mmHg. Mean difference M = 0.01, SD = 0.16mmHg. Statistically there was no difference between the measurements with and without contact lenses with the Corvis ST tonometer.
Zeri et al. (2015)	ICare RBT 28 subjects and 26 eyes	Acuvue 2 (Johnson & Johnson), etafilcon A, 58% water content, 8.70 mm base curve, 14.00 mm diameter, 40 Dk/t, 0.084 mm CT, modulus 0.25 MPa, and power +2.00 and +6.00 D	IOP's with and without the positive power etafilcon A lenses were significantly different: +2.00 t =-4.37, p = 0.0002 and +6.00 t =-3.95, p = 0.0005. ICare RBT measured over positive hydrogel lenses was

			significantly lower than IOP measured without the lenses.
Study	**Methods/Subjects**	**Lenses used**	**Results**
Takenaka et al. (2015)	NCT, GAT, ICare RBT, Tono-Pen XL 26 subjects	Acuvue 2 (Johnson & Johnson), etafilcon A, 58% water content, 8,70 mm base curve, 14.00 mm diameter, 40 Dk/t, 0.084 mm CT, modulus 0.25 MPa, power -5.00, -0.50, and +5.00 D	GAT without lenses was used as the standard against which the measurements with lenses were tested. NCT with -5.00 lenses showed a -0.50 mmHg difference (p = 0.42); with -0.50 lenses +0.30 mmHg p = 0.70, and with +5.00 lenses +2.00 mmHg (p < 0.01). Gat with -5.00 lenses showed a difference of -1.50 mmHg (p = 0.03); with -0.50 lenses -0.60 p = 0.36, and +5.00 +2.3 mmHg (p < 0.01). ICare RBT showed difference with -5.00 of +0.50 mmHg (p = 0.49); with -0.50 lenses -0.20mmHg p = 0.75 and with +5.00 lenses +1.1 mmHg (p= 0.18). Tono-Pen XL showed a differences with -5,00 lenses of +2.6 mmHg p < 0.01 and with -0.50 lenses +2.5 mmHg (p < 0.01) and with +5.00 +4.8 mmHg (p < 0.01). The authors concluded that the NCT and ICare RBT gave the most accurate IOP measurements with contact lenses *in situ.*

Table 1.7 Summary of the studies that have examined the validity of measuring IOP with contact lenses *in situ* with different tonometers.(Accurate IOP measurement with contact lenses *in situ* is possible with a variety of instruments. It is generally accepted that as long as the lens thickness does not exceed 0.15 mm - 0.30 mm, the lens is fairly new, well hydrated and has a low prescription, the accuracy of the measurements is not significantly different from measurements without the contact lenses on the eye)

It is evident that accurate measurement of IOP with contact lenses *in situ* may be possible with a variety of instruments. However, factors such as lens prescription or power; lens modulus or stiffness; lens thickness; lens anterior curvature; and hydration seem to affect the accuracy of the measurements. It is generally accepted that as long as the lens thickness does not exceed 0.15 − 0.30 mm, the lens is fairly new, well hydrated and has a low prescription, the accuracy of the measurements is not significantly different from measurements without the contact lenses on the eye. Higher power plus lenses lead to overestimation, and higher power minus lenses to underestimation of intraocular pressure.

1.9 Aims of this programme of research

According to the South African agent for the ICare rebound tonometer, it is possible to accurately measure the IOP while a patient is wearing soft contact lenses. Although this assurance is not corroborated by the parent company, it nonetheless intrigued me into prompting an investigation which led to this study. An exhaustive literature review revealed a number of studies (Table 1.7) dealing with tonometry over disposable soft contact lenses. According to the 2001 International Standards Organization (ISO), GAT measurements corrected for CCT remains the main reference instrument for clinical measurements of IOP; in other words, the gold standard for tonometry (ISO, 2001). However, the ICare RBT is a popular screening device in ophthalmic practice and many studies have demonstrated that it compares favourably with GAT and NCT (Table 1.5). Therefore, GAT measurements were not taken in this study. Only two studies comparing the ICare and ORA (Table 1.6) and only one study on the accuracy of ORA measurements with soft lenses *in situ* (Table 1.7) could be found. In the current programme of research ICare and ORA measurements with and without contact lenses on the eye were compared.

Although the general consensus suggests that it is possible to measure IOP with various instruments and soft lenses *in situ*, some questions remain unanswered. More information is needed on which specific lens characteristics such as lens material; refractive power; modulus of elasticity; water content; centre thickness; and base curve affect the accuracy of the IOP measurements. The ORA measures instrument-specific corneal biomechanical metrics (CH and CRF) which is used to calculate corneal compensated IOP as well as Goldmann-correlated IOP. The fact that the biomechanical metrics can be measured *in vivo* created further opportunity to study the effects of soft contact

lenses on these measurements which are known to influence the measurements of IOP with the ICare RBT and other tonometers.

Hence, this research will examine the accuracy of ICare RBT and ORA IOP measurements with four commonly used soft disposable contact lenses (in South Africa) *in situ* and evaluated the physical and physiological factors that influenced the accuracy of IOP measurement with the lenses on the eye. Corneal thickness and corneal curvature are also known to affect IOP measurements and therefore the Pentacam corneal analysis system was used to measure the differences between corneal thickness and corneal curvature without and with lenses *in situ*, enabling the study of the differences on the accuracy of IOP measurements with the ICare RBT and ORA instruments. Repeatable and reproducible measurements are prerequisites for any ophthalmic measurement instruments. The research was designed to evaluate the repeatability and reproducibility of the ICare RBT and repeatability of the ORA with and without soft contact lenses *in situ*. At the time of writing no studies could be found examining repeatability and reliability of the ICare RBT and ORA with soft contact lenses on the eye.

Research on the use of contact lenses as drug delivery systems to the cornea and eye are continuing and soft disposable lenses are often used as bandage lenses to treat corneal injuries, abrasions and dry eye problems. If it is possible to accurately measure IOP with contact lenses *in situ* with popular tonometers such as the ICare RBT, patient care will be enhanced and valuable chair time saved. Knowledge of the physical contact lens properties which influence the measurements of IOP with lenses *in situ* will benefit manufactures of bandage and drug delivery contact lenses enabling the design of lenses which have a minimal influence on the accuracy tonometry.

1.9.1 Supporting publications

The following papers have been published or presented at conference from the literature review.

- Progression of Ocular Hypertension: Lessons from the Literature (Booysen, 2012).
- In Vivo Measurement of Corneal Biomechanics: A Discussion on the Relevance of these Measurements in Refractive Surgery (Booysen, 2013).
- Corneal Biomechanics: Clinical Insights and Applications (Booysen, 2013; Booysen, 2013).
- Tonometry (Booysen, 2015).

Chapter 2

Methodology and analysis

2.1 Subjects

Fifty healthy subjects comprising 15 males and 35 females between 18 to 55 years (M = 38.90, SD = 9.23 years) without ocular pathology, adapted to soft disposable contact lens wear were enrolled in this programme of research. All subjects were healthy volunteers visiting a private optometry practice for routine eye care. The principles contained in the Declaration of Helsinki (Williams, 2008) and the South African Department of Health Clinical Trial and Ethics in Health Research Guidelines (DOH, 2015) were complied with throughout this research process. In addition, the study was reviewed by Aston University Research Ethics Committee (UK) and the South African Pharma-Ethics Committee (Appendix 1). Written informed consent was obtained from the subjects after explaining the procedures and reasons for the study (Appendix 4). Inclusion criteria were: healthy subjects with healthy eyes (no pathology or medication that might influence the measurement of IOP or corneal biomechanics), having normal corneas free of scarring, and having no corneal pathology and/or prior surgery as assessed by slit lamp biomicroscopy and Scheimpflug (Oculus Pentacam) corneal analysis.

It is well known that corneal astigmatism affects the accuracy of GAT (Whitacre and Stein, 1993). With-the-rule astigmatism over 4.00 DC results in underestimation and against-the-rule astigmatism in overestimation of the IOP by 1 mmHg − it is statistically significant, but not clinically significant (Whitacre and Stein, 1993; Akram et al., 2009; Hamilton-Maxwell, 2014; Townsend and McSoley, 2015). Although research shows the accuracy of IOP measurements with ICare RBT and NCT is not affected by corneal astigmatism (De Moraes et al., 2008; Johannesson et al., 2008; Hamilton-Maxwell, 2014; Townsend and McSoley, 2015), subjects with more than 2.50 Dioptres of corneal astigmatism were excluded from this study. Figure 2.2 shows the range and frequency distribution of corneal astigmatism in the study population. All subjects had to achieve unaided or aided visual acuity of 6/6 or better in each eye.

Contact lens wear, soft as well as rigid gas permeable lenses, results in lower IOP measurements after the lenses have been removed. This effect is most probably due to a variation in the properties of the cornea which includes biomechanics and corneal swelling caused by the lens wear (Xu et al., 2008; Hamilton-Maxwell, 2014; Mahjoob et al., 2014). In this study all subjects were long-term soft

lens wearers resulting in lower IOP and corneal biomechanical properties being measured upon lens removal compared to values measured after lens wear was discontinued. Recent research show these values to be still decreased more than two weeks after discontinuing lens wear (Xu et al., 2008). Although it is important to consider the long-term effect of contact lenses on the cornea and the accuracy of these measurements, the differences are relatively small (Xu et al., 2008; Hamilton-Maxwell, 2014; Mahjoob et al., 2014). It is impractical to discontinue lens wear for an extended period in order to measure the "correct" IOP and biomechanical properties in soft contact lens wearers in a clinical setting. Other technical and clinical factors that may affect the accuracy of IOP measurements include: possible reading errors; calibration issues; Valsalva manoeuvre; nervousness or forced eyelid closure; and the effects of variation in corneal stiffness (Bao et al., 2015).

All participants in this study removed their contact lenses at least 24 hours before any measurements were taken and data collected. According to the ISO (2001), GAT corrected for CCT remains the reference instrument for clinical measurement of IOP; in other words, the gold standard for tonometry (ISO, 2001). IOP measurements with both instruments used in this study had previously been compared to the gold standard and these studies as well as their results are listed in Tables 1.4 and 1.5. The instruments had also been compared to each other and Table 1.6 lists these studies and their results. The aim of this programme of research was to evaluate the accuracy of the ICare RBT and ORA instruments with contact lenses on the eye and therefore no GAT measurements with or without contact lenses *in situ* were taken during the course of this research.

2.2 Materials and procedure

The contact lens materials used in this programme of research included silicone hydrogel (Pure Vision [Bausch & Lomb]; Acuvue Oasys [Johnson & Johnson]) and hydrogel lenses (Frequency XC [Coopervision], and Acuvue 1-Day Moist [Johnson & Johnson]). Euromcontact data for South Africa indicate these brands are commonly and routinely used by South African eye care practitioners (Euromcontact, 2013). The properties of the contact lenses are listed in Table 2.1. Contact lens powers ranged between -6.00 and +6.00 D and Figure 2.2 shows the range and frequency distribution of the mean spherical equivalent refractive error in the study population.

Material	A.Balafilcon (Pure Vision)	B. Omafilcon A (Frequency XC)	C. Etafilcon A (Acuvue 1-Day Moist)	D. Senofilicon A (Acuvue Oasys)
Base curve (mm)	8.6	8.5	8.5 & 8,9* *Only 8.5 used in this study	8.4 & 8,8* * Only 8.4 used in this study
Overall diameter (mm)	14.00	14.20	14.50	14.00
Modulus (MPa)	1.1	0.3-0.4	0.26	0.75
Dk/t ($x10^{-9}$)	101	44	25.5	147
Water content (%)	36	60	58	38
Central thickness (-3.00 in μm)	90	75	84	70

Table 2.1 Lens materials and specifications used in the study

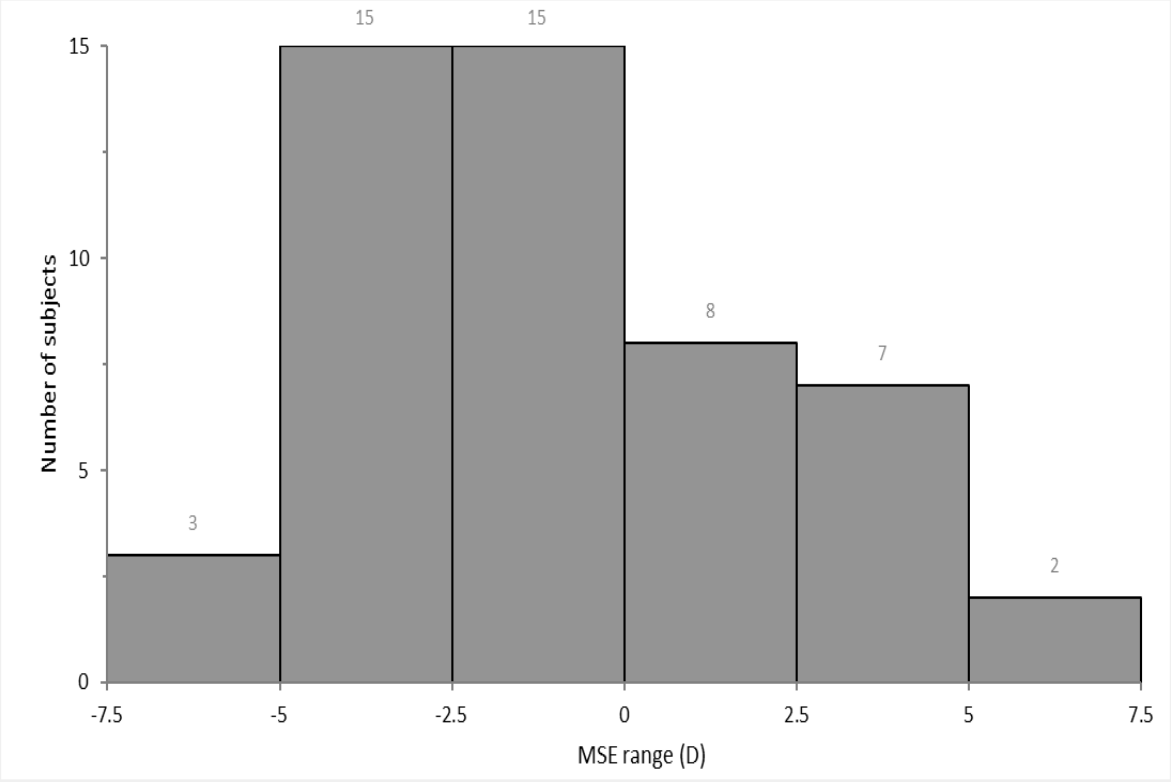


Figure 2.1 Range and frequency distribution of mean spherical equivalent refractive error in the study population, n = 50.(MSE = mean spherical equivalent refractive error)

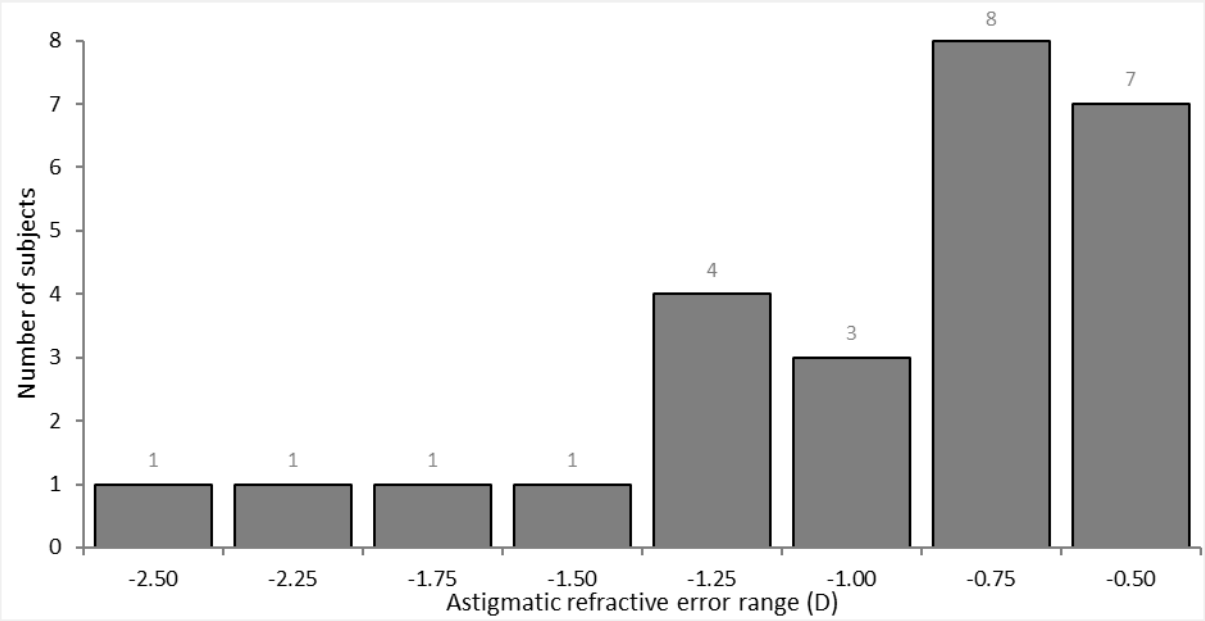


Figure 2.2 Range and frequency distribution of the subjects with corneal astigmatism in the study population, n = 26.

Very high plus (≥ +12.00 D) silicone aphakic lenses (Silsoft [Bausch & Lomb]) were initially included in the study as it seemed it may be beneficial to measure IOP with lenses *in situ* for patients wearing these lenses on a long-term extended wear basis. However, neither the ICare RBT nor the ORA could measure IOP with these lenses *in situ,* and the decision was made to limit the plus powers to +6.00 D. The sale of Silsoft (Bausch & Lomb) lenses were discontinued during the course of this study and no other of-the-shelf silicone aphakic lenses were and are currently available for commercial use in South Africa.

Astigmatic prescriptions were converted to best spherical equivalent when recorded (sphere + ½ cylinder = spherical equivalent). Each subject was fitted consecutively and randomly with each of the four brands of contact lenses. Only new lenses stored in saline fresh from blister packs were used.

The average MSE refractive error or lens prescription in the group was (M = -0.95, SD = 2.69D, range -6.00 to +6.00 D). (Figure 2.1 and figure 2.2). All rebound tonometry measurements were carried out with a recently calibrated rebound tonometer (ICare TA01i, Tiolat Oy, Helsinki, Finland) in the manner recommended by the manufacturer (Tiolat, 2006). The ICare tonometer is pre-programmed for six measurements and the IOP measured is displayed for each measurement. The software discards the highest and lowest values to calculate the average IOP from the remaining measurements (Kontiola and Puska, 2004). The software can also detect erroneous measurements that may occur when the probe speed was too high or too low, if the probe did not move, the probe

hit the lid, or the probe did not hit the central cornea. In these cases the tonometer displays an error message and does not accept the measurement as correct (Kontiola and Puska, 2004). The software also considers the relationship between all the measures taken by estimating the standard deviation to ensure a coherent final result. If the instrument detects a discrepancy an error sign, ('-'), is displayed. If the standard deviation of the measurements is higher than normal the 'P' blinks, 'P_' (P bottom) indicates a slightly higher than normal standard deviation but the effect will most likely not affect the final result. 'P-' (P middle) indicates the standard deviation is clearly higher than normal, but a new measurement is only recommended if the IOP is higher than 19 mmHg. 'P¯' (P top) indicates the standard deviation of the measurements is large and a new set of measurements is recommended (Fernandes et al., 2005) (Figure 1.7).

The position and alignment of the ICare tonometer can affect the measurement accuracy of IOP (Fernandes et al., 2005). In normal healthy subjects the ICare tonometer is relatively insensitive to misalignments; even with the probe deviated 10˚ nasally, Beasley et al. (2013) found the ICare underestimated the IOP by less than 1 mmHg which is statistically but not clinically significant (Beasley et al., 2013). Extreme care was taken during operation of the button to prevent the instrument from shaking and ensure that the tip of the probe hit the centre of the cornea.

The two experienced optometrists (DJB and GHK) independently carried out two measurements with the ICare tonometer on each subject. The repeated measurement design was used and a period of at least two minutes was allowed between successive measurements to ensure the tonometry measurements were as accurate as possible (Recep et al., 1998). With the ICare tonometer this design includes six consecutive measurements of the right eye followed by six consecutive measurements of the left eye, repeated in the left eye and then again repeated in the right eye (R.L.L.R), first with the contact lenses on the eye and then without the contact lenses on the eye (Pekmezci et al., 2011). The order of measurement with or without lenses was randomised. A ten minute or longer interval after lens insertion was allowed before measurements were taken (Tonnu et al., 2005). The interval ensured proper hydration and optimal fit and allowed for recovery after lens removal or insertion.

An experienced optometric assistant (MLG) checked the position of the tonometer during measurements. To reduce between observer biases, the assistant then recorded the second IOP measurement on the left eye if no errors were displayed, blinding the two optometrists. The two optometrists and assistant remained the same for the entire study period. Only measurements for

the left eye were recorded mainly due to the fact that the optometric assistant was positioned on the right of the optometrist taking the measurements making it easy to see the subjects left eye (Pekmezci et al., 2011). The contact lens centration, fit, and surface hydration were evaluated by slit-lamp biomicroscopy. In cases of poorly centring lenses (low riding, temporal or nasal decentration) with excessive movement (more than 1.5 mm) and obvious dry spots, the lenses were discarded and a new lens fitted.

Additional tonometry and corneal biomechanical measurements were carried out with a recently calibrated ocular response analyser (ORA, Reichert Inc., Depew, NY) in the manner described by the Reichert Inc. (Reichert, 2013). The current recommended protocol for the Reichert ORA requires that one image with the highest waveform score be selected among four measurements for analysis (Reichert, 2013). It is well known that the ocular pulse amplitude (OPA) as well as "aqueous massage" significantly affects the ORA measurement repeatability (Moreno-Montanes et al., 2008; Sullivan-Mee et al., 2009; Kotecha et al., 2010; Wang et al., 2013). Endeavouring to alleviate this effect in the current study, four measurements per eye were taken by one optometrist (DJB) and the average values of the four measurements (IOPg, IOPcc, CH, and CRF) were recorded. The graphic representation of the corneal response after each measurement was examined to ensure that the force-in and force-out applanation signal peaks were fairly symmetrical in height and similar between repeated measurements ensuring good quality readings. Only measurements with a waveform score (WS) of more than six were considered and images with scores lower than this were repeated (Kotecha et al., 2010; Lau and Pye, 2011) (Figure 1.6). A lower WS increases the variability of repeated ORA measures and thus intrasession variability. Hence, it is important to record only good quality ORA measurements when assessing patients (Kotecha et al., 2010). As with the ICare RBT, at least two minutes were allowed between successive measurements to ensure the tonometry measurements were as accurate as possible (Recep et al., 1998). Only measurements for the left eye were recorded (Pekmezci et al., 2011).

In addition to the ICare and ORA tonometry, a recently calibrated Oculus Pentacam (Oculus, Wetzlar, Germany) corneal analysis system was used on each patient to screen for corneal pathology and to record central corneal thickness at the thinnest location on the corneal thickness map as well as RM corneal curvature (RM – arithmetic mean of the simulated keratometry readings – corneal curvature [Ks]) with and without contact lenses. Only one experienced optometrist (DJB) took the Pentacam

measurements which were recorded by the optometric assistant if the QS (quality score) was acceptable. (Figures 1.14 and 1.15).

IOP tends to be higher in the morning and lower in the afternoon. This diurnal variation is typically ≤5 mmHg in normal eyes but higher in ocular hypertensive and glaucomatous eyes. The cause of this variation is not clear but may be related to the diurnal variation of plasma cortisol (Harper and Henson, 2007; Spry and Harper, 2010). To minimise the effects of diurnal variation in IOP in this study, all measurements were taken between 13h00 and 17h00 on the days subjects visited the practice. In order to control accommodation which may influence IOP during repeated measurements (Read et al., 2010), subjects were instructed to view a distance target consisting of a 6/24 Snellen letter.

Finally, in an attempt to alleviate the possible effects of the Valsalva manoeuvre, nervousness and forced eyelid closure on the accuracy of IOP measurements, care was taken to explain the procedures to the subjects and they were asked to breathe normally (not hold their breath) while the measurements were being taken.

2.3 Statistical analysis

The data recorded included: age, gender, contact lens brand, contact lens power, ICare IOP with and without contact lenses by each of the two optometrists, ORA: CH, CRF, IOPcc, and IOPg with and without contact lenses as well as Pentacam CCT and K-readings with and without contact lenses measured by one optometrist. Data were analysed using the statistical package SPSS v. 22.0, and Microsoft Excel (Microsoft Corporation, Redmond, WA) with Analyse-it v 4.10.2 (Analyse-it Software, Ltd.). G*Power 3.0.10 (Franz Faul, Universität Kiel, Germany) was used for sample size analysis. A comprehensive discussion of the statistics used will be discussed in each experimental chapter. What follows is a summary of the statistics used throughout the thesis. Table 2.2 gives the descriptive statistics for each of the variables measured.

Variable	n	Minimum	Maximum	M	SD	Variance
AGE (years)	50	19	55	38.90	9.23	85.23
Rx (diopters)	50	-6.00	+6.00	-0.95	2.96	8.77
ICare IOP (mmHg)	50	9.00	24.5	14.58	3.38	11.46
Corneal hysteresis (mmHg)	50	7.15	13.38	9.68	1.41	2.01
Corneal resistance factor (mmHg)	50	6.83	13.40	9.57	1.65	2.72
Corneal corrected IOP (mmHg)	50	10.10	23.68	16.02	3.50	12.22
Goldmann equivalent IOP (mmHg)	50	9.00	24.40	14.64	3.58	12.84
CCT without C/L (µm)	50	469	613	531.46	35.51	1260.91
K-reading Without C/L (mm)	50	7.30	8.33	7.80	0.28	0.08
ICare with Pure Vision (mmHg)	50	10.8	33.50	18.49	5.43	29.45
ICare with Frequency XC (mmHg)	50	8.80	22.50	14.08	3.15	9.93
ICare with 1-Day Moist (mmHg)	50	7.80	20.80	13.12	3.11	9.68
ICare with Oasys (mmHg)	50	8.50	22.50	13.74	3.24	10.50
CH with Pure Vision (mmHg)	50	5.78	24.18	14.56	3.38	11.45
CH with Frequency XC (mmHg)	50	7.10	12.88	10.08	1.34	1.80
CH with 1-Day Moist (mmHg)	50	5.98	12.45	9.80	1.39	1.94
CH with Oasys (mmHg)	50	7.70	14.25	10.59	1.64	2.70
CRF with Pure Vision (mmHg)	50	9.73	23.45	14.21	3.40	11.53
CRF with Frequency XC (mmHg)	50	6.90	14.93	9.60	1.64	2.70
CRF with 1-Day Moist (mmHg)	50	6.80	12.68	9.34	1.53	2.35
CRF with Oasys (mmHg)	50	6.90	16.00	9.99	2.05	4.20
IOPcc with Pure Vision (mmHg)	50	4.63	18.15	11.72	3.18	10.09
IOPcc with Frequency XC (mmHg)	50	9.85	22.25	14.83	3.09	9.52
IOPcc with 1-Day Moist (mmHg)	50	9.38	21.00	15.06	2.61	6.84
IOPcc with Oasys (mmHg)	50	8.78	19.70	14.00	2.68	7.17
IOPg with Pure Vision (mmHg)	50	9.48	26.33	15.79	3.75	14.04
IOPg with Frequency XC (mmHg)	50	7.23	23.90	13.55	3.48	12.12
IOPg with 1-Day Moist (mmHg0)	50	7.13	19.93	13.62	2.86	8.18
IOPg with Oasys (mmHg)	50	6.73	23.18	13.48	3.33	11.10
CCT with Pure Vision (µm)	50	493	669	569.14	43.89	1926.37
CCT with Frequency XC (µm)	50	502	721	599.98	56.10	3147.78
CCT with 1-Day Moist (µm)	50	471	652	551.92	41.16	1694.40
CCT with Oasys (µm)	50	497	694	590.92	49.50	2450.52
K-reading with Pure Vision (mm)	50	6.56	8.79	7.79	0.42	0.18
K-reading with Frequency XC (mm)	50	6.82	8.76	7.93	0.44	0.19
K-reading with 1-Day Moist (mm)	50	6.73	8.53	7.88	0.39	0.15

Variable	n	Minimum	Maximum	M	SD	Variance
K-reading with Oasys (mm)	50	6.84	8.71	7.90	0.43	0.18
Valid N (list wise)	50					

Table 2.2 Descriptive statistics. (M = mean and SD = standard deviation)

The parametric statistical tests used in this study demand normal distribution of the data. Researchers recommend the Shapiro-Wilk normality test as the best choice for testing the normality of the data. This test is based on the correlation between the data and the corresponding normal scores (assesses the data against a normal population) providing better power than the Kolmogorov-Smirnov test even after the Lilliefors correction has been applied (Ghasemi and Zahediasl, 2012). If the data are not normally distributed, the value of the statistical tests will still be correct but the significance levels will not be accurate. However, Sawilowsky and Hillman (1992) found that even with a radically non-normal distribution of the data, significance levels are accurate except when the sample sizes are small and the groups differ in sample size (Sawilowsky and Hillman, 1992). The Shapiro-Wilk test and Q-Q plots confirmed a normal distribution of all the data (Appendix 6); $p < 0.05$ was considered significant.

In ophthalmic research, inter-eye correlations need to be considered when attempting statistical analyses. It has been shown that the correlation between the right and left eye intraocular pressure measurements is on the order of 0.9, indicating strong inter-eye correlation (Ray and O'Day, 1985). Positive inter-eye correlation leads to artificially low estimates of the standard error of the differences between experimental groups which overstate precision and produce falsely significant results. Only data from the left eye of all subjects were therefore used for statistical analysis in this study (Ray and O'Day, 1985; Newcombe and Duff, 1987; McAlinden et al., 2011).

It was observed from the work of Walter et al. (1998) that the required number of subjects as well as the optimal number of observers had to be calculated for the reliability part of the study (Walter et al., 1998). Considering an expected ICC of 90% and the lowest acceptable ICC of 70%, nineteen subjects were needed based on $\alpha = 0.05$ and $\beta = 0.20$. The number of observers based required to test the hypotheses were two. The results of this reliability and agreement study were reported in accordance with the Guidelines for Reporting Reliability and Agreement Studies (GRRAS) (Kottner et al., 2011). Intraclass correlation coefficients (ICCs) were specifically designed to examine reliability; thus, to provide a reliability index to indicate measurement error (Bartko, 1966). ICCs are calculated

from the results obtained from analysis of variance (ANOVA) for repeated measures. ICC in isolation cannot give a true picture of reliability (ICC is dependent on the range of values measured – the greater the variability between subjects, the greater the value of ICC) and should be complemented by Bland and Altman 95% limits of agreement tests as these tests are independent (unlike ICCs) of true variability in the observations (Rankin and Stokes, 1998; Patton et al., 2006). ICC is measured on a scale of 0 to 1. Perfect reliability is represented by a value of 1 which indicates no measurement error whereas 0 indicates no reliability and lots of measurement errors (Patton et al., 2006). According to Spitzer and Endicott (1980), any ICC > 0.75 can be classified as "good" (Spitzer and Endicott, 1980).

Several paired two-tailed *t*-tests were performed to test the hypotheses that ICare RBT and ORA measurements were not significantly different. Additionally, Bland-Altman scatter plots were used to assess the agreement and confidence intervals in the clinical comparison of the ICare RBT and Reichert ORA measurements. The mean of the differences and the standard deviation of the differences were also calculated. The closer the mean of the differences or bias is to zero and the smaller the value of the standard deviation of the differences the better the agreement between measures (Bland and Altman, 1986). The Bland Altman plot only defines the intervals of agreement, it does not give information whether the limits are acceptable or not. Acceptable limits must be defined based on clinical necessity, biological considerations or other goals. Ninety-five per cent (95%) confidence intervals were plotted and $p < 0.05$ was considered statistically significant (Armstrong et al., 2011; McAlinden et al., 2011).

To test the hypothesis that IOP measurements with the ICare RBT and ORA are not affected by the presence of a soft contact lens on the eye, different statistical methods of analysis were employed, including Pearson's correlation coefficients, paired two-tailed *t*-tests, 1-way ANOVA tests and Bland-Altman plots. 1-way ANOVA tests provide an exact test of the hypothesis for multiple groups and in combination with planned comparisons is an exact and elegant (the only) alternative to multiple *t*-tests (Norman and Streiner, 2008).

In order to evaluate the effects of corneal thickness, corneal curvature, and refractive error on ICare RBT and Reichert ORA measurements, multiple regression analyses were used with ICare IOP and ORA metrics designated as the dependent or response variables and corneal curvature, corneal thickness, and refractive error the independent or predictor variables. Pearson's r and Spearman's r_s as well as standard errors between variables were used to estimate the strength of the relationship

between the dependent and the predictor variables, and regression lines were used to predict the response variable from the predictor variables. Significance levels were evaluated by the paired two-tailed *t*-test and $p < 0.05$ was considered statistically significant (Armstrong et al., 2011; McAlinden et al., 2011).

Chapter 3

Reproducibility and repeatability of the ICare RBT and repeatability of the Reichert ocular response analyser (ORA) in a population of normal subjects measured with and without soft disposable contact lenses *in situ*

3.1 Introduction

IOP is currently the only modifiable risk factor for prevention of glaucoma development and progression (Weih et al., 2001). Precise IOP measurements are therefore crucial for proper management of glaucoma patients. The ideal tonometer needs to be accurate, repeatable, reproducible, and minimally influenced by factors such as corneal properties and different examiners. It is also important when following-up patients on glaucoma treatment and when switching from one tonometer to another to consider expected limits of IOP errors and differences in measurements between the different instruments.

Reliability can be defined as "the degree to which a measurement technique can secure consistent results upon repeated measuring on the same subjects either by multiple clinicians or test-retest trials by one clinician at different time points on the same subjects" (Patton et al., 2006). In other words; are the measurements recorded by the instrument reproducible at different time intervals (test-retest reliability), and are the clinicians making the measurements under similar assessment conditions producing repeatable or consistent results, both for the same observer over a period of time (intraobserver reliability) and between different observers on the same subject (interobserver reliability)? Reliability can also be used to assess the agreement between different methods of measuring (method comparison or parallel reliability) (Patton et al., 2006). Therefore, information regarding reliability as well as sensitivity and specificity is a prerequisite to using any instrumentation of measurement and forms a major component of ophthalmic research (Margo et al., 2002).

Inter- and intraobserver reliability and agreement have been examined for both the ICare RBT as well as the ORA (Table 3.1). Depending on the way results of reliability and agreement studies are reported the information provided is often insufficient to understand how the study was designed, conducted, and how the results were obtained (Bland and Altman, 1986; Patton et al., 2006). Reliability and agreement estimates are affected by various sources of variability in the measurement setting (e.g., observer and sample characteristics, type of instrument, administration process, and

the statistical approach). These reliability estimates are not fixed properties of measurement but rather reflect interactions between the tools/instruments, the subjects, clinicians/technicians, and the context of measurement). Information about sample selection, study design, and statistical analysis is often incomplete making interpretation of results difficult (Kottner et al., 2011). Study results are therefore only interpretable when the sources of variability are sufficiently described (Kottner et al., 2011). It is worthwhile noting that regardless of which reliability test is selected, comparison of reliability results between studies are not possible unless the size and attributes of the samples tested in each case is virtually identical (Rankin and Stokes, 1998). Furthermore, when using ICCs, the choice of equation, study design and intended application need to be defined clearly (Rankin and Stokes, 1998). Table 3.1 highlights the interobserver and intraobserver reliability of some of the different tonometers commonly used in practice. The following section describes the studies relating to the ICare RBT and ORA in more detail.

Asrani et al. (2011) compared the reliability readings obtained by inexperienced users (patients) with trained ophthalmic technicians using the ICare tonometer as well as GAT. The patients repeated the measurement three times and the technician took one measurement. The interclass correlation coefficient (ICC) was 0.88 (95% CI [0.82 to 0.92]) and mean deviation 0.60 mmHg, $p = 0.50$ indicating excellent agreement between the patients and the technician. The ICCs between measurements by the patients were 0.69 (95% CI [0.45 to 0.84]), mean deviation -0.05 mmHg $p = 0.61$ for measurements 1 and 2, 0.71 (95% CI [0.47 to 0.85]), mean deviation 0.62 mmHg $p = 0.18$ for measurements 1 and 3, and 0.81 (95% CI [0.64 to 0.90]), mean deviation 0.67 mmHg $p = 0.33$ for measurements 2 and 3 indicating a high degree of reproducibility of the measurements (Asrani et al., 2011).

Sahin et al. (2007) conducted a study on 152 healthy schoolchildren to establish the intra- and interobserver reliability of the ICare RBT tonometer. Two experienced ophthalmologists made three consecutive measurements on 304 eyes. The intraobserver correlation coefficient for the examiner 1 was: right eye $r = 0.97$ (95% CI [0.955 to 0.979]), left eye $r = 0.97$ (95 % CI [0.962 to 0.983]) $p < 0.0001$. For examiner 2 it was: right eye $r = 0.96$ (95% CI [0.947 to 0.975]), left eye $r = 0.97$ (95% CI [0.956 to 0.980]) $p < 0.0001$. Interobserver correlation coefficients were $r = 0.80$ for the right eye and $r = 0.86$ for the left eye ($p < 0.0001$). The study concluded that the ICare RBT tonometer offers highly reproducible IOP measurements in school children showing high intra- and interobserver correlation coefficients (Sahin, Basmak, et al., 2007).

Martinez-de-la-Casa et al. (2005) established the reproducibility of the ICare RBT tonometer in 12 healthy adult subjects. Three ophthalmologists undertook three consecutive measurements. Intraobserver correlation coefficients were 0.82 (95% CI [0.62 to 0.94]) for the first examiner; 0.73 (95% CI [0.46 to 0.90]) for the second examiner, and 0.87 (95% CI [0.72 to 0.96]) for the third examiner. The interobserver correlation coefficient was 0.82 (95% CI [0.62 to 0.94]). All three examiners concluded the ICare RBT tonometer offers reproducible IOP measurements in adult humans (Martinez-de-la-Casa et al., 2005). Davies et al. (2006) found intersessional measurements made with the ICare RBT tonometer were less repeatable than those made with GAT, but are comparable or better than other non-GAT type tonometers. The mean difference between measurements was: M = 0.46, SD = 2.61 mmHg (Davies et al., 2006). In another study Detry-Morel et al. (2006) examined the intra- and interobserver variability of the ICare IOP measurements and their correlations with GAT and CCT. Their results show the interobserver variation coefficient was 6.4% and the intraobserver variation coefficients ranged from 5 to 5.4%, close to those of GAT (Detry-Morel et al., 2006).

In a study by Wang et al. (2013) the intraoperator variability of the Pascal dynamic contour tonometer (DCT), ocular response analyser (ORA), and the Goldmann applanation tonometer (GAT) was evaluated in a single population of 26 normal individuals. The intraobserver reliability of the DCT (CV = 3.7, ICC = 0.89) was significantly lower than that of GAT (CV = 9.7, ICC = 0.79), IOPg (CV = 7.0, ICC = 0.79), and IOPcc (CV = 9.8, ICC = 0.57). All the tonometers showed good repeatability with ICC values above 0.75 except the IOPcc with an ICC of 0.57. IOPcc had the poorest test-retest reproducibility and was the most variable for intraoperator assessment. IOPcc is calculated from CRF and IOPg which could explain the poor repeatability. CRF intraobserver reliability was ICC = 0.76. GAT and IOPg had similar ICCs but GAT had a larger coefficient of variation (CV) than IOPg (Wang et al., 2013). Moreno-Montanes et al. (2008) found the intraobserver reliability ICC ranged from 0.78 to 0.93 (“good” to “excellent”) for the ORA biomechanical metrics. CH and CRF were also slightly more reliable than the ORA IOPg and IOPcc readings possibly due to the fact that IOP varies with the cardiac cycle while corneal biomechanical properties remain fairly constant (Moreno-Montanes et al., 2008). Sullivan-Mee et al. (2009) found the ORA derived parameters (IOPcc and IOPg) were almost twice as variable when compared to GAT and DCT; however, the repeatability and reproducibility of the ORA was still clinically acceptable. Mean difference between measurements for intraobserver reliability were M = 0.48, SD = 1.66 mmHg for examiner 1, and M = 0.10, SD = 1.75 mmHg for examiner 2. Interobserver reliability was M = 0.04, SD = 1.73 mmHg. The two examiners

concluded that the ocular pulse amplitude (OPA) fundamentally affects repeatability of the ORA IOPcc and IOPg measurements (Sullivan-Mee et al., 2009). Kotecha et al. (2010) also found the intraobserver variability of the ORA measurements was significantly associated with OPA and, to a lesser degree, with the quality of the ORA waveform. ORA measurements were dependent on the magnitude of the OPA. Eyes with larger OPA displayed more intraobserver or intrasession variability in ORA measurements. Measurements with lower waveform scores also displayed greater intrasession variability. Interobserver repeatability among observers 1, 2, and 3 measured as mean difference between measurements was M = 0.30 mmHg 95% LoA [-4.2 to 3.6]. Intraobserver repeatability of the ORA were 4.3 mmHg for observers 2 and 3 and 4.4 mmHg for observer 1 and this was calculated as the within-subject-standard-deviation (wsSD x 2.77) (Kotecha et al., 2010). Comparing DCT, GAT, and ORA the DCT showed the best measurement precision, repeatability and reproducibility of the three instruments (Kotecha et al., 2010).

Although the reproducibility and the reliability of the measurements provided by the ICare RBT have been evaluated in humans, it has not been evaluated with contact lenses on the eye. It might be expected that reproducibility and reliability are negatively impacted by the presence of a contact lens on the eye and therefore the present study was designed to evaluate the intra- and interobserver reliability of the ICare RBT in a group of healthy subjects not only with but also without soft disposable contact lenses on the eye. The intraobserver reliability of the ORA was evaluated without the contact lenses *in situ*.

Because of inadequate information about sample selection, study design, and statistical analyses in reliability and agreement studies, the interpretation and synthesis of study results are often difficult (Kottner et al., 2011). The Guidelines for Reporting Reliability and Agreement Studies (GRRAS) published in 2011 aims to improve the quality of reporting results of reliability and agreement studies in the health care and medical field. The results of this reliability and agreement study were reported in accordance with the GRRAS guidelines (Kottner et al., 2011).

Study	Examiner number/type/cohort	Number of measurements	Interobserver reliability	Intraobserver reliability	Comments
DCT					
Kaufmann et al. (2004)	**DCT:** four examiners **GAT:** four examiners 150 healthy normal eyes and 228 enucleated eyes	**DCT:** 3 measurements **GAT**: 3 measurements	**DCT:** 0.65 mmHg residual variance estimate **GAT:** 1.10 mmHg residual variance estimate	**DCT:** 0.40 mmHg investigation plus interaction variance estimate **GAT:** 1.28 mmHg investigator plus interaction variance estimate	ANOVA model with examiner, subject and examiner–subject interaction as factors.
Doyle & Lachkar (2005)	**DCT:** two ophthalmologists **GAT:** Not recorded 25 subjects	**DCT:** 2 measurements; if reading ≥ 2 mmHg a third measurement was taken **GAT:** 2 measurements; if ≥ 2 mmHg of difference a third measurement was taken		**DCT:** 0.62 mmHg **GAT:** 0.52 mmHg	
Kotecha et al. (2005)	**DCT:** one of two technicians **GAT:** one optometrist 130 subjects and 130 eyes	**DCT:** 3 measurements **GAT:** 2 measurements	**DCT:** mean difference of .2 (95% LoA [−4.9 to 5.3]) mmHg. Based only on measurements 2 and 3 **GAT:** average readings between clinician and technician was mean difference of 0.4 (95% LoA [−3.5 to 4.2]) mmHg	**Technician:** **DCT:** RC 4.2 mmHg and 3.2 mmHg respectively for measurements 1 and 2, and 2 and 3 **GAT:** corresponding RC 1.6 mmHg **Clinician:** **DCT:** RC 3.3 mmHg and 2.6 mmHg, respectively **GAT:** corresponding RC 1.7 mmHg	
Pourjavan et al. (2007)	**DCT:** one ophthalmologist **GAT:** one ophthalmologist 28 subjects and 52 eyes	**DCT:** 4 measurements **GAT:** 2 measurements		**DCT:** ICC 0.78 (one measurement) and 0.91 (mean of three measurements)	
Herdener et al. (2008)	**DCT:** one experienced ophthalmologist; **GAT:** not recorded 50 subjects and 50 eyes	**DCT:** not recorded **GAT:** not recorded		**DCT:** short-term (same day) and long-term (2 – 8 days) reproducibility was 1.2 and 1.5 mmHg, respectively **GAT:** short-term (same day) and	Sensitivity analyses excluding lower-quality DCT readings showed greater intraobserver reliability.

				long-term (2–8 days) reproducibility was 1.1 and 1.2 mmHg, respectively	
Study	**Examiner number/type/Cohort**	**Number of measurements**	**Interobserver reliability**	**Intraobserver reliability**	**Comments**
Johannesson et al. (2008)	**DCT:** one student **GAT:** one clinician 150 eyes	**DCT:** 6 measurements **GAT:** 6 measurements		95% CI (may be LoA) for RC **DCT:** ±1.7 mmHg (*n* = 149) **GAT:** ±1.9 mmHg (*n* = 150)	IOP appeared to decrease (aside from tonometer) as multiple measurements were taken.
Sullivan-Mee et al. (2009)	**DCT:** two optometrists **GAT:** two optometrists 60 subjects and 120 eyes	**DCT:** 2 measurements **GAT:** 2 measurements	**DCT:** mean difference of 0.34, SD = 1.16 (95% LoA [−1.9 to 2.6]) mmHg; CoV 6.6%; CCC 0.92 (95% CI [0.88 to 0.96]) (*n* = 60 eyes) **GAT:** mean difference of 0.83, SD = 1.14 (95% LoA [−1.4 to 3.1]) mmHg; CoV 7.8%; CCC 0.93 (95% CI [0.90 to 0.96])	**Examiner 1**: (*n* = 30 eyes) **DCT:** mean difference 1.18, SD = 1.33 (95% LoA [−1.4 to 3.8]) mmHg, CoV 8.0%, CCC 0.92 (95% CI [0.86 to 0.97]); **GAT:** mean difference 0.67, SD = 1.54 (95% LoA [−2.4 to 3.7]) mmHg, CoV 11%, CCC 0.95 (95% CI [0.91 to 0.98]) **Examiner 2:** (*n* = 30 eyes) **DCT:** mean difference 0.06, SD = 1.62 (95% LoA [−3.1 to 3.2]) mmHg, CoV 9.3%, CCC 0.84 (9 % CI [0.75 to 0.94]); **GAT:** mean difference 0.64, SD = 1.45 (95% LoA [−2.2 to 3.5]) mmHg, CoV 10%, CCC 0.85 (95% CI [0.75 to 0.95]) **Both examiners:** **DCT:** RC of 2.0; **GAT:** RC of 2.5	RC calculated using measurements on both eyes.
Roszkowska et al. (2009)	**DCT:** one observer **GAT:** not recorded 35 subjects and 70 eyes	**DCT:** 2 measurements **GAT:** 2 measurements		**DCT:** 1.4 mmHg **GAT:** 0.8 mmHg (coefficient uncertain, probably RC)	

Fogagnolo et al. (2010)	**DCT:** one experienced investigator per site **GAT:** not recorded 350 subjects	**DCT:** measurements were repeated if Q > 3; this occurred in 8% of the readings and twice for 2% of the time **GAT:** 2 measurements: if ≥ 2 mmHg of difference a third measurement was taken	**DCT:** ICC 0.96 (*n* = 350 eyes) and test–retest variability was significant (*p* = 0.01, *F* = 2.86 > 2.12, 6 df)	**DCT:** CoV 5.0%; RC 3.24 mmHg	
Study	**Examiner number/type/cohort**	**Number of measurements**	**Interobserver reliability**	**Intraobserver reliability**	**Comments**
Kotecha et al. (2010)	**DCT**: one optometrist and two others (non-ophthalmologists) **GAT:** not recorded 100 subjects	**DCT:** 3 measurements **GAT:** 2 measurements	**DCT:** −0.20 (95% LoA ± 2.8) mmHg (between observer 1 and observers 2 and 3) **GAT:** mean difference of −0.80 (95% LoA ± 3.9) mmHg	**Observer 1:** **DCT:** 1.8 mmHg **GAT:** 2.2 mmHg **Observers 2 and 3:** **DCT:** 2.0 mmHg **GAT:** 2.3 mmHg (*n* = 100, all RC)	Only good-quality measurements accepted (DCT) – value 1 or 2.
NCT					
Hansen (1995)	**NCT:** one examiner **GAT:** one examiner 130 subjects and 130 eyes	**NCT:** 3 measurements GAT: 3 measurements		**NCT:** 2.90 (Varmid), mean difference 0.10 (95% LoA [−4.88 to 5.08]) mmHg **GAT:** 0.98 (Varmid), mean difference 0.36 (95% LoA [−2.76 to 3.48]) mmHg	
Mackie et al. (1996)	**NCT:** one optometrist **GAT:** one of three ophthalmologists 45 subjects and 89 eyes	**NCT:** 4 measurements **GAT:** 2 measurements		**NCT:** SDs of measurements from individual patients range from 2 to 6.7mmHg	
Lam et al. (2004)	**NCT:** possibly a consultant ophthalmologist but paper is unclear **GAT:** not recorded 31 subjects and 31 eyes	**NCT:** 3 measurements **GAT:** 3 measurements		**NCT:** mean CoV 4.5%, SD = 3.4% **GAT:** mean CoV 3.7%, SD = 1.8%	
Tonnu et al. (2005)	**NCT:** one examiner **GAT:** one examiner 105 subjects and 105 eyes	**NCT:** 3 measurements **GAT:** 3 measurements		**NCT:** RC 3.2 mmHg **GAT:** RC 2.2 mmHg	
Ogbuehi. 2006	**NCT:** one examiner **GAT:** one ophthalmologist 60 subjects and 60	**NCT:** 4 measurements (only last three readings were averaged) **GAT:** 3		**NCT:** mean difference between both sessions of 0.1, SD = 1.3 (95%	

	eyes	measurements. Readings taken in four sessions, two each for GAT and NCT		LoA [−2.5 to 2.7]) mmHg **GAT:** mean difference between both sessions of 0.2, SD = 1.4 (95% LoA [−2.54 to 2.94]) mmHg	
Study	**Examiner number/type/cohort**	**Number of measurements**	**Interobserver reliability**	**Intraobserver reliability**	**Comments**
Regine et al. (2006)	**NCT:** two ophthalmologists **GAT:** not recorded 10 subjects	**NCT:** 3 measurements **GAT:** 3 measurements		**NCT:** RC 3.59 mmHg (right eye) **GAT:** RC 3.98 mmHg (right eye) Mean difference of 1.94 mmHg	Only 10 subjects
Lafaut et al. (2007)	**NCT:** one examiner **GAT:** one examiner 78 subjects and 148 eyes	**NCT:** 3 measurements **GAT:** 3 measurements		**NCT:** within-session mean difference 1.2, SD = 0.7 mmHg **GAT:** within-session mean difference 0.1, SD = 0.2 mmHg	Pertains to subgroup only. Similar results for the other participants were also reported.
AlMubrad and Ogbuehi (2008)	**NCT:** not recorded **GAT:** not recorded 65 subjects and 65 eyes	**NCT:** 4 measurements(mean of last three used) **GAT:** 3 measurements		**NCT:** within-session mean difference 0.1, SD = 1.) and 0.2, SD = 1.3 mmHg for the first two sessions, respectively (95% LoA [−2.3 to 2.5] and [−2.4 to 2.8] mmHg respectively). Between-session 95% LoA [−2.6 to 3.0] mmHg **GAT:** within-session mean difference 0.1, SD = 1.1 and .0, SD = 1.0 mmHg respectively (95% LoA [−2.2 to 2.3] and [−2.0 to 2.0] mmHg respectively). Between-session 95% LoA [−2.2 to 2.8] mmHg	Intraobserver repeatability within session taken from second and third measurements (for both GAT and NCT) and between sessions 1 week apart. Unclear if a single observer or not.
Ogbuehi and AlMubrad (2008)	**NCT:** one ophthalmologist; **GAT:** one of three	**NCT:** 3 measurements **GAT:** 3 measurements		**NCT:** within-session RC (first session) 1.8	

	clinicians 72 subjects and 72 eyes			mmHg and (second session) 1.7 mmHg; test–retest reproducibility 3.1 mmHg **GAT:** 1.7 (first session) and 1.9 (second session); test–retest reproducibility 2.5 mmHg	
Study	**Examiner number/type/cohort**	**Number of measurements**	**Interobserver reliability**	**Intraobserver reliability**	**Comments**
Ocuton S					
Marchini et al. (2002)	**Ocuton S:** two operators and patient for self-tonometry **GAT:** not recorded 80 subjects and 80 eyes	**Ocuton S:** 3 measurements; if there was a difference ≥ 5 mmHg between one and the other two, a fourth measurement was taken **GAT:** not recorded	**Ocuton S:** first measurement between two observers 0.61 (95% CI [0.30 to 0.93]) mmHg; second measurement between two observers 0.41 (95% CI[0.02 to 0.80]) mmHg	**First observer:** **Ocuton S:** 0.66 (95% CI [0.31 to 1.00]) mmHg; **Second observer:** **Ocuton S:** 0.42 (95% CI [0.06 to 0.78])mmHg **Self-tonometry:** **Ocuton S:** mean difference 0.6, SD = 2.1 (95% LoA [−3.6 to 4.8]) mmHg Each measurement was the mean of three consecutive readings	
Wells (2003)	**Ocuton S:** patient **GAT:** 1 researcher Not known	**Ocuton S:** 3 measurements **GAT:** not recorded		**Ocuton S:** RC 9.17 mmHg	
ORA					
Kotecha et al. (2006)	**ORA:** one optometrist **GAT:** Not recorded 105 subjects and 144 eyes	**ORA:** 3 measurements **GAT:** 2 measurements		Appear to be intra (not explicitly stated). **ORA:** CoV 8.9% (*n* = 144)	
Moreno-Montanes et al. (2008)	**ORA:** Two independent examiners/not recorded 30 eyes	**ORA:** 3 repeated readings (each measurement the average of three good quality readings) by two examiners *n* = 30 eyes	The mean difference between examiners were 0.06 95% LoA [-1.07, 1.19] mmHg for CH; -0.023 95% LoA [-1.38 to 1.34] mmHg for CRF; 0.05 95% LoA [-2.68 to 2.79] for IOPcc;	wsSD was 1.45 mmHg for CH; 1.95 mmHg for CRF; 2.3 8mmHg for IOPcc; and 3.33 mmHg for IOPg. ICCs were 0.84 95% CI [0.67 to 0.92] for CH; 0.93 95% CI [0.84to 0.96] for CRF; 0.78 95% CI	Intra and interobserver reliability was better for the biomechanical metrics than ORA IOP readings.

			and 0.05 95% LoA [-2.87 to 2.97] for IOPg. CCCs were 0.92 95% CI [0.87 to 0.98] for CH; 0.93 95% CI [0.89 to 0.98] for CRF; 0.81 95% CI [0.68 to 0.94] for IOPcc; and 0.89 95% CI [0.82 to 0.97] for IOPg.	[0.48 to 0.89] for IOPcc, and 0.93 95% CI [0.87 to 0.95] for IOPg.	
Study	**Examiner number/type/cohort**	**Number of measurements**	**Interobserver reliability**	**Intraobserver reliability**	**Comments**
Kynigopoulos et al. (2008)	**ORA:** one experienced technician **GAT:** not recorded Not known	**ORA:** 4 measurements **GAT:** not recorded		**ORA:** RC 2.22 mmHg; CoV 6.5%; ICC 0.89 (lower 95% CI [0.82] (*n* = 49)	
Ehongo et al. (2009)	**ORA:** not recorded **GAT:** not recorded 23 subjects and 46 eyes	**ORA:** 2 measurements (8 readings) **GAT:** 2 measurements		**ORA:** before and after anaesthetised right eye were 1.44 and 1.11 (RE) mmHg	
Sullivan-Mee et al. (2009)	**ORA:** two optometrists **GAT:** two optometrists **DCT:** two optometrists 60 subjects and 120 eyes	**ORA:** 2 measurements (8 readings) **GAT:** 2 consecutive readings **DCT:** 2 consecutive readings	**ORA:** mean difference 0.04, SD = 1.73 (95% LoA [−3.4 to 3.4]) mmHg; CoV 9.6%; ICC 0.89 (95% CI [0.84 to 0.94]) (*n* = 60 eyes)	**Examiner 1:** (*n* = 30 eyes): **ORA:** mean difference 0.48, SD = 1.66 (95% LoA [−2.8 to 3.7]) mmHg; CoV 9.9%; CCC 0.92 (95% CI [0.86 to 0.98]) **Examiner 2:** (*n* = 30 eyes) **ORA:** mean difference 0.10, SD = 1.75 (95% LoA [−3.3 to 3.5]) mmHg; CoV 10.1%; CCC 0.91 (95% CI [0.71 to 0.96]) **Both examiners:** **ORA:** RC 3.9 **GAT:** RC 2.0	RC calculated using measurements on both eyes.
Kotecha et al. (2010)	**ORA:** one optometrist and two others (non-ophthalmologists) **GAT:** not recorded 100 subjects	**ORA:** 3 measurements **GAT:** 2 measurements	**ORA:** mean difference of 0.30 (95% LoA [−4.2 to 3.6]) mmHg (between observer 1 and observers 2 and	**ORA:** **Observer 1:** RC 4.4 mmHg; **Observers 2 and 3:** RC 4.3 mmHg (*n* = 100 eyes)	Only good-quality measurements accepted (ORA).

			3)		
Wang et al. (2013)	Three experienced examiners/ possibly ophthalmologists but not recorded as such 26 subjects and 52 eyes	One operator measured IOP 3 times with each tonometer (GAT, DCT, and ORA). Two additional operators measured IOP with each instrument once only (*n* = 52 eyes)	**DCT:** CV=6.1, ICC=0.73 **GAT:** CV=9.0, ICC=0.82 **IOPg:** CV=10.8, ICC=0.63 **IOPcc:** CV=11.7, ICC=0.49	**DCT:** CV = 3.7, ICC = 0.89 **GAT:** CV = 9.7, ICC = 0.79 **IOPg:** CV = 7.0, ICC = 0.79 **IOPcc:** CV = 9.8, ICC = 0.57	GAT and IOPg ICCs were similar but CVs differed. IOPg and IOPcc both showed more variability than GAT and DCT.
RBT					
Martinez-de-la-Casa et al. (2005)	**RBT:** three experienced ophthalmologists **GAT:** not recorded 12 subjects and 12 eyes	**RBT:** 3 measurements **GAT:** 3 measurements	**RBT:** ICC 0.82 (range 0.62 – 0.94) (*n* = 12 eyes) CoV 8.9%	**RBT:** **First examiner:** ICC 0.82 (range 0.62 – 0.94) **Second examiner:** ICC 0.73 (range 0.46 – 0.90) **Third examiner:** ICC 0.87 (range 0.72 – 0.96) 'Intra-subject variation coefficient': 8.9%	Only 12 observations.
Study	**Examiner number/type/cohort**	**Number of measurements**	**Interobserver reliability**	**Intraobserver reliability**	**Comments**
Davies et al. (2006)	**RBT:** not recorded **GAT:** one of two optometrists 42 subjects	**RBT:** 2 measurements **GAT:** 2 measurements		**RBT:** mean difference 0.46, SD = 2.61 95% LoA [±5.11] mmHg	
Detry-Morel et al. (2006)	**RBT:** three ophthalmologists **GAT:** one ophthalmologist 138 subjects	**RBT:** 3 consecutive measurements **GAT:** 3 consecutive measurements	Interobserver variation coefficient of 6.4%	Intraobserver correlation coefficient of 5 - 6%	
Sahin et al. (2007)	**RBT:** two experienced ophthalmologists 152subjects and 304 eyes	**RBT:** 3 consecutive readings on 304 eyes	**RBT:** r = 0.798 for the right eye and r = 0.858 for the left eye, $p < 0.0001$	**RBT:** **First examiner:** r = 0.970 for the right and 0.974 for the left eye, $p < 0.0001$ **Second examiner:** r = 0.963 for the right and 0.970 for the left eye, $p < 0.0001$	The use of correlation coefficients (r) is questionable.
Abraham et al. (2008)	**RBT:** two ophthalmologists **GAT:** two ophthalmologists 100 subjects	**RBT:** 6 measurements (highest and lowest discarded) **GAT:** 2 measurements		**RBT:** RC 2.38 mmHg	Unclear if RC based on data for one or both examiners.

Johannesson et al. (2008)	**RBT:** one student **GAT:** one student 150 eyes	**RBT:** 6 measurements **GAT:** 6 measurements		**RBT:** ±2.0 mmHg (*n* = 150) 95% CI (may be LoA) for repeatability **GAT:** ±1.9 mmHg (*n* = 150) 95% CI (may be LoA) for repeatability	IOP appeared to decrease (aside from tonometer) as multiple measurements were taken.
Asrani et al. (2011)	**RBT:** two - inexperienced user (patient) and trained ophthalmic technician **GAT:** second trained ophthalmic technician 100 subjects and 100 eyes	**RBT:** 2 measurements (*n* =100); 30 patients repeated the measurement 3x **GAT:** 1 measurement	**All measurements:** **RBT:** ICC 0.80 95% CI [0.85 to 092] **Patient:** **RBT & GAT:** ICC 0.81 95% CI [0.73 to 0.87], mean difference -0.17 mmHg *p* = 0.501 **Technician:** **RBT & patient** **RBT:** ICC 0.88 95% CI [0.82 to 0.92], mean difference 0.06 mmHg *p* = 0.497 **Technician:** **RBT & GAT:** ICC 0.85 95% CI [0.79 to 0.90], mean difference 0.23 mmHg *p* = 0.671	**RBT:** Patient Measurement 1-2 ICC 0.69 95% CI [0.45 to 0.84], mean difference -0.05 mmHg, *p* = 0.614 Measurement 1-3 ICC 0.71 95% CI [0.47 to 0.85], mean difference 0.62 mmHg, *p* = 0.184 Measurement 2-3 ICC 0.81 95% CI [0.64 to 090], mean difference 0.67 mmHg, *p* = 0.333	
Study	**Examiner number/type/cohort**	**Number of measurements**	**Interobserver reliability**	**Intraobserver reliability**	**Comments**
TonoPen					
Bafa et al. (2001)	**TonoPen:** one examiner **GAT:** one examiner 99 eyes	**TonoPen:** 4 mmeasurements **GAT:** 1measurement		**TonoPen:** CoV 5% to < 10% (*n* = 2); CoV < 5% (*n* = 97)	
Horowitz et al. (2004)	**TonoPen:** two ophthalmologists **GAT:** not recorded 138 subjects and 138 eyes	**TonoPen:** 2 measurements **GAT:** 2 measurements		**TonoPen:** mean difference 0.74, SD = 1.50 (95% LoA [−2.26 to 3.74]) mmHg; ICC 0.97 **GAT:** mean difference 0.13, SD =−1.75 (95% LoA [−3.34 to 3.63]) mmHg; ICC 0.95	
Tonnu et al. (2005)	**TonoPen:** one examiner **GAT:** one examiner 105 subjects and 105 eyes	**TonoPen:** 3 measurements **GAT:** 3 measurements		**TonoPen:** 4.3 (RC) mmHg **GAT:** 2.2 (RC)mmHg	Only measurement < 5% accepted for TonoPen.

Transpalpebral					
Alvarez et al. (2004)	**Transpalpebral:** patient **GAT:** one trained clinician 137 subjects	**Transpalpebral:** each subject tried 5 different Proview devices; thus 5 measurements with each device (25 total). Up to 10 attempts per device were permitted to achieve 5 successful measurements **GAT:** 2 or 3 if > 2 mmHg difference for first 2		**Transpalpebral:** within-subject and within-device variance was 3.4 mmHg (620 means considered = means of each of five devices for each of 124 subjects) (18.2% of variation). RC of 5.11 mmHg	Five devices were all Proview which varied in a minor way.
Lam et al. (2004)	**Transpalpebral:** patient **GAT:** two of the investigators Not known	**Transpalpebral:** 3 measurements **GAT:** 3 measurements. Two different visits 1 week apart. Patients requested to practice at home		**Transpalpebral:** CoV 7.3% (*n* = 194) **GAT:** CoV 4.4% (unclear if intraobserver)	Median of the three readings was used for comparison among tonometers. Random order. Masked investigators.
Brigatti and Maguluri (2005)	**Transpalpebral:** patient **GAT:** one physician 36 subjects and 72 eyes	**Transpalpebral:** 3 measurements **GAT:** 2 sets of 3 readings		**Transpalpebral:** mean difference 1.76, SD = 1.76 mmHg; 0.71 (CC) for first and third readings **GAT:** mean difference 1.73, SD = 1.4 mmHg; 0.94 (CC)	
Study	**Examiner number/type/cohort**	**Number of measurements**	**Interobserver reliability**	**Intraobserver reliability**	**Comments**
Naruse et al. (2005)	**Transpalpebral:** patient **GAT:** one ophthalmologist 101 eyes	**Transpalpebral:** 3 (sets of five consecutive readings) **GAT:** 3 measurements		**Transpalpebral:** mean difference 0.2, SD = 0.50 (95% LoA [−0.83 to 1.27]) mmHg (*n* = 26); RC 1.07 mmHg	Second and third measurements compared
Rai et al. (2005)	**Transpalpebral:** patient and technician **GAT:** one examiner 135 subjects	**Transpalpebral:** 3 measurements **GAT:** not recorded		**Transpalpebral:** 0.83 (CC) patient **GAT:** 0.78 (CC) examiners	
Troost et al. (2005)	**Transpalpebral:** two examiners **GAT:** one examiner 20 subjects and 40 eyes	**Transpalpebral:** 3 measurements **GAT:** 3 measurements	**Transpalpebral:** mean difference of −1 (95% LoA [−8 to 6]) mmHg		
Herse et al. (2005)	**Transpalpebral:** patient **GAT:** one	**Transpalpebral:** 3 measurements **GAT:** 3 measurements		**Transpalpebral:** 4.21 (RC) mmHg; mean difference	

	experienced clinician 107 subjects			0.1, SD = 2.1 mmHg **GAT:** 0 .96 (RC) mmHg; mean difference 0.1, SD = 0.60 mmHg	
Morledge-Hampton et al.(2006)	**Transpalpebral:** one ophthalmologist **GAT:** not recorded 30 subjects	**Transpalpebral:** 2 measurements **GAT:** 3 measurements. First and second measurements used in main analysis		**Transpalpebral:** 0.82 (CC) for first and second readings **GAT:** 0.97 (CC) for first and second readings May not be intraobserver as number of observers not reported.	The third GAT reading was compared with the first two, which showed evidence of a tonometry effect (i.e. lowering of IOP).

Table 3.1 Inter and intraobserver reliability of different tonometers used in practice.(From the table it is evident that many different techniques of data analysis are employed making it difficult to interpret the results of the studies. This is especially true for studies conducted prior [as well as some after] to 2011 when the GRRAS guidelines were introduced) (ICC = intraclass correlation coefficient, RC = reliability coefficient, CC = correlation coefficient, LoA = limits of agreement, SD = standard deviation, CoV = coefficient of variation, VARMID = variance of difference between middle reading and the average of the first and last readings, df = degrees of freedom, and CCC = concordance correlation) (Burr et al., 2012)

3.2 Subjects and methods

Chapter two gave a complete description of the subjects, materials and methodology used in this specific study. To evaluate the inter- and intraobserver reliability of the ICare RBT with and without different disposable lenses on the eye, two optometrists (DJB and GHK) independently took two ICare RBT measurements on the left eye (of each and every subject enrolled in this study) with and without each of the four contact lens *in situ* in accordance with the protocol established for the study. The two measurements for the left eye were recorded by an experienced optometric assistant effectively blinding the optometrist taking the measurements and thereby reducing observer bias. To evaluate intraobserver reliability of the ORA, four measurements were taken by one experienced optometrist (DJB) without the contact lenses on the eye. The measurements were taken according to the protocol established for the study and recorded by an experienced optometric assistant (MLG), blinding the optometrist and reducing observer bias. Measurements 1 and 2, 1 and 3, and 1 and 4 were compared to establish intraobserver reliability of the ORA.

3.3 Statistical analysis

Previously Pearson's correlation coefficient, paired *t*-tests, and correlation of variation (CV) have been used to calculate reliability (Rankin and Stokes, 1998) (Table 3.1). Pearson's correlation coefficient was considered inappropriate because it measures the strength of linear association and

not agreement (it is possible to have a high degree of correlation when agreement is poor) (Rankin and Stokes, 1998; McAlinden et al., 2011). Paired *t*-tests assess whether the two sets of measurements agree on average (Rankin and Stokes, 1998; Norman and Streiner, 2008) but it is the difference between within-subject scores that was of interest in this study.

Intraclass correlation coefficients (ICCs) were specifically designed to examine reliability, providing a reliability index to indicate measurement error (Bartko, 1966). ICCs are calculated from the results obtained from ANOVA for repeated measures. Several formulas for ICCs exist and can give quite different results when applied to the same data. Each formula is appropriate for specific situations which are defined by the experimental design and the potential use of the results (Rankin and Stokes, 1998). ICC in isolation cannot give a true picture of reliability (ICC is dependent on the range of values measured – the greater the variability between subjects, the greater the value of ICC) and should be complemented by the Bland and Altman 95% limits of agreement tests because these tests are independent (unlike ICCs) of true variability in the observations (Rankin and Stokes, 1998; Patton et al., 2006). ICC is measured on a scale of 0 to 1; 1 represents perfect reliability with no measurement error whereas 0 indicates no reliability (Patton et al., 2006).

According to Spitzer and Endicott any ICC >0.75 can be classified as "good" (Spitzer and Endicott, 1980). In this study the same observers measured IOP in each case, therefore a "Two-Way Random" model (ICC 2,1) was used as it models both an effect of observer and subject (two effects). Both observers and subjects are drawn randomly from larger representative populations, professional optometrists and the public (random effects model). The reliability of a single observer was calculated for consistency with a 95% confidence interval. The Bland and Altman analysis were performed with the differences between the two measurements plotted against the mean of the two measurements. The mean of the differences and the standard deviation of the differences were also calculated. The closer the mean of the differences or bias was to zero and the smaller the value of the standard deviation of the differences, the better the agreement was between measures. The bias could be a constant or an average result arising from problems for specific values. It is therefore important to evaluate the differences at different magnitudes of the measured variable. Hence, 95% limits of agreement as well as 95% confidence intervals for these limits of agreement were also calculated (Bland and Altman, 1986).

The wsSD (within-subject-standard-deviation) is calculated by taking the square root of the residual mean square (also known as the within subject variance) from the ANOVA table (Bland and Altman,

1996). wsSD represents the measurement error or the variation between measurements (in this case IOP) on the same subject. It is important to ensure that the SD is unrelated to the magnitude of the IOP measurement. Analytically this can be done by calculating a rank correlation coefficient – Kendall's τ. From the wsSD it is then possible to calculate repeatability which is the √2 x 1.96wsSD, or 2.77wsSD (Bland and Altman, 1996).

Equation 3.1 Repeatability

$$\boldsymbol{Repeatability} = \sqrt{2}\boldsymbol{x1.96wsSD}$$ *(Bland and Altman, 1996)*

From the work of Walter et al. (1998) the required number of subjects as well as the optimal number of observers was calculated for this reliability study. Considering an expected ICC of 90% and the lowest acceptable ICC of 70%, nineteen (19) subjects were needed based on α = 0.05 and β = 0.20. The number of observers required for the same parameters was two (Walter et al., 1998). The Shapiro-Wilk test confirmed a normal distribution of the data (Ghasemi and Zahediasl, 2012) (Appendix 6) and $p < 0.05$ was considered significant.

3.4 Results

3.4.1 Intraobserver reliability of ICare Rebound tonometer measurements

To investigate the intraobserver reliability or test-retest reliability of the ICare RBT, the first and second measurements of each of the two observers were compared, first with and then without contact lenses *in situ*.

	ICC 2.1	Bland Altman analyses
Observer DJB		
Without contact lenses N = 50	0.95 95% CI (0.905 to 0.968)	M = 0.30, SD = 1.3 mmHg 95% LoA (-2.1 to -2.8)
With contact lenses N = 250	0.95 95% CI (0.925 to 0.954)	M = -0.1, SD = 1.50 mmHg 95% LoA (-3.0 to 2.9)
Observer GHK		
Without contact lenses N = 50	0.88 95% CI (0.795 to 0.929)	M = 0.1, SD = 1.7 mmHg 95% LoA (-3.20 to 3.50)
With contact lenses N = 250	0.92 95% CI (0.902 to 0.939)	M = 0.1, SD = 1.6 mmHg 95% LoA (-3.1 to 3.3)

Table 3.2 Intraobserver reliability of the ICare RBT. Summary of findings..(ICC – Interclass correlation coefficient, M = Mean, SD – Standard deviation, LoA - Limits of agreement, DJB – observer 1, GHK – observer 2)

For observer DJB the first measurements without contact lenses (*n* = 50*)* was slightly higher than the second measurement, M = 14.78, SD = 3.81 and M = 14.46, SD = 3.75 mmHg respectively. Similar results were obtained for observer GHK with the first and second measurements (*n* = 50) being, M = 14.60, SD = 3.49 and M = 14.46, SD = 3.51 mmHg respectively. ICCs (2.1 for consistency and single measures) were 0.95 (95% CI [0.905 to 0.968]) and 0.88 (95% CI [0.795 to 0.929]) for DJB and GHK respectively. When all the measurements (with and without contact lenses) were combined (*n* = 250), the findings were as follows. For observer DJB the mean of the second measurement was slightly higher than the first measurement, M = 14.99, SD = 4.44 and M = 15.04, SD = 4.04 mmHg respectively. For GHK the mean of the first measurement was slightly higher than the second measurement, M = 14.66, SD = 4.12 and M = 14.60, SD = 4.16 mmHg respectively. ICCs (2.1 for consistency and single measures) were 0.94 (95% CI [0.925 to 0.954]) and 0.92 (95% CI [0.902 to 0.939]) for DJB and GHK respectively (Table 3.2).

The Bland-Altman analyses revealed differences between observer DJB's first and second measurement without lenses (*n* = 50) was M = 0.30, SD = 1.3 mmHg (95% CI [-0.04 to 0.68]) and the 95% LoA (-2.1 to 2.8) (Figure 3.2). There was a strong linear relationship between the two measurements, $r = 0.95$, $p < 0.001$. For observer GHK the difference between the two measurements without contact lenses (*n* = 50) was M = 0.1, SD = 1.7 mmHg (95% CI [-0.34 to 0.62]) and the 95% LoA (-3.2 to 3.5) (Figure 3.1). There was a strong linear relationship between the two measurements, $r = 0.90$, $p < 0.001$.

ICare RBT	**DJB – Repeatability and measurement error**	**GHK – Repeatability and measurement error**
Without contact lenses (*n* = 50)	wsSD = 0.89 mmHg Repeatability = 2.45 mmHg ME = 1.74 mmHg	wsSD = 1.20 mmHg Repeatability = 3.31 mmHg ME = 2.35mmHg
All measurements with and without contact lenses (*n* = 250)	wsSD = 1.08 mmHg Repeatability = 2.98 mmHg ME = 2.12 mmHg	wsSD = 1.15 mmHg Repeatability = 3.19 mmHg ME = 2.54 mmHg

Table 3.3 Intraobserver repeatability (variability) and measurement error (variation between measurements) of the ICare RBT.(The difference between the subject's measurement and the true value would be expected to be < 1.96 x wsSD for 95% of observations and the difference between the two measurements for the same subject would be expected to less than < 2.77 x wsSD for 95% of pairs of observations) (Bland and Altman, 1996). (wsSD = within-subject-standard-deviation. ME = Measurement error).

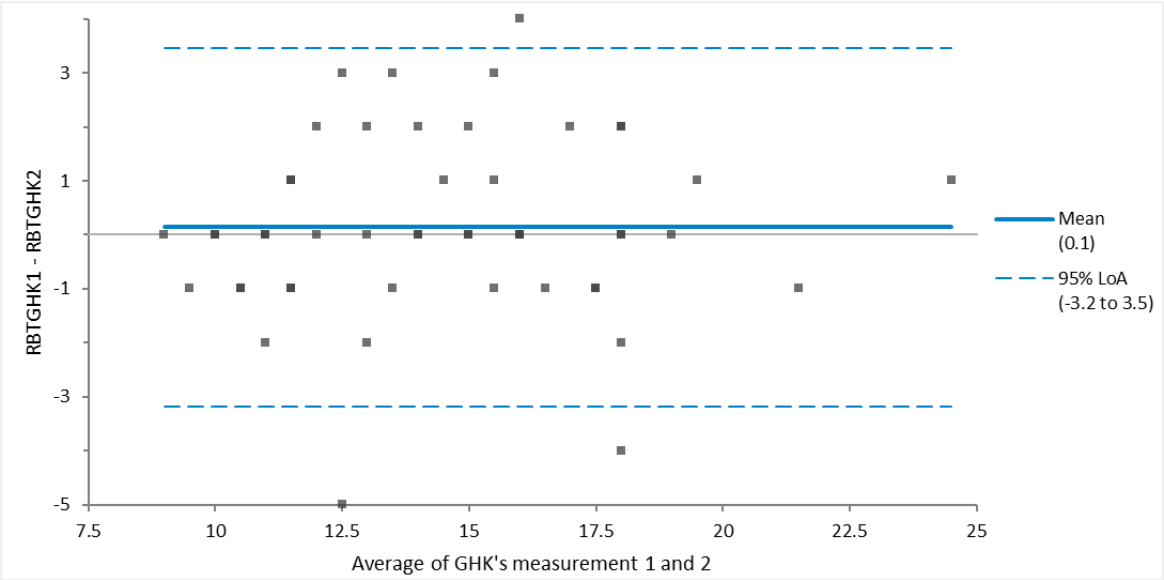


Figure 3.1 Bland-Altman plot of observer GHK's first and second ICare RBT measurement without contact lenses *in situ*. Bias was consistent for different magnitudes of the measured variable. (GHKRBT (1&2) = Observer GHK rebound tonometry measurements 1 & 2).

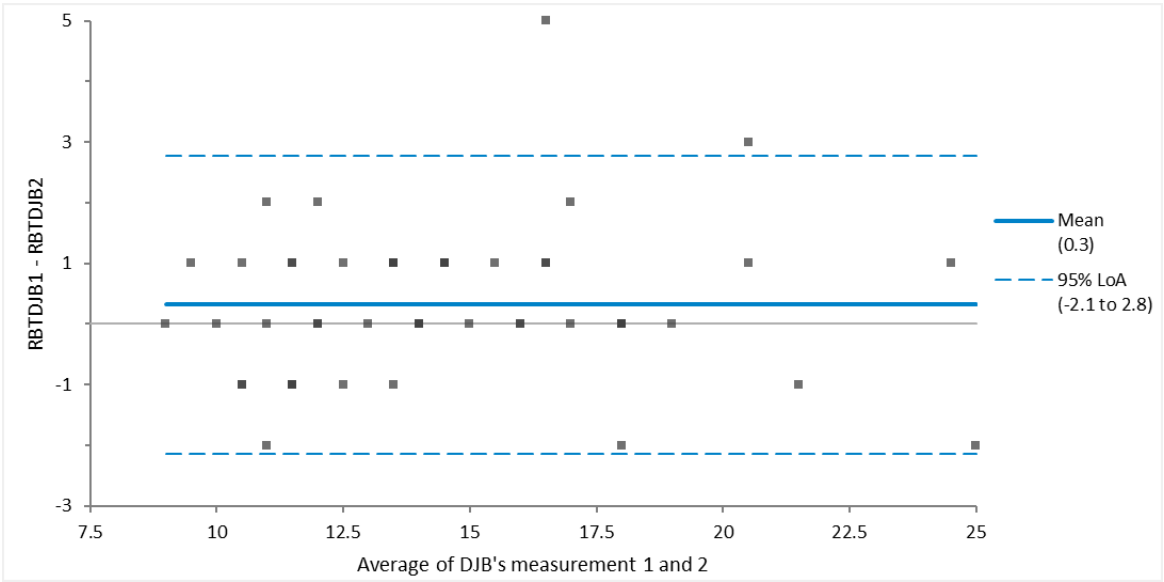


Figure 3.2 Bland-Altman plot of observer DJB's first and second ICare RBT measurement without contact lenses *in situ*.Bias was consistent for different magnitudes of the measured variable.(DJBRBT (1&2) = Observer DJB rebound tonometry measurements 1 & 2).

When all the measurements (with and without contact lenses) of the two observers were combined the results of the Bland-Altman analyses were as follows: the difference between observer DJB's first and second measurements (n = 250) with lenses was M = -0.1, SD = 1.5 mmHg (95% CI [-0.25 to 0.13]) and the 95% LoA (-3.0 to 2.9) (Figure 3.3). There was a strong linear relationship between the two measurements: r = 0.94, p < 0.001. For observer GHK the difference between the two measurements with contact lenses (n = 250) was M = 0.1, SD = 1.6 mmHg 95% CI [-0.14 to 0.27] and the 95% LoA (-3.1 to 3.3) (Figure 3.4). There was a strong linear relationship between the two measurements: r = 0.92, p < 0.001.

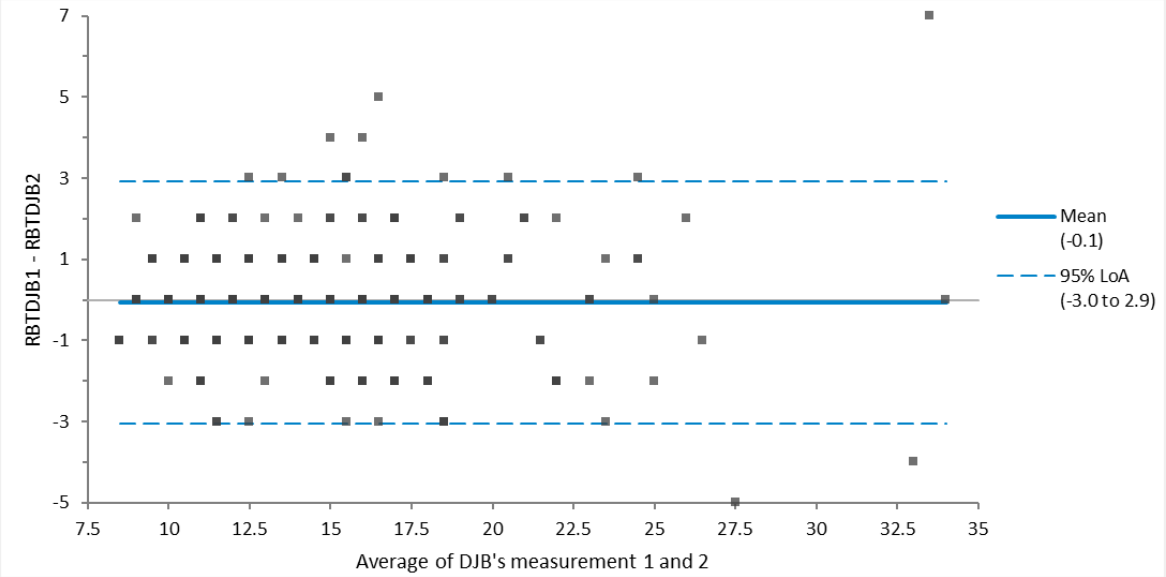


Figure 3.3 Bland-Altman plot of observer DJB's first and second ICare RBT measurement with and without contact lenses *in situ*.Bias was consistent for different magnitudes of the measured variable. (DJBRBT (1&2) = Observer DJB rebound tonometry measurements 1 & 2).

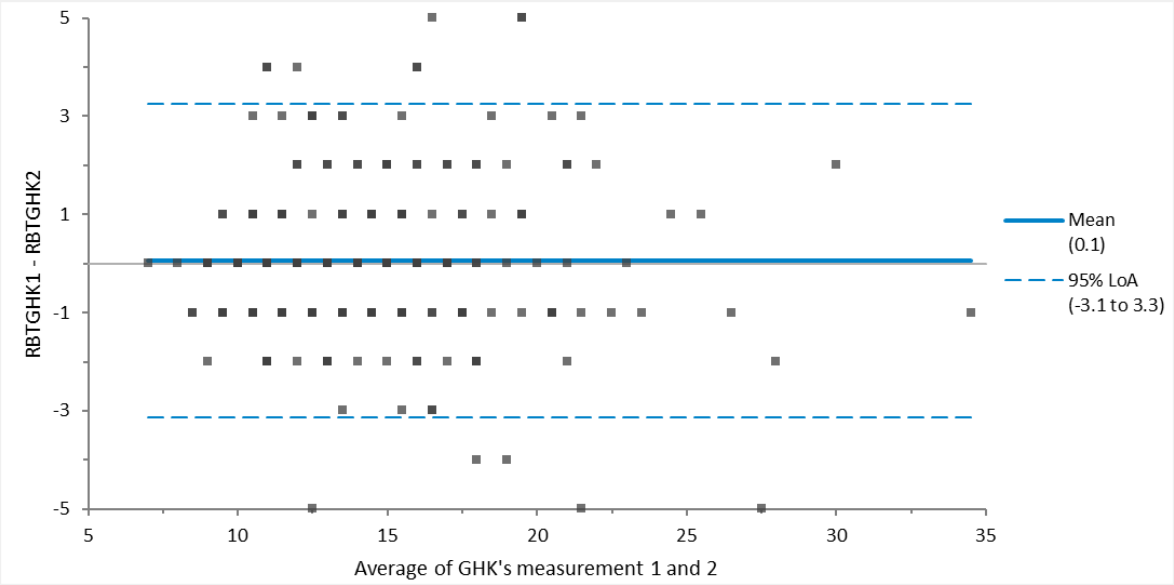


Figure 3.4 Bland-Altman plot of observer GHK's first and second ICare RBT measurement with and without contact lenses *in situ*. Bias was consistent for different magnitudes of the measured variable (GHKRBT (1&2) = Observer GHK's rebound tonometry measurements 1 & 2).

3.4.2 Interobserver reliability and agreement of the ICare Rebound tonometer measurements

Two measurements per observer were recorded: first, without contact lenses and then with each of the four different brands of contact lenses (as listed in Table 2.1) on the eye. The measurement process was standardised and an independent observer recorded the IOP measurements blinding the observers. In order to investigate the interobserver reliability and agreement of the ICare RBT, the measurements of each of the two observers were compared, first without and then with the different contact lenses *in situ*.

Observers DJB & GHK	ICC 2.1	Bland Altman analyses
Without contact lenses N = 100	0.81 95% CI (0.724 to 0.865)	M = 0.1, SD = 2.2 mmHg 95% LoA (-4.3 to 4.5)
With contact lenses N = 500	0.88 95% CI (0.577 to 0.897)	M = 0.40, SD = 2.1 mmHg 95% LoA (-3.8 to 4.5)

Table 3.4 Interobserver reliability of the ICare RBT. Summary of findings. (ICC – Interclass correlation coefficient, M = Mean, SD – Standard deviation, LoA - Limits of agreement)

Without the contact lenses on the eye observer DJB's mean measurement (*n* = 100) was slightly higher (M = 14.62, SD = 3.77 mmHg) than that of observer GHK (M = 14.53, SD = 3.41 mmHg). ICC (2.1 for consistency and single measures) was 0.81 (95% CI [0.724 to 0.865]). When all the measurements (with and without contact lenses, [*n* = 500]) were considered, observer DJB's mean measurements (M = 14.96, SD = 4.14 mmHg) were once again slightly higher than that of observer

GHK (M = 14.59, SD = 4.13 mmHg). ICC (2.1 for consistency and single measures) was 0.88 (95% CI [0.857 to 0.897]). The Bland-Altman analyses revealed a difference of M = 0.1, SD = 2.2 mmHg (95% CI [-0.35 to 0.53]) and the 95% LoA (-4.3 to 4.5) (Figure 3.5). There was a strong linear relationship between the two measurements without contact lenses (n = 100): r = 0.81, p < 0.001. When all the measurements (n = 500) are considered, there was a difference of M = 0.4, SD = 2.1 mmHg (95% CI [0.18 to 0.55]) and the 95% LoA (-3.8 to 4.5) (Figure 3.6 and table 3.4). There was a strong linear relationship between the two measurements: r = 0.88, p < 0.001.

ICare RBT	DJB vs GHK – Repeatability
Without contact lenses (n = 100)	wsSD = 1.59 mmHg Repeatability = 4.39 mmHg
With contact lenses (n = 500)	wsSD = 1.49 mmHg Repeatability = 4.12 mmHg

Table 3.5 Interobserver repeatability and measurement error (variation between measurements) of the ICare RBT.(The difference between the two measurements for the same subject would be expected to less than < 2.77xwsSD for 95% of pairs of observations) (Bland and Altman, 1996). (wsSD = within-subject-standard-deviation)

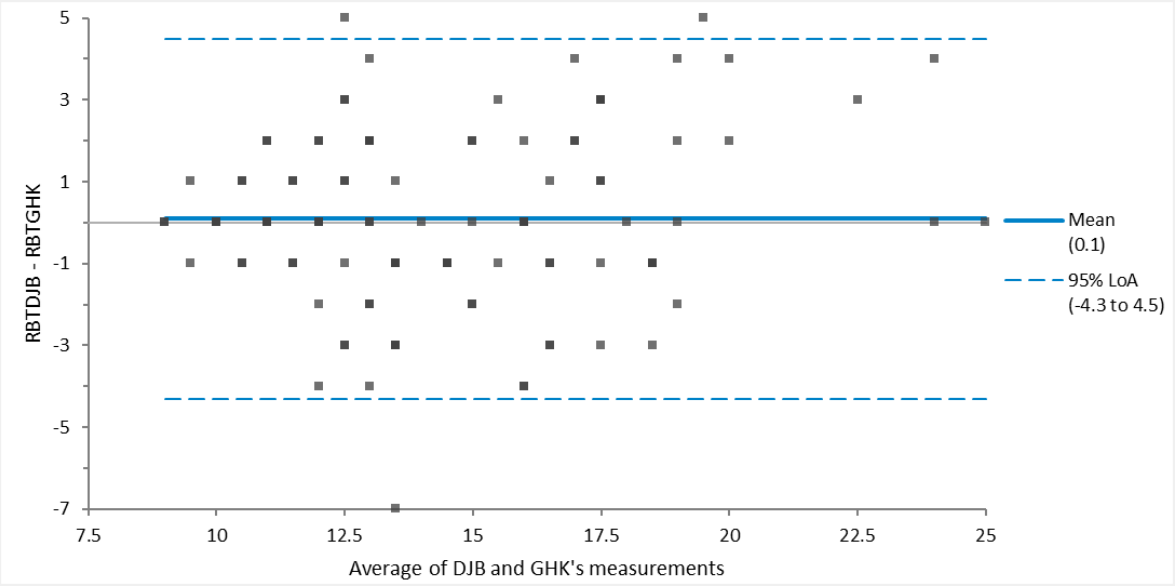


Figure 3.5 Bland-Altman plot of observers DJB and GHK's ICare RBT measurement without contact lenses *in situ*. Bias was consistent for different magnitudes of the measured variable. (DJBRBT & GHKRBT = Observer DJB & GHK rebound tonometry measurements)

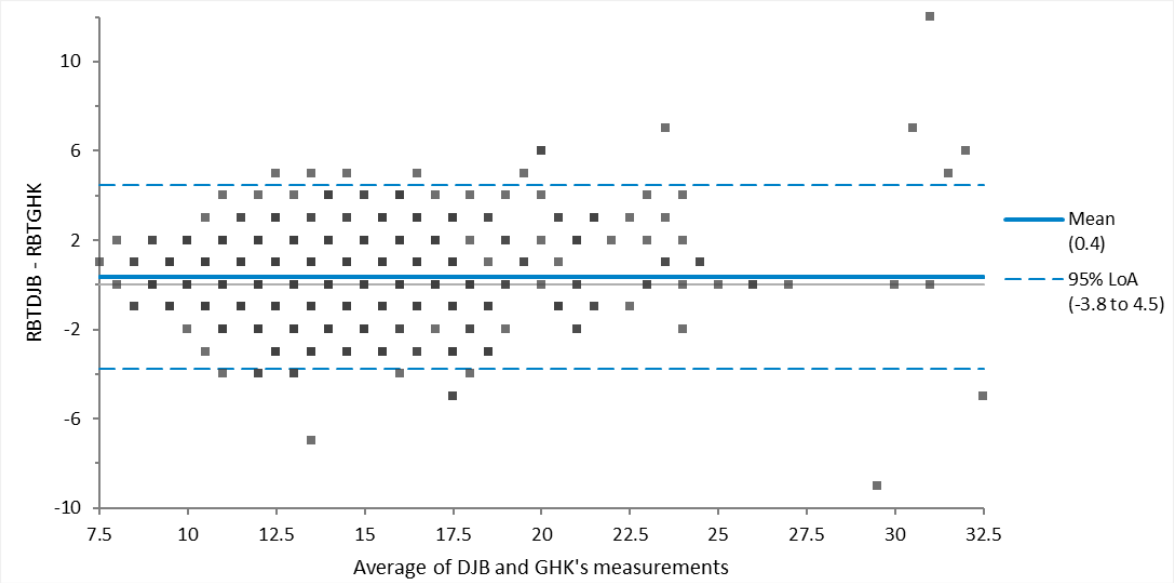


Figure 3.6 Bland-Altman plot of observers DJB and GHK's ICare RBT measurements with and without contact lenses *in situ*.Bias was consistent for different magnitudes of the measured variable. (DJBRBT & GHKRBT = Observer DJB & GHK rebound tonometry measurements)

3.4.3 Intraobserver reliability of the Reichert ocular response analyser (ORA) without contact lenses *in situ*

An experienced optometrist (DJB) performed tonometry and corneal biomechanical measurements with a recently calibrated ocular response analyser (ORA, Reichert Inc., Depew, NY) in the way described in chapter two (section 2.2). To measure ORA test-retest reliability and intraobserver reliability, ICCs and Bland-Altman analyses were calculated for measurements 1 and 2, measurements 1 and 3, and measurements 1 and 4 without contact lenses *in situ*.

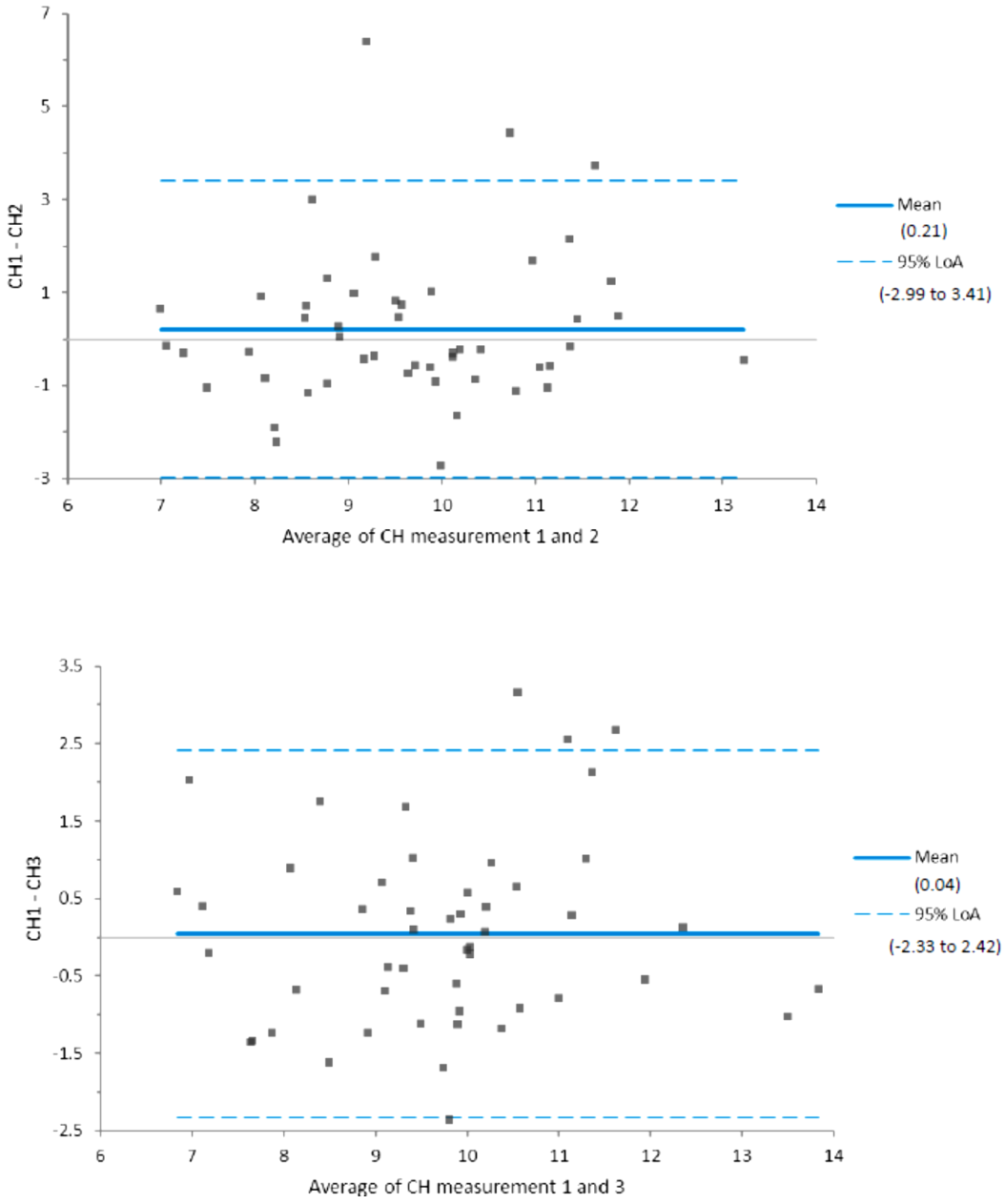
Observer DJB	ICC 2.1	Bland Altman analyses
CH **N = 50**	0.63 95% CI (0.499 to 0.753)	
Measurement 1 & 2		M = 0.21, SD = 1.63 mmHg 95% LoA (-2.99 to 3.41)
Measurement 1 & 3		M = 0.04, SD = 1.21 mmHg 95% LoA (-2.33 to 2.42)
Measurement 1 & 4		M = 0.013, SD = 1.33 mmHg 95% LoA (-2.5 to 2.61)
CRF **N = 50**	0.79 95% CI (0.694 to 0.859)	
Measurement 1 & 2		M = 0.18, SD = 1.31 mmHg 95% LoA (2.38 to 2.74)
Measurement 1 & 3		M = 0.25, SD = 1.21 mmHg 95% LoA (-2.11 to 2.62)
Measurement 1 & 4		M = 0.008, SD = 1.35 mmHg 95% LoA (-2.64 to 2.66)
IOPcc **N = 50**	0.77 95% CI (0.679 to 0.851)	
Measurement 1 & 2		M = 0.21, SD = 2.27 mmHg 95% LoA (-4.23 to 4.66)
Measurement 1 & 3		M = 0.45, SD = 2.27 mmHg 95% LoA (-3.99 to 4.88)
Measurement 1 & 4		M = 0.42, SD = 2.18 mmHg 95% LoA (-0.2 to 1.04)
IOPg **N = 50**	0.87 95% CI (0.810 to 0.918)	
Measurement 1 & 2		M = 0.41, SD = 1.87 mmHg 95% LoA (-3.25 to 4.07)
Measurement 1 & 3		M = 0.65, SD = 2.10 mmHg 95% LoA (-0.06 to 1.25)
Measurement 1 & 4		M = 0.57, SD = 1.99 mmHg 95% LoA (-3.33 to 4.66)

Table 3.6 Intraobserver reliability of the ORA metrics. Summary of findings. (ICC – Interclass correlation coefficient, M = Mean, SD – Standard deviation, LoA - Limits of agreement, CH – Corneal hysteresis, CRF – Corneal resistance factor, IOPcc – Corneal compensated IOP, IOPg – Goldman correlated IOP)

Corneal hysteresis (CH)

CH is one of the two instrument specific metrics of corneal biomechanics measured by the ORA (Equation 1.2). Of the four measurements recorded by DJB the means of the first, third and fourth measurements were all higher than that of the second measurement: M = 9.56, SD = 1.68 mmHg for the first; M = 9.55, SD = 1.52 mmHg for the second; M = 9.72, SD = 1.60 mmHg for the third; and M = 9.74, SD = 1.94 mmHg for the fourth measurements (n = 50). ICC (2.1 for consistency and single measures) was 0.63 (95 %CI [0.499 to 0.743]). Bland-Altman analyses were performed and plotted. The difference between measurements 1 and 2 was M = 0.21, SD = 1.63 mmHg (95% CI [-0.26 to 0.67]) and the 95% LoA (-2.99 to 3.41) (Table 3.6). There was a poor linear correlation between the measurements r = 0.49, p < 0.001. The difference between measurement 1 and 3 was M = 0.04, SD = 1.21 mmHg (95% CI [-0.30 to 0.39]) and the 95% LoA (-2.33 to 2.42). The linear correlation between

the measurements was slightly better than between measurements 1 and 2: $r = 0.73$, $p < 0.001$. The difference between measurement 1 and 4 was M = 0.013, SD = 1.33 mmHg (95% CI [-0.36 to 0.39]) and the 95% LoA (-2.58 to 2.61). The linear correlation between measurements was: $r = 0.74$ $p < 0.001$. The Bland-Altman plots are presented in Figure 3.7.



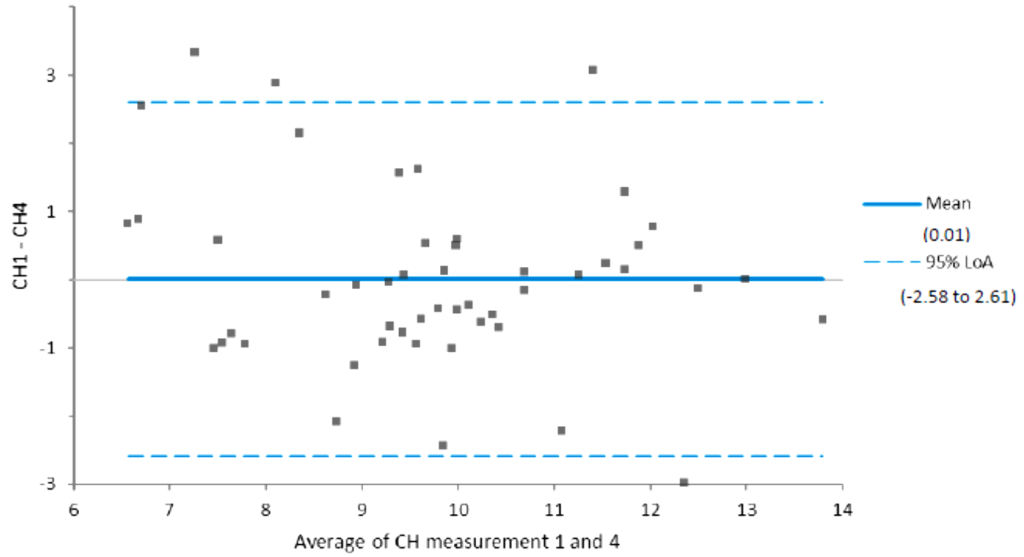
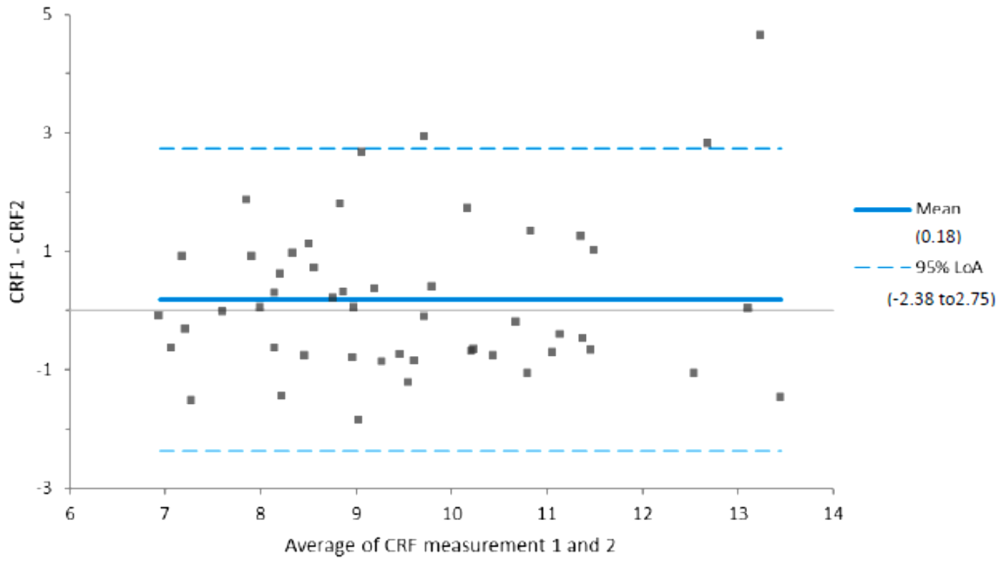
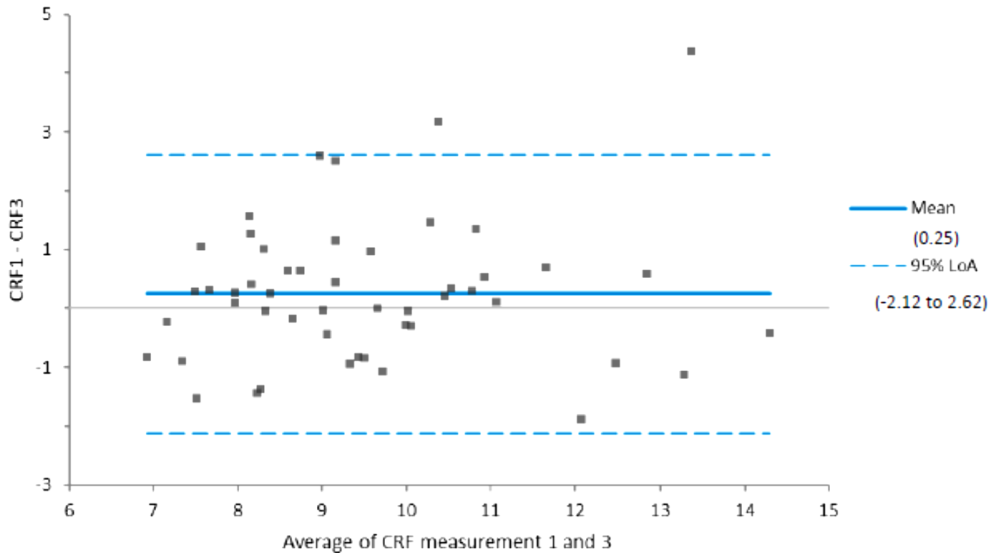


Figure 3.7 Bland-Altman plots of ORA CH measurements. Bias was consistent for different magnitudes of the measured variable (First is the difference between measurement 1 and 2 plotted against the mean of the two measurements. Second represent plots for measurements 1 and 3, and last for measurements 1 and 4) (CH = Corneal hysteresis)

Corneal resistance factor (CRF)

CRF is the other instrument specific metric of corneal biomechanics measured by the ORA (Equation 1.4, page 35). It is calculated from a formula which includes a constant derived from an empirical analysis of the relationship between P1, P2 and CCT (Lau and Pye, 2011). Of the four measurements recorded by DJB the means of the second and third measurements were lower than that of the first and fourth measurement: M = 9.66, SD = 1.90 mmHg for the first; M = 9.48, SD = 1.74 mmHg for the second; M = 9.41, SD=1.78 mmHg for the third; and M = 9.66, SD = 2.13 mmHg for the fourth measurements (n = 50). ICC (2.1 for consistency and single measures) was 0.79 (95% CI [0.694 to 0.859]). The Bland-Altman analyses were calculated and plotted. The difference between measurements 1 and 2 was M = 0.18, SD = 1.31 mmHg (95% CI [-0.19 to 0.56]) and the 95% LoA (-2.38 to 2.74). There was a good linear correlation between the measurements: r = 0.75, p < 0.001. The difference between measurements 1 and 3 was M = 0.25, SD = 1.21 mmHg (95% CI [-0.09 to 0.59]) and the 95% LoA (-2.11 to 2.62) (Table 3.6). The linear correlation between the measurements was: r = 0.79, p < 0.001. The difference between measurements 1 and 4 was M = 0.008, SD = 1.35 mmHg (95% CI [-0.38 to 0.39]) and the 95% LoA (-2.64 to 2.66). The linear correlation between measurements was: r = 0.78 p < 0.001. The Bland-Altman plots are represented in Figure 3.8.


CRF1 - CRF2
Average of CRF measurement 1 and 2
Mean
(0.18)
95% LoA
(-2.38 to2.75)


CRF1 - CRF3
Average of CRF measurement 1 and 3
Mean
(0.25)
95% LoA
(-2.12 to 2.62)

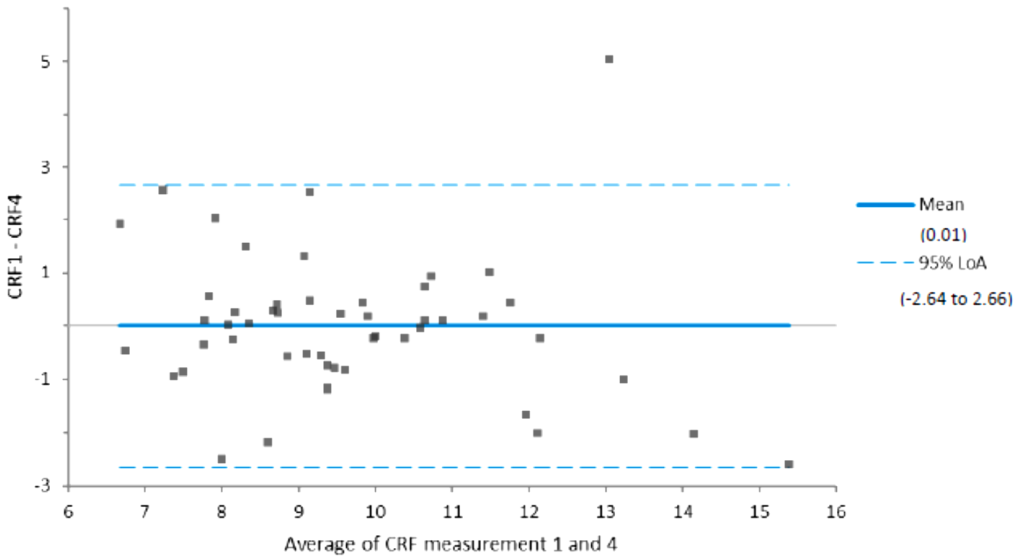
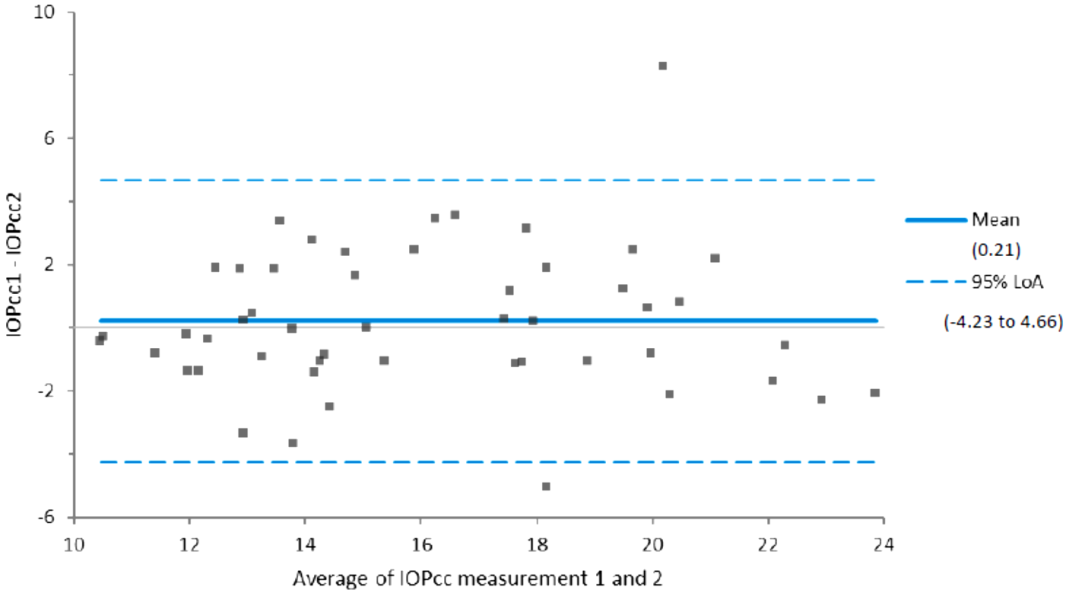
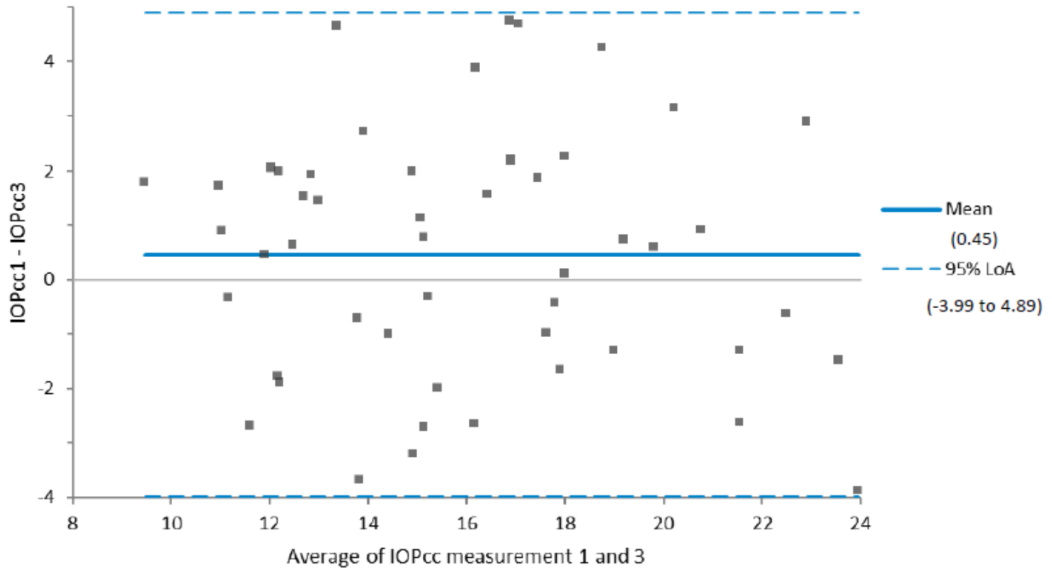


Figure 3.8 Bland-Altman plots of ORA CRF measurements.Bias was consistent for different magnitudes of the measured variable (First is the difference between measurement 1 and 2 plotted against the mean of the two measurements. Second represent plots for measurements 1 and 3, and last for measurements 1 and 4) (CRF = Corneal resistance factor)

Cornea compensated IOP (IOPcc)

IOPcc is calculated from individual corneal elasticity and viscosity information and is therefore less affected by corneal thickness and other corneal characteristics thus giving more accurate IOP measurements. The formula once again includes empirically derived constants as well as the P1 and P2 measurements (Lau and Pye, 2011) (Equation 1.3). Of the four measurements recorded by DJB the means of the first and second measurements were higher than that of the third and fourth measurements: M = 16.24, SD = 3.72 mmHg for the first; M = 16.03, SD = 3.63 mmHg for the second; M = 15.79, SD = 3.94 mmHg for the third; and M = 15.82, SD = 3.64 mmHg for the fourth measurements (n = 50). ICC (2.1 for consistency and single measures) was 0.77 (95% CI [0.679 to 0.851]). Bland-Altman analyses were calculated and plotted. The difference between measurements 1 and 2 was M = 0.21, SD = 2.27 mmHg (95% CI [-0.43 to 0.86]) and the 95% LoA (-4.23 to 4.66). There was good linear correlation between the measurements: r = 0.81, p < 0.001. The difference between measurements 1 an 3 was M = 0.45, SD = 2.27 mmHg (95% CI [-0.20 to 1.09]) and the 95% LoA (-3.99 to 4.88) (Table 3.6). The linear correlation between the measurements was good: r = 0.83, p < 0.001. The difference between measurements 1 and 4 was M = 0.42, SD = 2.18 mmHg (95% CI [-0.20 to 1.04]) and the 95% LoA (-3.86 to 4.70). The linear correlation between measurements was: r = 0.83 p < 0.001. The Bland-Altman plots are represented in Figure 3.9.


10
6
2
-2
-6
10
12
14
16
18
20
22
24
IOPcc1 - IOPcc2
Average of IOPcc measurement 1 and 2
Mean
(0.21)
95% LoA
(-4.23 to 4.66)


4
2
0
-2
-4
8
10
12
14
16
18
20
22
24
IOPcc1 - IOPcc3
Average of IOPcc measurement 1 and 3
Mean
(0.45)
95% LoA
(-3.99 to 4.89)

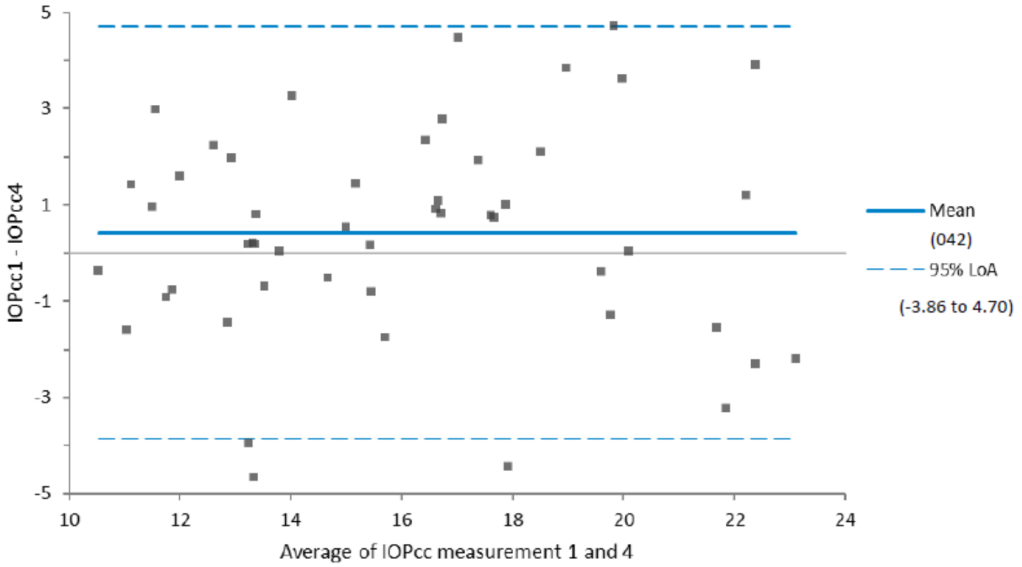
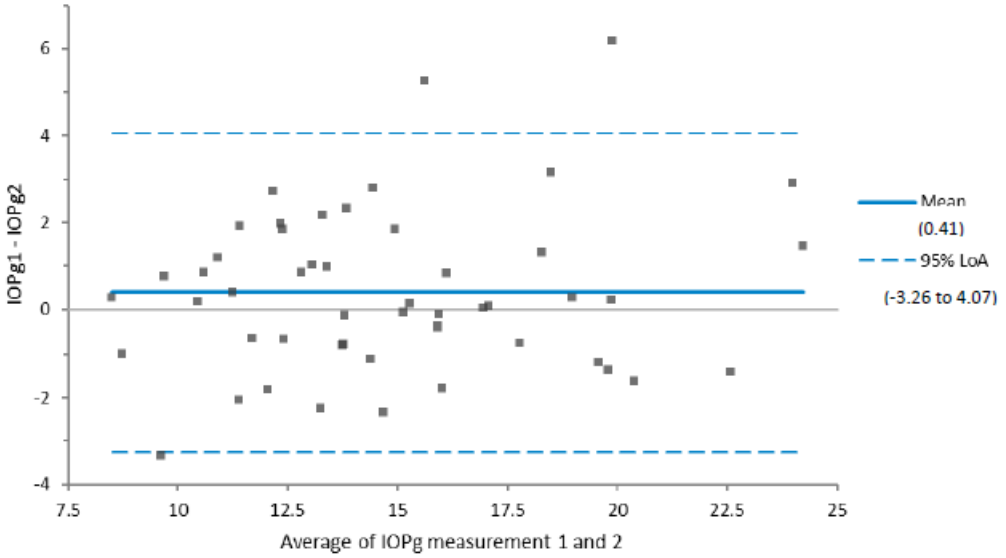
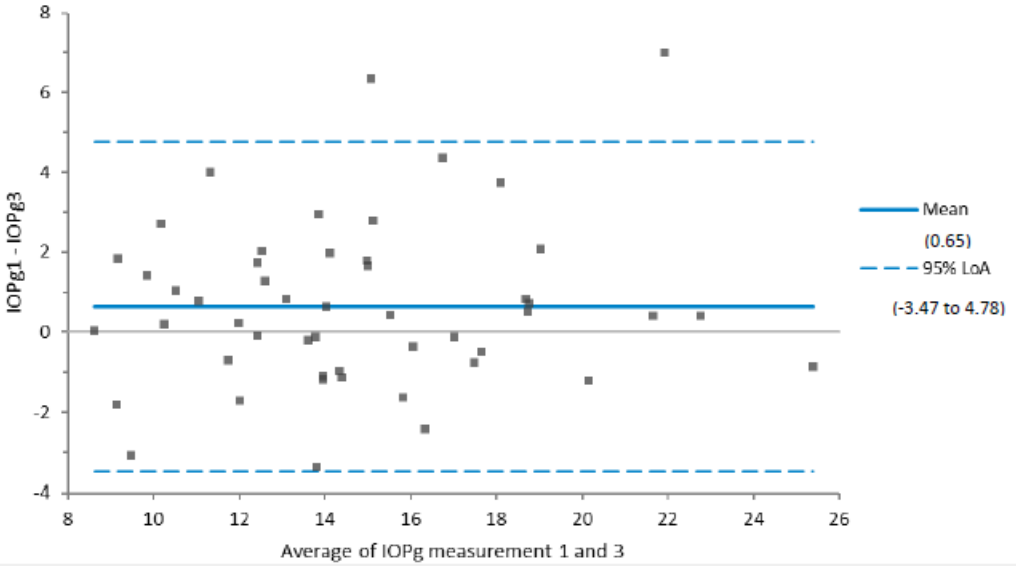


Figure 3.9 Bland-Altman plots of ORA IOPcc measurements.Bias was consistent for different magnitudes of the measured variable. (First is the difference between measurement 1 and 2 plotted against the mean of the two measurements. Second represent plots for measurements 1 and 3, and last for measurements 1 and 4) (IOPcc = Corneal corrected IOP)

Goldmann correlated IOP (IOPg)

IOPg is the average of measurement P1 and P2 (Lau and Pye, 2011) (Equation 1.1). Of the four measurements recorded by DJB the means of the first measurements were slightly higher than that of the second, third and fourth measurements: M = 15.06, SD = 4.04 mmHg for the first; M = 14.66, SD = 3.78 mmHg for the second; M = 14.41, SD = 3.82 mmHg for the third; and M = 14.49, SD = 3.38 mmHg for the fourth measurements (n = 50). ICC (2.1 for consistency and single measures) was 0.87 (95% CI [0.810 to 0.918]). The Bland-Altman analyses were calculated and plotted. The difference between measurements 1 and 2 was M = 0.41, SD = 1.87 mmHg (95% CI [-0.13 to 0.94]) and the 95% LoA (-3.25 to 4.07). There was good linear correlation between the measurements: r = 0.89, p < 0.001. The difference between measurements 1 and 3 was M = 0.65, SD = 2.10 mmHg (95% CI [-0.06 to 1.25]) and the 95% LoA (-3.47 to 4.78) (Table 3.6). The linear correlation between the measurements was: r = 0.86, p < 0.001. The difference between measurements 1 and 4 was M = 0.57, SD = 1.99 mmHg (95% CI [-0.002 to 1.13]) and the 95% LoA (-3.33 to 4.46). The linear correlation between measurements was: r = 0.87, p < 0.001. The Bland-Altman plots are represented in Figure 3.10.


IOPg1 - IOPg2
6
4
2
0
-2
-4
7.5
10
12.5
15
17.5
20
22.5
25
Average of IOPg measurement 1 and 2
Mean
(0.41)
95% LoA
(-3.26 to 4.07)


IOPg1 - IOPg3
8
6
4
2
0
-2
-4
8
10
12
14
16
18
20
22
24
26
Average of IOPg measurement 1 and 3
Mean
(0.65)
95% LoA
(-3.47 to 4.78)

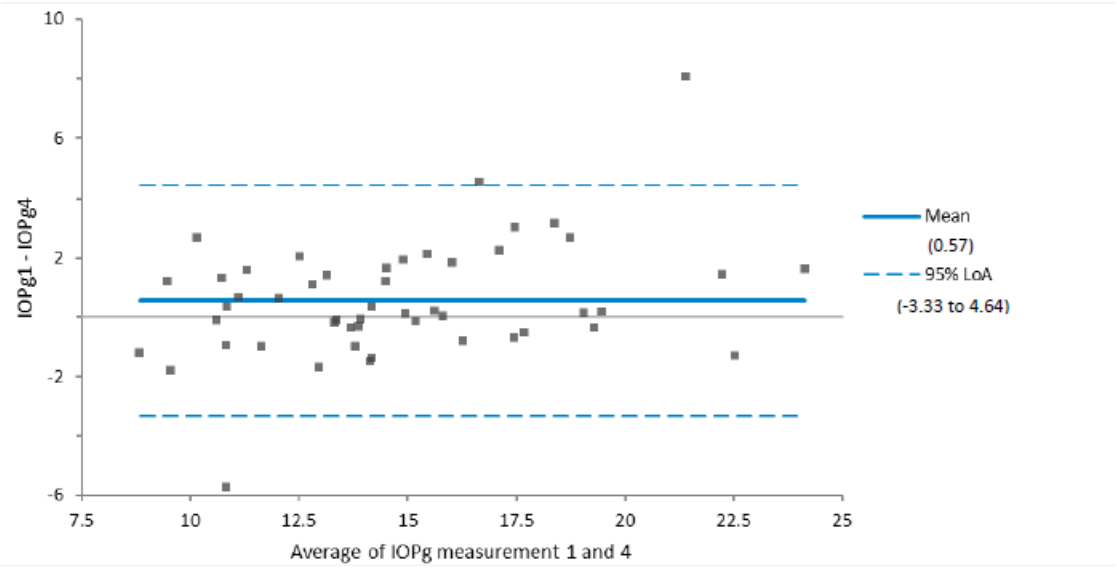


Figure 3.10 Bland-Altman plots of ORA IOPg measurements.Bias was consistent for different magnitudes of the measured variable. (First is the difference between measurement 1 and 2 plotted against the mean of the two measurements. Second represent plots for measurements 1 and 3, and last for measurements 1 and 4) (IOPg = Goldmann equivalent IOP)

ORA	**Intraobserver repeatability and measurement error or variation between measurements**
CH (*n* = 50)	wsSD = 1.03 mmHg Repeatability = 2.86 mmHg ME = 2.12 mmHg
CRF (*n* = 50)	wsSD = 0.88 mmHg Repeatability = 2.44 mmHg ME = 1.73 mmHg
IOPcc (*n* = 50)	wsSD = 1.78 mmHg Repeatability = 4.94 mmHg ME = 3.5 mmHg
IOPg (*n* = 50)	wsSD = 1.35 mmHg Repeatability = 3.75 mmHg ME = 2.65 mmHg

Table 3.7 Intraobserver repeatability (test-retest reliability) of the ORA measurements.(The difference between the subject's measurement and the true value would be expected to be < 1.96 x wsSD for 95% of observations and the difference between the two measurements for the same subject would be expected to less than < 2.77xwsSD for 95% of pairs of observations) (Bland and Altman, 1996). (wsSD = within subject standard deviation. ME = Measurement error) (Bland and Altman, 1996)

3.5 Discussion

Information regarding reliability as well as sensitivity and specificity is a prerequisite for using any instrumentation of measurement and forms a major component of ophthalmic research (Margo et al., 2002). Because studies on the reproducibility and reliability of the ICare RBT and ORA have previously been done on human subjects (Table 3.1), it can be postulated *de facto* that the reproducibility and reliability would be expected to be negatively impacted by the presence of a contact lens on the eye due to the induced biomechanical, thickness and curvature changes with the lens *in situ*. Therefore, the present study was designed according to the GRRAS guidelines to evaluate the intra- and interobserver reliability of the ICare RBT in a group of healthy subjects not only with but also without soft disposable contact lenses on the eye. Intraobserver reliability of the ORA was evaluated without contact lenses on the eye.

3.5.1 Intraobserver reliability of the ICare RBT

Without contact lenses the ICCs were 0.95 and 0.88 for DJB and GHK respectively. When considering all the measurements, with and without contact lenses on the eye, the ICCs remained high: 0.94 and 0.92 for DJB and GHK respectively. Intraobserver repeatability of ICare RBT in this group of patients by the two experienced optometrists was excellent according to Spitzer and Endicott's criteria (Spitzer and Endicott, 1980). This compares well to previous published data by Asrani et al. (2011), Sahin et al. (2007), and Martinez-de-la-Casa et al. (2005) who all found the ICare RBT produced repeatable measurements by the same examiner (Martinez-de-la-Casa et al., 2005; Sahin, Basmak, et al., 2007; Asrani et al., 2011). The Bland-Altman analyses confirmed the results obtained by ICC with mean differences between measurements without lenses of M = 0.30, SD = 1.3 mmHg and M = 0.10, SD = 1.7 mmHg for DJB and GHK respectively. When considering all the measurements, with and without contact lenses by the two observers, the mean differences between measurements were M = -0.1, SD = 1.5 mmHg and M = 0.1, SD = 1.6 mmHg for DJB and GHK respectively. Clinically, IOP measurement variation within ±3 mmHg is considered acceptable (Mackie et al., 1996; Choudhari et al., 2009). Most tonometers measure in increments of 1 mmHg (Doughty and Zaman, 2000). Differences > 1 mmHg was considered clinically significant in this study and therefore the small differences between measurements by each observer were considered clinically insignificant with the ICare RBT.

Bland and Altman also proposed that measurement error as well as repeatability of measurements can be calculated from wsSD (Bland and Altman, 1996). In this study the measurement error for the measurements taken without contact lenses was 1.74 mmHg and 2.35 mmHg for DJB and GHK respectively. The measurement error for all the measurements was 2.12 mmHg and 2.45 mmHg for DJB and GHK respectively. This means that for 95% of the measurements the true value would be expected to be less than the measurement errors indicated here. Repeatability without lenses was 2.45 mmHg and 2.98 mmHg for DJB and GHK respectively and with all measurements 2.98 mmHg and 3.19 mmHg for DJB and GHK respectively. Therefore, for 95% of the measurements the difference between the two measurements would be expected to be less than these values (Table 3.3). Compared to GAT with repeatability of 1.7 – 2.0 mmHg the ICare RBT intraobserver repeatability was poor (Thorburn, 1978; Dielemans et al., 1994; Kotecha et al., 2005). However, for clinical IOP screening purposes the intraobserver repeatability of the ICare RBT is as good, if not better, than comparative noncontact tonometers (Hansen, 1995; Mackie et al., 1996; Tonnu et al., 2005; Ogbuehi, 2006; Regine et al., 2006; Lafaut et al., 2007; AlMubrad and Ogbuehi, 2008; Ogbuehi and Almubrad, 2008). Intraobserver measurement repeatability was not affected by the presence of the disposable contact lenses on the eye.

3.5.2 Interobserver reliability of the ICare RBT

Without contact lenses (*n* = 100) the ICC was 0.81 and the mean difference determined by the Bland-Altman analyses between observer DJB and GHK was M = 0.10, SD = 2.2 mmHg. When all the measurements were considered (*n* = 500) the ICC was 0.88 and the mean difference by the Bland-Altman analyses between observer DJB and GHK was M = 0.4, SD = 2.1 mmHg. Clinically these small measurement differences were not significant. Repeatability calculated from wsSD was 4.39 mmHg without lenses and 4.12 mmHg with all measurements considered. Therefore, for 95% of the measurements the difference between the two observers' measurements was expected to be < 4.39 mmHg (Table 3.5). This study found that the interobserver measurement reliability with the ICare RBT was as good without contact lenses on the eye as it was with the four different disposable lenses on the eye. The interobserver reliability values determined in this study also compared well with previous studies for the same instrument (Martinez-de-la-Casa et al., 2005; Detry-Morel et al., 2006; Sahin, Basmak, et al., 2007; Asrani et al., 2011).

Independent experienced clinicians making IOP measurements under similar conditions with the ICare RBT produced repeatable and consistent results.

3.5.3 Intraobserver reliability of the Reichert ORA without contact lenses *in situ*

It is well know that the OPA affects the accuracy of IOP measurements with the NCT. Several studies have shown that the OPA affects the intraobserver repeatability of the ORA, IOPcc and IOPg measurements and to a lesser extent the instrument specific biomechanical measurements CH and CRF (Sullivan-Mee et al., 2009; Kotecha et al., 2010). In this study, four measurements taken by the same observer with the ORA revealed the following results. ICCs (*n* = 50) were 0.63 for CH; 0.79 for CRF; 0.77 for IOPcc; and 0.87 for IOPg. The best test-retest reproducibility results were derived from IOPg followed by CRF, IOPcc and CH. This contrasted with the results of Wang et al. (2013) who found the IOPcc to have the poorest test-retest reproducibility (Wang et al., 2013). However, except for CH, the ORA measurements performed well considering Spitzer and Endicott's criteria (all ICCs > 0.70). The Bland-Altman analysis revealed that the differences between measurements for CH ranged from M = 0.013, SD = 1.21 mmHg to M = 0.21, SD = 1.63 mmHg depending on which measurements were compared.

Using the wsSD the measurement error for CH was calculated at 2.12 mmHg and the repeatability at 2.86 mmHg. This means that for 95% of the measurements the true value would be within 2.12 mmHg and the difference between the measurements would be less than 2.86mmHg (Table 3.7). The differences between measurements for CRF ranged from M = 0.08, SD = 1.35 mmHg to M = 0.25, SD = 1.21 mmHg. Using the wsSD, the measurement error for CRF was calculated at 1.73 mmHg and the repeatability at 2.44 mmHg. This means for 95% of the measurements the true value would within 1.72 mmHg and the difference between the measurements would be less than 2.44 mmHg (Table 3.7). Clinically IOP measurement variation within ±3 mmHg is considered acceptable (Mackie et al., 1996; Choudhari et al., 2009). The test-retest repeatability for the two corneal biomechanical metrics (CH and CRF) measured by the ORA was therefore excellent.

The Bland-Altman analyses revealed the differences between measurements for IOPcc ranged from M = 0.45, SD = 2.18 mmHg to M = 0.21, SD = 2.27 mmHg. Using the wsSD, the measurement error for IOPcc was calculated at 3.5 mmHg and the repeatability at 4.94 mmHg. This means that for 95% of the measurements the true value would be within 3.5 mmHg and the difference between the measurements would be less than 4.94 mmHg (Table 3.7). The differences between measurements for IOPg ranged from M = 0.41, SD = 1.87 mmHg to M = 0.65, SD = 2.10 mmHg. Measurement error for IOPg was 2.65 mmHg and the repeatability 3.75 mmHg. This means that for 95% of the measurements the true value would be within 2.65 mmHg and the difference between the

measurements would be less than 3.75 mmHg (Table 3.7). These findings agree with those of Wang et al. (2013), Moreno-Montanes et al. (2008), and Kotecha et al. (2010) who found intraobserver reliability for the IOPcc and IOPg was not as good as that of the two biomechanical metrics CH and CRF (Moreno-Montanes et al., 2008; Kotecha et al., 2010; Wang et al., 2013). Reasons for this difference were attributed to the OPA as well as the fact that the two IOP values were calculated from the biomechanical metrics. The repeatability of < 4.94 mmHg found in this study also compared well to the 4.3 mmHg found by Kotecha et al. (2010). As mentioned before, most tonometers measure in increments of 1 mmHg (Doughty and Zaman, 2000) and clinically IOP measurement variation within ±3 mmHg is considered acceptable (Mackie et al., 1996; Choudhari et al., 2009). Although in this study the repeatability of IOPg and IOPcc was not as good as that of CH and CRF the mean differences were slight and therefore clinically not significant.

Intraobserver reliability of the ORA was therefore considered good for all the parameters measured.

3.6 Conclusion

It is clear that although the intraobserver reliability of the ICare RBT is not as good as that of GAT. It compared well with that of the NCT and outperformed the ORA IOPcc and IOPg test-retest reliability in this study. The ORA biomechanical metrics, CH and CRF, had the best test-retest reliability. In both instruments the mean differences between repeated measurements were > 1 mmHg and < 5 mmHg. Intraobserver reliability was not affected by the presence of a contact lens on the eye. For both the ICare RBT and ORA test re-test reliability was good.

Independent experienced clinicians making IOP measurements under similar conditions with the same ICare RBT produced repeatable and consistent results. The interobserver repeatability was not affected by the presence of a contact lens on the eye and the mean differences between measurements were < 1 mmHg.

3.7 Summary of findings

- The intraobserver repeatability (test-retest reliability) of the ICare RBT was not as good as that of GAT, but it compared favourably with comparative non-contact tonometers.
- Interobserver repeatability with the ICare RBT was good with and without contact lenses on the eye. Repeated IOP measurements by independent experienced clinicians with the ICare RBT produced repeatable and consistent results.

- The intraobserver repeatability (test-retest reliability) of the ORA was excellent for the CH and CRF metrics, but not as good for the IOPg and IOPcc measurements. The difference could be attributed to the OPA and the fact that the two IOP values were calculated from the biomechanical metrics

Chapter 4

Clinical comparison of ICare rebound tonometry and Reichert ocular response analyser (ORA) measurements in a population of normal subjects with and without soft disposable contact lenses *in situ*

4.1 Introduction

This chapter clinically compares the ICare IOP measurement with the ORA CH, CRF, IOPcc and IOPg measurements with and without soft disposable contact lenses *in situ*. Although previous studies have been done to compare the two instruments, no published studies comparing the two instruments with soft disposable contact lenses *in situ* were identified. The results between the measurements with and without lenses had also not been compared previously. Chapter three showed for both the ICare RBT and ORA the test-retest reliability is excellent and, furthermore, if independent experienced clinicians make IOP measurements under similar conditions with the same ICare RBT, it is very likely that repeatable and consistent results would be produced.

Although GAT IOP has a significant association with CCT, the IOPcc produced by the ORA was found to have no significant association with ocular variables such as CCT, corneal curvature, and axial length (Medeiros and Weinreb, 2006; ElMallah and Asrani, 2008). Studies of the ORA have produced conflicting results: two studies in untreated glaucoma patients showed promising results with the ORA, IOPcc seeming to compensate for corneal factors (Kotecha et al., 2006; Medeiros and Weinreb, 2006). In another study of glaucoma patients undergoing therapy with topical medication, the ORA IOPcc and IOPg consistently overestimated GAT IOP by 8.3 mmHg and 7.2 mmHg respectively. In this group of patients the ORA IOP measurements were not independent of CCT (Martinez-de-la-Casa, Garcia-Feijoo, Fernandez-Vidal, et al., 2006). Medeiros and Weinreb (2006) reported a difference of M = 0.07, SD = 2.77 mmHg between ORA IOPcc and GAT. The difference was significantly influenced by CCT. Thicker CCT resulted in higher GAT compared to ORA IOPcc and thinner CCT resulted in lower GAT compared to ORA IOPcc (Medeiros and Weinreb, 2006). Kotecha et al. (2006) reported that ORA IOPcc overestimated GAT by 1.7 mmHg (Kotecha et al., 2006). In their study Lam et al. (2007) found 80% of the subjects (100 of 125 eyes) in IOPg and seventy nine percent (99 of 125 eyes) in IOPcc could achieve ±3 mmHg agreement with GAT. The 95% limits of agreement with GAT were similar for IOPg and IOPcc respectively. Good agreement was found between GAT and ORA. The mean difference was only 0.33 mmHg between IOPg and GAT, and 0.24 mmHg between IOPcc and GAT.

The conclusion reached in the Lam et al. (2007) study indicated when IOP was in the teens, ORA measurements are comparable with GAT measurements in normal subjects (Lam et al., 2007). Vandewalle et al. (2009) found that although the ORA overestimated IOP compared to GAT, 41.8% of ORA IOPg and 35.2% of IOPcc measurements were within ±3 mmHg of GAT measurements (Vandewalle et al., 2009). Studies by Carbonaro et al. (2010) and Kotecha et al. (2010) confirmed that the ORA IOPg and IOPcc overestimated GAT by ±2 mmHg and that the differences were independent of CCT (Carbonaro et al., 2010; Kotecha et al., 2010). Ehrlich et al. (2010) reported that the ORA IOPg overestimated GAT by 0.1 mmHg and that 53.9% of the ORA IOPg measurements were within 2 mmHg and 92.3% within 5 mmHg of GAT (Ehrlich et al., 2010). Lau and Pye (2011) also found that the ORA IOPg and IOPcc overestimated GAT IOP by 3.2 - 3.7 mmHg (Lau and Pye, 2011). In a more recent systematic review of agreement between different tonometers and GAT, 42% of the measurements with the ORA were estimated to be within ±2 mmHg of the GAT measurements (Cook et al., 2012). However, it is not clear from the review if the ORA's corneal corrected IOP (IOPcc) or Goldmann equivalent IOP (IOPg) were used in the comparison (Cook et al., 2012). Differences within ±3 mmHg of GAT measurements for any other tonometers are clinically acceptable.

In summary, it is obvious that the ORA (IOPg and IOPcc) tend to overestimate GAT IOP (Table 1.4). The exact magnitude of this difference is not clear and depends on the CCT and biomechanical properties of the cornea. However, differences of more than 3 mmHg are rare. The suitability of the NCT process used by the ORA for determining corneal biomechanics and the "true" IOP have up to date not yet been demonstrated with traditional biomechanical testing and manometry in human subjects. Validation of the ORA IOP measurements using manometric data therefore needs to be performed (Lau and Pye, 2011).

Currently the studies comparing the IOP measured with GAT and RBT have somewhat divergent results (Table 1.5). ICare tonometry measurements were similar to GAT measures in pathologic corneas, and in some cases could obtain measurements where GAT could not (Moreno-Montanes et al., 2007). It seems as if the ICare RBT was able to estimate IOP within a range of ±3 mmHg in more than 80% of the population (Fernandes et al., 2005; Iliev et al., 2006; Munkwitz et al., 2008) and was influenced by CCT, corneal curvature, and corneal biomechanics (Brusini et al., 2006; Nakamura et al., 2006; Sahin, Niyaz, et al., 2007; Chui et al., 2008; Jorge, Gonzales-Meijome, et al., 2008; Salvetat et al., 2011). Although The RBT measurements were highly correlated with GAT measurements, they were not interchangeable (Salvetat et al., 2011).

Jorge, Gonzales-Meijome et al. (2008) examined the correlations between the corneal biomechanical properties measured with the ORA and the IOP measured with the ICare RBT. They found that ICare RBT and ORA IOPg was strongly positively correlated (R^2 = 0.64 p < 0.001) but ORA IOPcc less so (R^2 = 0.32 p < 0.001). Regarding the two biomechanical measurements, ORA CRF correlated well with the ICare RBT (Spearman correlation coefficient r_s = 0.70 p < 0.001) and ORA CH less so (Spearman correlation coefficient r_s = 0.23 p = 0.012). According to these investigators, the significant positive correlation between ICare RBT and ORA CRF − and to a lesser extent ORA CH − indicates that individual physiologic variations in the corneal material properties (elastic and viscoelastic responses) may be more important than CCT in determining the ICare RBT measurements (Jorge, Gonzales-Meijome, et al., 2008).

Previous research showed the corneal modulus of elasticity (Young's modulus) significantly affected the accuracy of IOP measurement (Liu and Roberts, 2005). In some studies it was found that CCT and corneal curvature significantly affected ICare RBT measurements (Brusini et al., 2006; Nakamura et al., 2006; Sahin, Niyaz, et al., 2007; Avitabile et al., 2010; Salvetat et al., 2011). The biomechanical properties CH and CRF measured by the ORA are composite measurements characterising the structural response of the eye to the ORA tonometer and they can therefore not be seen as intrinsic elastic or viscoelastic properties of the cornea (Jorge, Gonzales-Meijome, et al., 2008; Lau and Pye, 2011). Currently Young's modulus of elasticity of the cornea can only be measured *ex vivo* (Kerautret et al., 2008; Lau and Pye, 2011). According to the manufacturer, CH represents ocular resistance due to the combined effects of CCT, ocular rigidity as well as the cornea's elastic properties – CH is therefore a function of the energy absorbed by the cornea. CRF is dominated by the combined effects of the viscous and elastic properties of the cornea and appears to be an indicator of the overall resistance of the cornea (Luce, 2005; Kotecha, 2007; Jorge, Gonzales-Meijome, et al., 2008; Kniestedt et al., 2008; Reichert, 2013).

To summarise, Jorge, Gonzales-Meijome et al. (2008) found that the ICare RBT overestimated ORA IOPg and IOPcc while other researchers such as Vandewalle et al. (2009) found the opposite (Table 1.6, page 48). Theoretically, due to ICare RBT's dependence on the corneas biomechanics, IOP measurement with this instrument should correlate well with ORA IOPg and poorly with IOPcc (Chui et al., 2008; Jorge, Gonzales-Meijome, et al., 2008).

The aim of this experimental chapter is to clinically compare the ICare RBT and ORA IOP measurements with and without four different disposable contact lenses *in situ*.

4.2 Subjects and methods

Chapter two gives a complete description of the subjects, materials and methodology used in this study. The four different contact lenses used remained the same for the entire study period and their individual properties are listed in Table 2.1. To compare the ICare RBT and ORA measurements, two experienced optometrists (DJB and GHK) took two ICare RBT measurements on every one of the subjects enrolled in the study according to the established study protocol: of each subject's left eye with and without each and every contact lens *in situ*. One of these experienced optometrists (DJB) took four ORA measurements according to the protocol established for the study of each subject's left eye with and without the contact lenses *in situ*. The measurements were recorded by an experienced optometric assistant (MLG) blinding the optometrists and reducing observer bias. The ICare RBT measurements were compared to each of the ORA metrics (CH, CRF, IOPcc, and IOPg).

4.3 Statistical analysis

The methods used to analyse the data included Pearson's correlation coefficient, paired *t*-tests, 1-way ANOVA tests as well as Bland-Altman plots. Pearson's correlation coefficient describes the closeness of the linear relationship between two variables. The test is potentially misleading as there may be a strong correlation between the two variables but poor agreement (Patton et al., 2006; Armstrong et al., 2011; McAlinden et al., 2011). Several two-sample paired *t*-tests were performed to test the hypotheses (with and without the contact lenses in situ) (Armstrong et al., 2011), Table 4.1. The *t*-test is the easiest way to compare two means and it estimates both the means and SD which introduces a dependency on sample size. It is not appropriate when there are more than two groups or when individuals in one group are matched to individuals in another group (Norman and Streiner, 2008).

H_o: RBT ≈ CH
H_o: RBT ≈ CRF
H_o: RBT ≈ IOPcc
H_o: RBT ≈ IOPg

Table 4.1 H_o – null hypothesis

Additionally 1-way ANOVA tests were performed to test the hypothesis H_o: RBT ≈ CH ≈ CRF ≈ IOPcc ≈ IOPg (without as well as with each of the lenses on the eye) (Armstrong et al., 2011). The 1-way

ANOVA provides an exact test of the hypotheses of multiple groups, and in combination with planned comparisons is the only alternative to multiple *t*-tests (Norman and Streiner, 2008).

Finally, Bland-Altman analyses were used to measure agreement between the IOP measurements without and with contact lenses *in situ* for both the ICare RBT and ORA. Bland and Altman tests have two distinct advantages compared to the other methods: the power of visual representation of the degree of agreement, and easy identification of bias by 95% confidence intervals, outliers, and any relationship between the variance in measures with the size of the mean (Bland and Altman, 1986). The 95% limits of agreement can also relate to clinical acceptability (Rankin and Stokes, 1998). All tests demanded normal distribution of the data. The Shapiro-Wilk test confirmed a normal distribution of the data (Appendix 6) and $p < 0.05$ was considered significant (Ghasemi and Zahediasl, 2012).

4.4 Results

Descriptive statistics for the parameters measured in the study are presented in Table 2.2. In Table 4.2 the means, standard deviations, and range of the relevant measurements from this study compared to published values are shown.

Pearson's correlations indicate strong positive correlations (changes in one variable will correlate with changes in the other) between the variables without as well as with contact lenses *in situ*. The only exceptions are between ICare RBT and ORA CH without lenses ($r = 0.13$, $p = 0.37$), ICare RBT and ORA CH with Acuvue 1-Day Moist lenses ($r = 0.27$, $p = 0.06$), as well as ICare RBT and ORA IOPcc with Pure Vision lenses ($r = 0.24$, $p = 0.10$) which show weak correlations (indicating that changes in one variable will not correlate with changes in the other). In Chapter 3 it was shown that the intraobserver reliability of the ICare RBT and ORA was excellent with differences between measurements < 0.30 mmHg, except for ORA IOPg with differences of 0.65 mmHg. Likewise, Interobserver reliability was < 0.40 mmHg. Although these variations in measurements are not clinically significant, they must be considered when comparing the two instruments.

	Results from this study Mean (M), standard deviation(SD), Range (min to max) ***N* = 50**	**Published normal values Mean (M), standard deviation (SD)**
Mean ICare IOP	M = 14.58, SD = 3.38 mmHg 9.0 to 24.5 mmHg	M = 15-16, SD = 2.5 mmHg (Harper and Reeves, 1999)
Mean ORA IOPg	M = 14.64, SD = 3.58 mmHg 9.0 to 24.4 mmHg	M = 15-16, SD = 2.5 mmHg (Harper and Reeves, 1999)
Mean ORA IOPcc	M = 16.02, SD = 3.50 mmHg 10.10 to 23.68 mmHg	M = 15-16, SD = 2.5 mmHg (Harper and Reeves, 1999)
CCT	Pentacam M = 531.46, SD = 35.51 µm 469 to 613 µm	UP M = 537-567 µm, SD not available (Argus, 1995; Bron et al., 1999; Shah et al., 1999; La Rosa et al., 2001; Nemesure et al., 2003)
Mean ORA CH	M = 9.68, SD = 1.42 mmHg 7.15 to 13.38 mmHg	M = 9.6-12 mmHg, SD not available (Ortiz et al., 2007; Shehadeh-Mashor et al., 2012)
Mean ORA CRF	M = 9.57, SD = 1.65 mmHg 6.83 to 13.40 mmHg	M = 9.5-12 mmHg, SD not available (Ortiz et al., 2007; Shehadeh-Mashor et al., 2012)
Mean corneal curvature (K)	Pentacam M = 7.80, SD = 0.28 mm 7.30 to 8.33 mm	M = 7.80 mm, SD not available (Pepose and Ubels, 1992)

Table 4.2 Means and standard deviations of the relevant results (without lenses) from this study compared to published population values.(UP = ultrasound pachymetry, CCT = central corneal thickness, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP)

4.4.1Without lenses

Hypotheses testing by 1-way ANOVA: $H_{o:}$ RBT ≈ CH ≈ CRF ≈ IOPcc ≈ IOPg for data without lenses were overwhelmingly rejected: $f = 132.55$, $p < 0.0001$. The results were also supported by the means and standard deviations of the variables (Table 4.3). Results for paired *t*-tests for the different hypotheses tested in Table 4.4 show that without lenses the ICare RBT and ORA IOPg measurement were comparable and the differences between the two were not clinically nor statistically significant.

Means and SD of ICare RBT and ORA CH,CRF, IOPcc and IOPg without lenses					
Variable	*RBT (mmHg)*	*CH (mmHg)*	*CRF (mmHg)*	*IOPcc (mmHg)*	*IOPg (mmHg)*
Mean (M), standard deviation (SD)	*M = 14.58, SD = 3.38*	*M = 9.68, SD = 1.42*	*M = 9.57, SD = 1.65*	*M = 16.02, SD = 3.50*	*M = 14.64, SD = 3.58*
Means and SD of ICare RBT and ORA CH,CRF, IOPcc and IOPg with Pure Vision lenses					
Variable	$RBT_{Pure\ Vision}$ (mmHg)	$CH_{Pure\ Vision}$ (mmHg)	$CRF_{Pure\ Vision}$ (mmHg)	$IOPcc_{\ Pure\ Vision}$ (mmHg)	$IOPg_{Pure\ Vision}$ (mmHg)
Mean (M), standard deviation (SD)	M = 18.49, SD = 5.43	M = 14.56, SD = 3.38	M = 14.22, SD = 3.40	M = 11.72, SD = 3.18	M = 15.79, SD = 3.75
Means and SD of ICare RBT and ORA CH,CRF, IOPcc and IOPg with Frequency XC lenses					
Variable	$RBT_{Freq.XC}$ (mmHg)	$CH_{Freq.XC}$ (mmHg)	$CRF_{Freq.XC}$ (mmHg)	$IOPcc_{Freq.XC}$ (mmHg)	$IOPg_{Freq.XC}$ (mmHg)
Mean (M), standard deviation (SD)	M = 14.09, SD = 3.15	M = 10.08, SD = 1.34	M = 9.60, SD = 1.64	M = 14.83, SD = 3.09	M = 13.55, SD = 3.48
Means and SD of ICare RBT and ORA CH,CRF, IOPccC and IOPgC with Acuvue 1-Day Moist lenses					
Variable	RBT_{Moist} (mmHg)	CH_{Moist} (mmHg)	CRF_{Moist} (mmHg)	$IOPcc_{Moist}$ (mmHg0	$IOPg_{Moist}$ (mmHg)
Mean (M), standard deviation (SD)	M = 13.12, SD = 3.11	M = 9.81, SD = 1.40	M = 9.34, SD = 1.53	M = 15.06, SD = 2.61	M = 13.62, SD = 2.86
Means and SD of ICare RBT and ORA CH,CRF, IOPcc and IOPg with Acuvue Oasys lenses					
Variable	RBT_{Oasys} (mmHg)	CH_{Oasys} (mmHg)	CRF_{Oasys} (mmHg)	$IOPcc_{Oasys}$ (mmHg)	$IOPg_{Oasys}$ (mmHg)
Mean (M), standard deviation (SD)	M = 13.74, SD = 3.24	M = 10.59, SD = 1.64	M = 9.99, SD = 2.05	M = 14.00, SD = 2.68	M = 13.48, SD = 3.33

Table 4.3 Means, and SD of ICare RBT and ORA CH, CRF, IOPcc and IOPg without lenses.(Shaded cells indicate small differences in the means between the different measurements – these differences are not significant).

Hypothesis	Paired t-tests df = 49
H_o: RBT ≈ CH	*t* = 9.924, *p* = 0.000 (reject H_0)
H_o: RBT ≈ CRF	*t* = 13.25, *p* = 0.000 (reject H_0)
H_o: RBT ≈ IOPcc	*t* = -3.946, *p* = 0.000 (reject H_0)
H_o: RBT ≈ IOPg	*t* =-0.224, *p* = 0.823 (cannot reject H_0)*
With Pure Vision lenses	
H_o: RBT ≈ CH	*t = 6.459, p = 0.000 (reject H_0)*
H_o: RBT ≈ CRF	*t = 9.408, p = 0.000 (reject H_0)*
H_o: RBT ≈ IOPcc	*t = 8.537, p = 0.000 (reject H_0)*
H_o: RBT ≈ IOPg	*t = 6.115, p = 0.000 (reject H_0)*
With Frequency XC lenses	
H_o: RBT ≈ CH	*t* = 9.572, *p* = 0.000 (reject H_0)
H_o: RBT ≈ CRF	*t* = 14.759, *p* < 0.000 (reject H_0)
H_o: RBT ≈ IOPcc	*t* = -2.053, *p* = 0.045 (reject H_0)
H_o: RBT ≈ IOPg	*t* = 1.837, *p* = 0.072 (cannot reject H_0)*
With Acuvue 1-Day Moist lenses	
H_o: RBT ≈ CH	*t* = 7.687, *p* = 0.0000 (reject H_0)
H_o: RBT ≈ CRF	*t* = 11.698, *p* = 0.000 (reject H_0)
H_o: RBT ≈ IOPcc	*t* = -5.703, *p* = 0.000 (reject H_0)
H_o: RBT ≈ IOPg	*t* = -2.225, *p* = 0.031(reject H_0)
With Acuvue Oasys lenses	
H_o: RBT ≈ CH	*t = 7.560, p = 0.000 (reject H_0)*
H_o: RBT ≈ CRF	*t = 11.750, p = 0.000 (reject H_0)*
H_o: RBT ≈ IOPcc	*t = -0.729, p = 0.469 (cannot reject H_0)**
H_o: RBT ≈ IOPg	*t = 1.140, p = 0.260 (cannot reject H_0)**

Table 4.4 Results of the t-tests for the hypotheses tested, with and without lenses in situ. (* - grey shaded cells indicate hypotheses that cannot be rejected)

4.4.2 With Pure Vision lens

Hypotheses testing by 1-way ANOVA: H_0: RBTA ≈ CHA ≈ CRFA ≈ IOPccA ≈ IOPgA for data with Pure Vision lenses were overwhelmingly rejected: f = 34.25, p < 0.0001. The results were also supported by the means and standard deviations of the variables (Table 4.3). Results for the paired t-tests (Table 4.4) showed that with Pure Vision lenses the ICare RBT and ORA measurements (CH, CRF, IOPcc, and IOPg) were not comparable and the differences between the two was clinically and statistically significant. The modulus of Pure

Vision (1.1 Mpa) significantly affected the accuracy of IOP measurement with the ICare RBT.

4.4.3 With Frequency XC lens

Hypotheses testing by 1-way ANOVA: H_0: RBTB ≈ CHB ≈ CRFB ≈ IOPccB ≈ IOPgB for data with Frequency XC lenses were overwhelmingly rejected: $f = 102.56$, $p < 0.0001$. The results were also supported by the means and standard deviations of the variables (Table 4.3). Results for the paired *t*-tests (Table 4.4) showed that with Frequency XC lenses the ICare RBT and ORA IOPg measurements were comparable and the differences between the two were neither clinically nor statistically significant. The lower modulus of Frequency XC (0.3–0.4 MPa) was similar to the modulus of the cornea (M = 0.29, SD = 0.06 MPa) (Hamilton and Pye, 2008) and therefore affected the accuracy of IOP measurement with the ICare RBT less.

4.4.4 With Acuvue 1-Day Moist lens

Hypotheses testing by 1-way ANOVA: H_0: RBTC ≈ CHC ≈ CRFC ≈ IOPccC ≈ IOPgC for data with Acuvue 1-day Moist lenses were overwhelmingly rejected: $f = 116.84$, $p < 0.0001$. The results were also supported by the means and standard deviations of the variables (Table 4.3). Results for the paired *t*-tests for the different hypotheses tested (Table 4.4) showed that with Acuvue 1-day Moist lenses the ICare RBT and ORA measurements (CH, CRF, IOPcc, and IOPg) were not comparable and the differences between the two were clinically and statistically significant. The lower modulus of Acuvue 1-Day Moist (0.26 MPa) was similar to the modulus of the cornea (M = 0.29, SD = 0.06 MPa) (Hamilton and Pye, 2008) and therefore affected the accuracy of IOP measurements with the ICare RBT less.

4.4.5 With Acuvue Oasys lens

Hypotheses testing by 1-way ANOVA: H_0: RBTD ≈ CHD ≈ CRFD ≈ IOPccD ≈ IOPgD for data with Acuvue Oasys lenses were overwhelmingly rejected: $f = 64.37$, $p < 0.0001$. The results were also supported by the means and standard deviations of the variables (Table 4.3). Results for the paired *t*-tests for the different hypotheses tested (Table 4.4) showed that with Acuvue Oasys lenses the ICare RBT and ORA IOPcc, and the IOPg were comparable and the differences between the two were neither clinically nor statistically significant.

4.4.6 Bland-Altman analyses

Figure 4.1 (page 125) shows a Bland-Altman plot of the difference between ICare RBT and ORA CH without lenses (*n* = 50), while figure 4.2) shows the Bland Altman plot for all measurements (*n* = 250) including measurements with and without lenses.

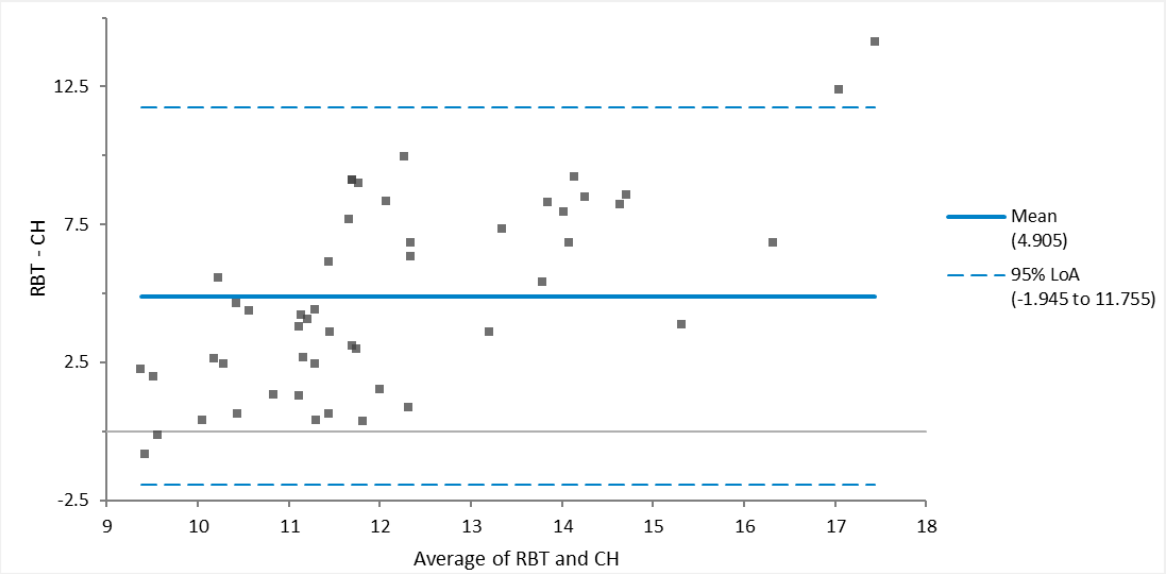


Figure 4.1 Bland-Altman plot of the difference or bias between ICare RBT and ORA CH without lenses (*n* = 50). Note the tendency of the bias to increase with higher IOP measurements.

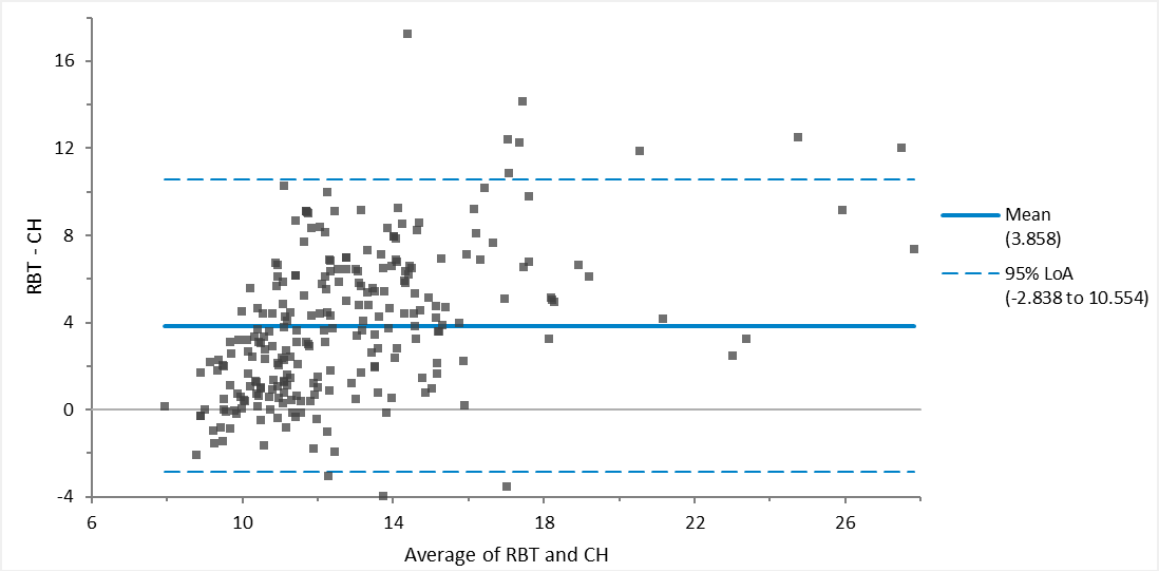


Figure 4.2 Bland-Altman plot of the difference or bias between ICare RBT and ORA CH for all measurements (*n* = 250) including measurements with and without lenses. Note the tendency of the bias to increase with higher IOP measurements.

The difference between RBT and CH without lenses was M = 4.91, SD = 3.46 mmHg (95% CI [3.91 to 5.89]). Visual examination of the scatter plot revealed two outliers. There was a poor linear correlation between the measurements: r = 0.13. The difference between RBT and CH for all measurements was M = 3.86, SD = 3.42 (95% CI [3.43 to 4.283). The scatter plot revealed a few outliers and the linear correlation between the measurements was poor: r = 0.58. The differences between these two measurements were clinically as well as statistically significant.

Figure 4.3 (page 126) shows a Bland-Altman plot of the difference between ICare RBT and ORA CRF without lenses (n = 50), while figure 4.4 shows the Bland Altman plot for all measurements (n = 250) including measurements with and without lenses.

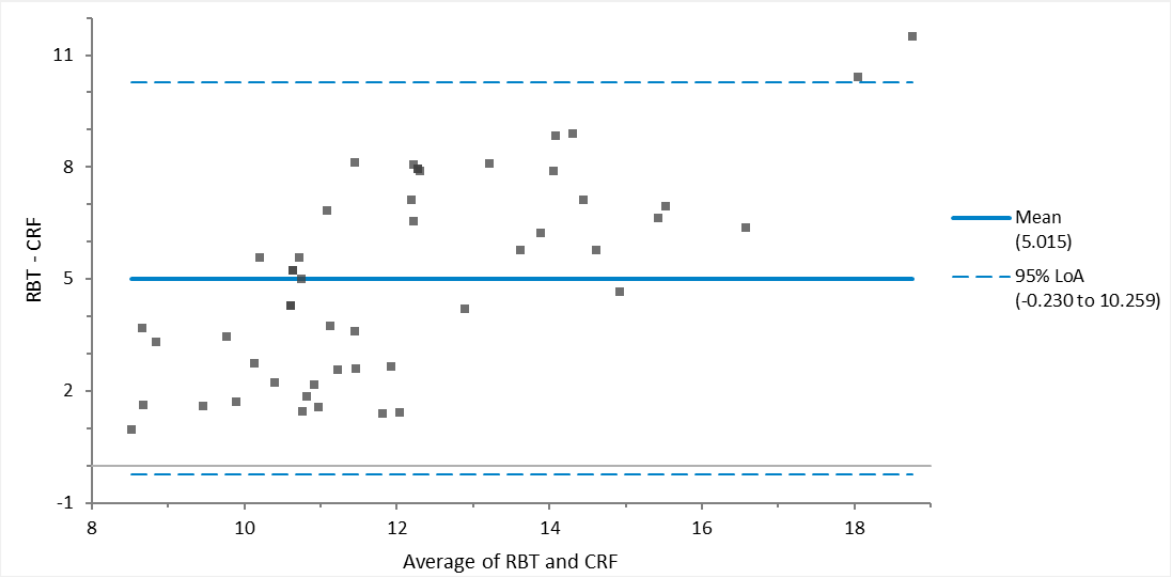


Figure 4.3 Bland-Altman plot of the difference or bias between ICare RBT and ORA CRF without lenses (n = 50). Note the tendency of the bias to increase with higher IOP measurements.

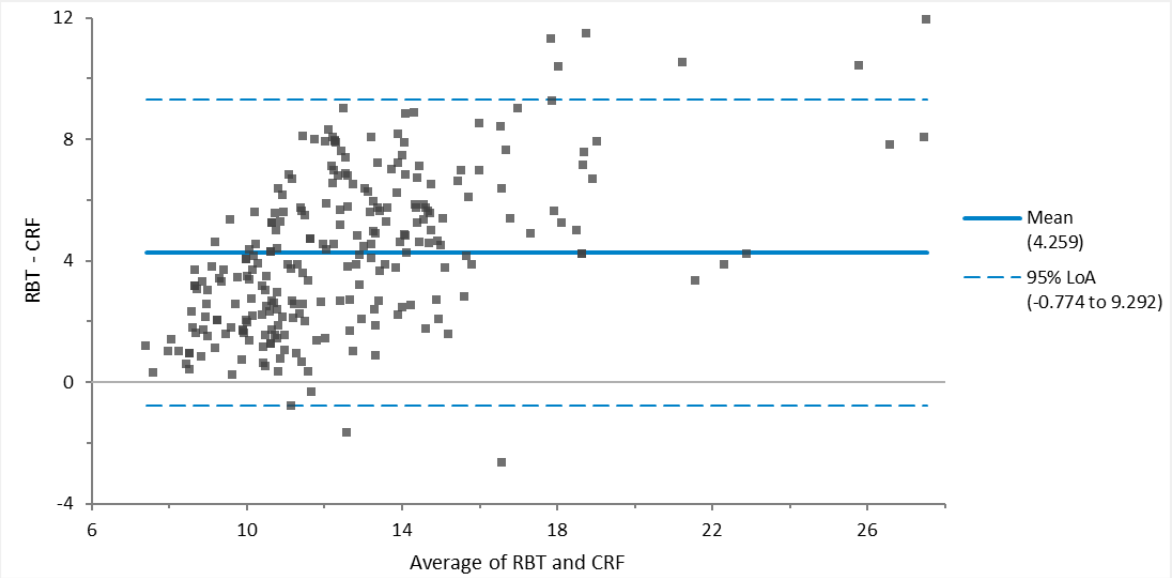


Figure 4.4 Bland-Altman plot of the difference or bias between ICare RBT and ORA CRF for all measurements (*n* = 250) including measurements with and without lenses. Note the tendency of the bias to increase with higher IOP measurements.

The difference between RBT and CRF without lenses was M= 5.02, SD = 2.68 mmHg (95% CI [4.25 to 5.77]). Visual examination of the scatter plot revealed two outliers. There was a poor linear correlation between the measurements: *r* = 0.63. The difference between RBT and CRF for all measurements was M = 4.26, SD = 2.57 (95% CI [3.93 to 4.58]). The scatter plot revealed a few outliers and the linear correlation between the measurements was good: *r* = 0.80. The differences between these two measurements were clinically as well as statistically significant.

Figure 4.5 (page 128) shows a Bland-Altman plot of the difference between ICare RBT and ORA IOPcc without lenses (*n* = 50), while figure 4.6 shows the Bland Altman plot for all measurements (*n* = 250) including measurements with and without lenses.

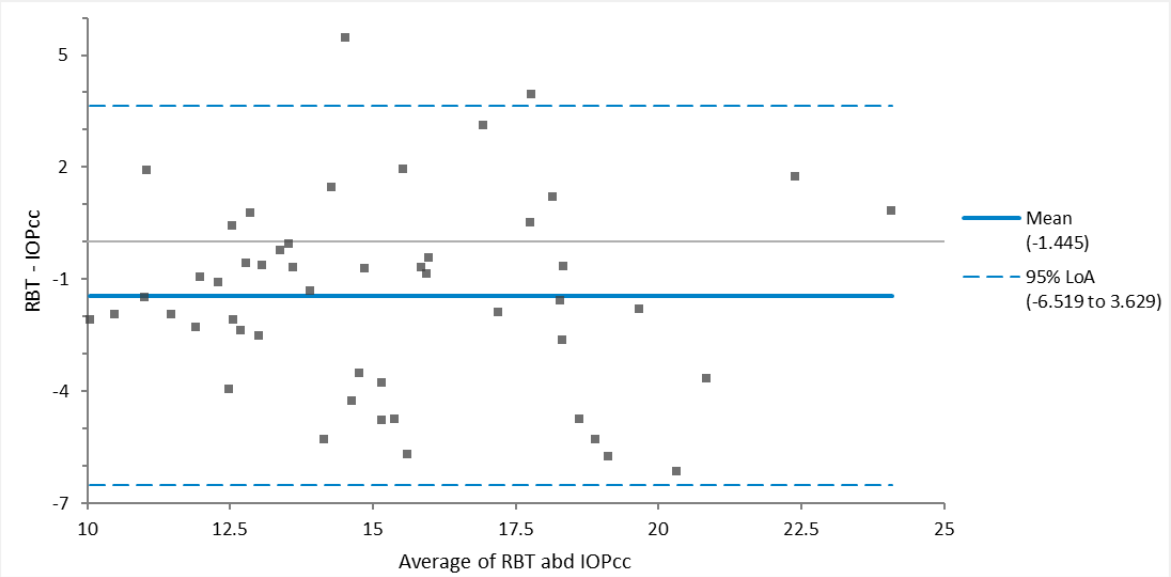


Figure 4.5 Bland-Altman plot of the difference or bias between ICare RBT and ORA IOPcc without lenses (*n* = 50).

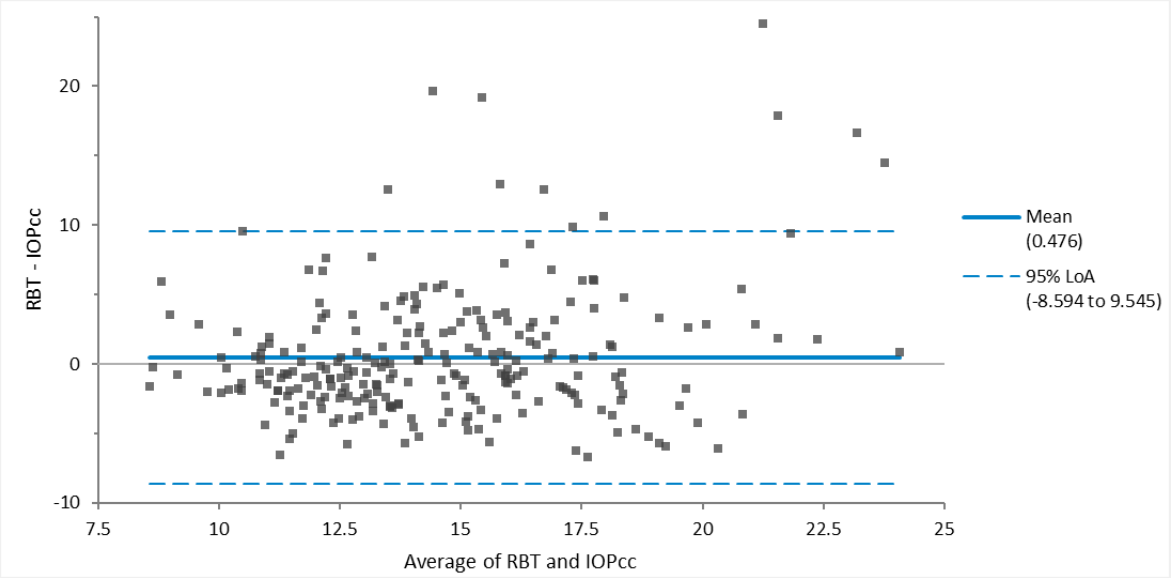


Figure 4.6 Bland-Altman plot of the difference or bias between ICare RBT and ORA CRF for all measurements (*n* = 250) including measurements with and without lenses.

The difference between RBT and IOPcc without lenses was M = -1.45, SD = 2.59 mmHg (95 % CI [-2.18 to -0.71]) with the ORA IOPcc significantly overestimating ICare RBT. Visual examination of the scatter plot revealed two outliers. There was a fairly good linear correlation between the measurements: *r* = 0.717. The difference between RBT and IOPcc for all measurements was M = 0.476, SD = 4.627 (95% CI [-0.10 to 1.05]). The scatter plot revealed a few outliers and the linear

correlation between the measurements was poor: r = 0.262. The differences between these two measurements were neither clinically nor statistically significant.

Figure 4.7 (page 129) shows a Bland-Altman plot of the difference between ICare RBT and ORA IOPg without lenses (n = 50), while Figure 4.8 shows the Bland Altman plot for all measurements (n = 250) including measurements with and without lenses.

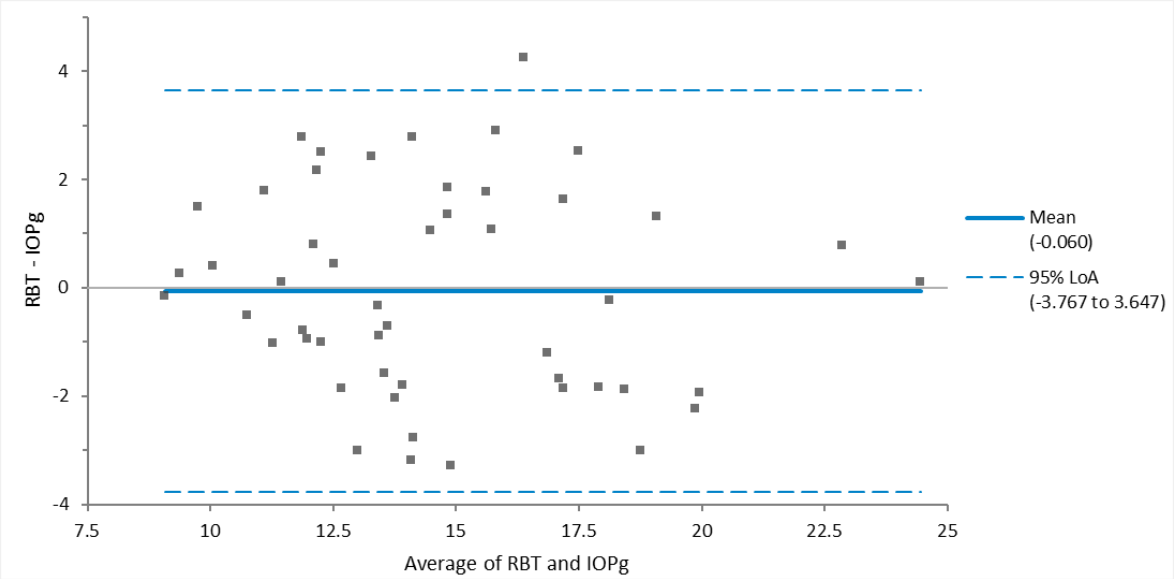


Figure 4.7 Bland-Altman plot of the difference or bias between ICare RBT and ORA IOPg without lenses (n = 50).

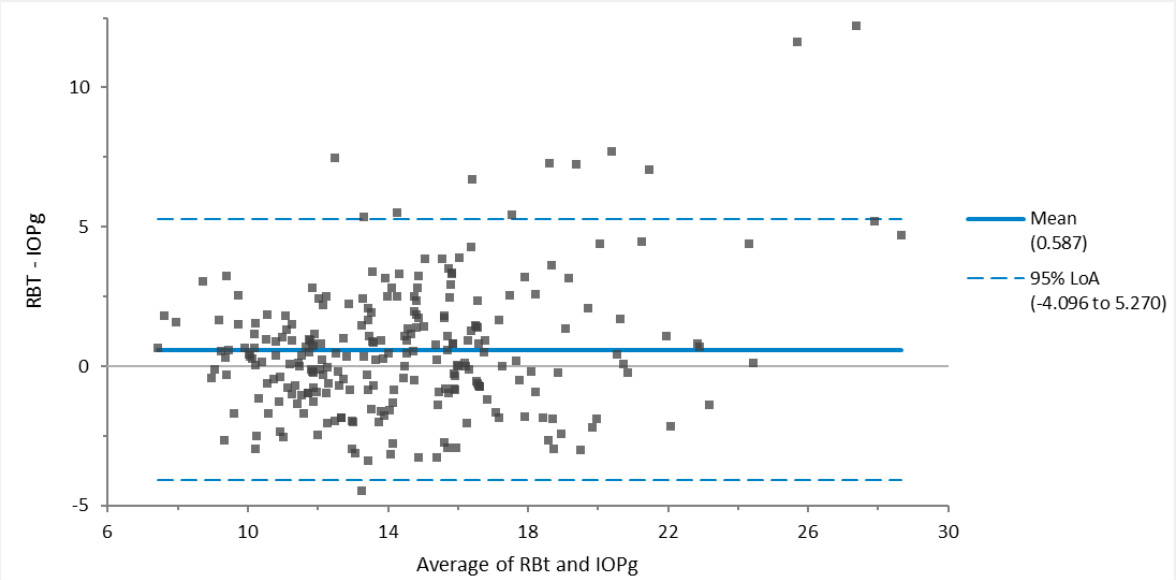


Figure 4.8 Bland-Altman plot of the difference or bias between ICare RBT and ORA IOPg for all measurements (*n* = 250) including measurements with and without lenses.

The difference between RBT and IOPg without lenses was M = -0.06, SD = 1.89 mmHg (95% CI [-0.60 to 0.48]). Visual examination of the scatter plot revealed one outlier. There was excellent linear correlation between the measurements: *r* = 0.85. The difference between RBT and IOPg for all measurements was M = 0.59, SD = 2.39 (95% CI [0.290 to 0.885]). The scatter plot revealed a few outliers and the linear correlation between the measurements was excellent: *r* = 0.82. The differences between these two measurements (with and without lenses) were neither clinically nor statistically significant.

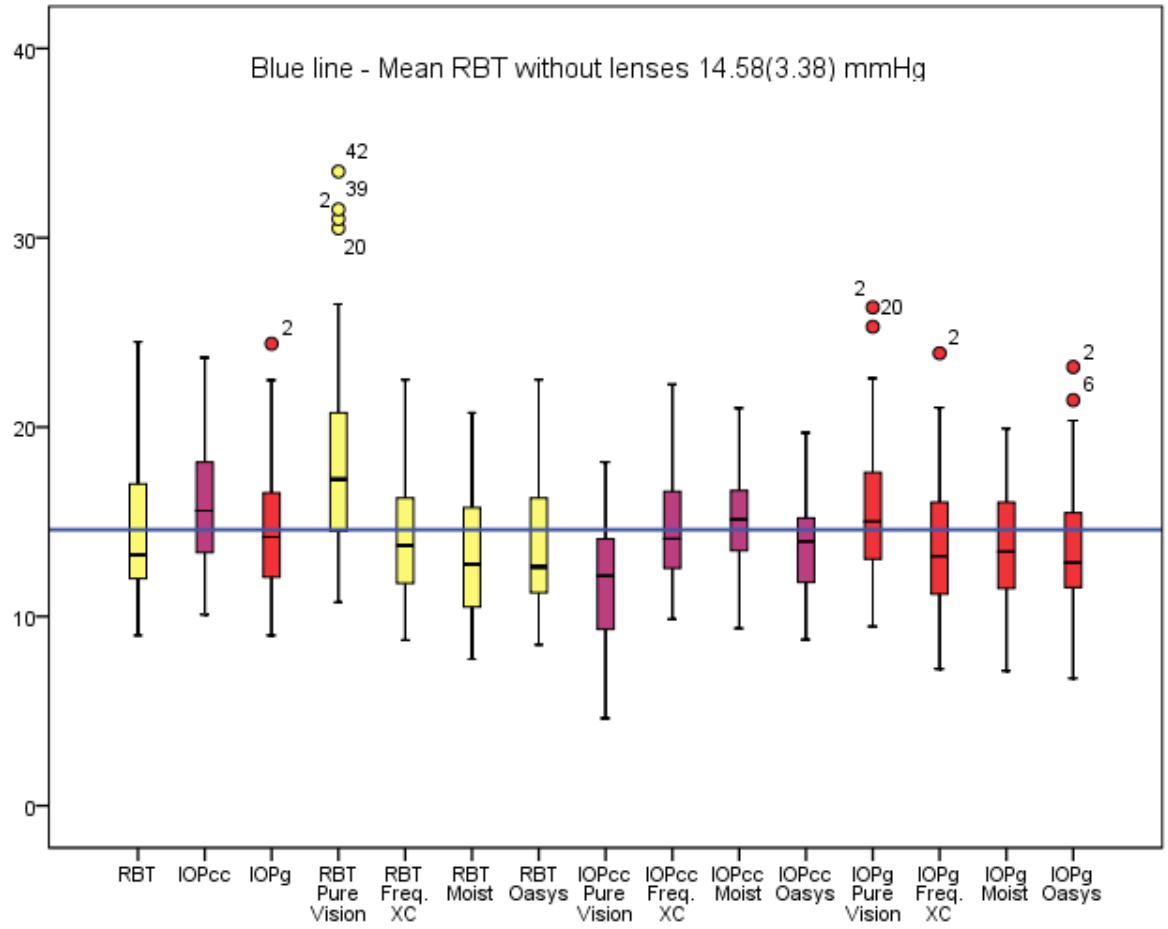


Figure 4.9 Box plots indicating the medians, upper and lower quartiles of the variables measured(ICare – yellow boxes, ORA IOPcc – purple boxes, and IOPg – orange boxes). Outliers are indicated by circles. The data represents measurements with and without contact lenses in situ in mmHg. The blue line indicates mean RBT without lenses. The means and confidence intervals show some overlap indicating that the groups are fairly similar. Further analyses are needed to reveal statistically significant differences between the groups (RBT = rebound tonometry, IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP)

4.5 Discussion

This experimental chapter aimed to add more information to the clinical comparison between ICare RBT and ORA IOP measurements. In the case of the ICare RBT, literature shows that corneal biomechanical properties (CH and CRF) play a major role in the accuracy of the IOP measurements, more so than CCT (Chui et al., 2008; Jorge, Gonzales-Meijome, et al., 2008; Salvetat et al., 2011). The other variables important to consider include CCT, corneal curvature, and refractive error (Detry-Morel et al., 2006; Lopez-Caballero et al., 2007; Avitabile et al., 2010; Salvetat et al., 2011; Hohmann

et al., 2012; Rao et al., 2012). With regard to the ORA, many of the same variables influence the accuracy of the measurements but not all of them influence each one of the four measurements. Age, corneal curvature, CCT, and corneal biomechanics are important variables which can affect the accuracy of the ORA measurements (Luce, 2005; Kotecha et al., 2006; Kniestedt et al., 2008; Kotecha et al., 2010). Individually, different measurements are affected differently by the variables − CRF is closely associated with CCT; IOPcc is not significantly associated with CCT; and IOPg is associated with CCT, corneal curvature as well as axial length (Moreno-Montanes et al., 2008; Sullivan-Mee et al., 2009; Kotecha et al., 2010; Terai et al., 2012; Wang et al., 2013). The ORA employs the same principles as the NCT and it was therefore was significantly affected by the OPA while the ICare RBT was not affected by the OPA (Moreno-Montanes et al., 2008; Sullivan-Mee et al., 2009; Kotecha et al., 2010; Wang et al., 2013). Jorge et al. (2008) evaluated the correlations between the corneal biomechanical properties with the IOP obtained with the ICare RBT. They found that the ICare RBT displayed higher and more variable results than the ORA with the IOPg and IOPcc being more reliable. ICare RBT had a strong positive correlation with IOPg, less so with IOPcc and CRF, and a poor correlation with CH. From their results they postulated the strong correlation with CRF indicates that ICare RBT has a higher correlation with the biomechanical properties of the cornea than CCT (Jorge, Gonzales-Meijome, et al., 2008). The ORA IOPcc and IOPg tend to overestimate IOP (results varied between 3 – 7 mmHg depending on the study) compared to GAT (Martinez-de-la-Casa, Garcia-Feijoo, Fernandez-Vidal, et al., 2006; Lau and Pye, 2011; Cook et al., 2012). Although the ICare RBT was able to estimate IOP within a range of ±3 mmHg in more than 80% of the population (Fernandes et al., 2005; Iliev et al., 2006; Munkwitz et al., 2008), most studies show it overestimates GAT IOP measurements (Table 1.5).

The results of the current study showed the ICare RBT and ORA IOPg measurements were comparable. Most tonometers measure in increments of 1 mmHg (Doughty and Zaman, 2000). Also, studies have shown that calibration errors of 2 mmHg are common (Choudhari et al., 2009). Therefore, for the purposes of this study differences of more than 1 mmHg were considered clinically significant. Without lenses the RBT measurement was M = 14.58, SD = 3.35 mmHg and IOPg M = 14.64, SD = 3.58 mmHg. The difference between the two measurements, according to the Bland-Altman analyses was M = -0.06, SD = 0.59 mmHg and a strong linear relationship existed between the two measurements: r = 0.85. ANOVA and t-tests confirmed the hypothesis that the two measurements were not significantly different: t = -0.04, p = 0.96. With the Pure Vision lenses the ICare RBT and ORA metrics did not compare well and the RBT significantly overestimated the IOP

when compared to the ORA. Pure Vision has a high modulus of elasticity (1.1 MPa) which might have affected the biomechanics of the cornea/lens combination and therefore the ICare RBT measurement.

With the Frequency XC lens the RBT measurement was M = 14.09, SD = 3.15 mmHg and IOPg M = 13.55, SD = 3.48 mmHg. Although the ANOVA showed the RBT and ORA metrics were not comparable the *t*-test showed the RBT and IOPg values were comparable (t = 2.06, p = 0.045) with the differences between them clinically and statistically insignificant. Although the hypothesis that RBT and IOPcc was comparable was rejected by the ANOVA and *t*-tests (t = -2.28, p= 0.03) the mean measurement for IOPcc (M = 14.83, SD = 3.09) was statistically significant: however, clinically it was not significantly different from the RBT mean (M = 14.09, SD = 3.15).

With the Acuvue 1-Day Moist lens the RBT measurement was M = 13.62, SD = 2.86 mmHg and IOPg M = 13.12, SD = 3.11 mmHg. The ANOVA showed RBT and IOPg values were comparable (f = 1.44, p = 0.2365), the *t*-tests rejected this hypothesis (t = -2.47, p < 0.017). But, although the difference between the means was statistically significant, clinically it was not significant.

With the Acuvue Oasys lens the RBT measurement was M = 13.74, SD = 3.24 mmHg, IOPcc M =14.00, SD = 2.68 mmHg, and IOPg M = 13.48, SD = 3.33 mmHg. The ANOVA confirmed the hypothesis that the RBT, IOPcc and IOPg measurements were comparable (f = 1.17, p = 0.2841 for IOPcc and f = 1.72, p = 0.1957 for IOPg). This hypothesis was further confirmed by the *t*-tests which indicate that the RBT and ORA IOPcc and IOPg measurements were statistically and clinically comparable (t =-1.08, p = 0.284 for IOPcc and t = 1.31, p < 0.196 for IOPg).

Finally, Bland-Altman analyses of all the measurements with as well as without lenses indicated that the mean differences between RBT and IOPcc were M = 0.48, SD = 4.63 mmHg with a weak linear correlation (r = 0.26) between the two measurements. The difference was neither statistically nor clinically significant. The mean difference between RBT and IOPg was M = 0.59, SD = 2.39 mmHg with a strong linear correlation (r = 0.82) between the two measurements. The difference was neither clinically nor statistically significant.

4.6 Conclusion

The present study confirms that the ICare RBT and ORA IOPg pressure measurements were highly correlated and comparable. Clinically the differences between the two measurements were less than

0.60 mmHg. This difference was apparently not affected by the presence of a contact lens on the eye.

With the Pure Vision lenses the ICare RBT and ORA metrics did not compare well and the RBT significantly overestimated the IOP compared to the ORA. Pure Vision has a high modulus of elasticity (1.1 MPa) which might have affected the biomechanics of the cornea/lens combination and therefore the ICare RBT measurements. The ICare RBT and IOPcc pressure measurements were also correlated and comparable but to a lesser extent than the ICare RBT and IOPg measurements. Clinically the difference was larger than 1 mmHg with ORA IOPcc overestimating the ICare RBT. However, when the measurements with contact lenses were included in the analysis, the difference becomes clinically insignificant (0.50 mmHg). This could be ascribed to the induced biomechanical differences and their effects on the ICare RBT measurements. The lower correlation with ORA IOPcc also suggests that ICare RBT measurements were affected by corneal biomechanical properties and not only the IOP or CCT of the eye which confirms previously reported findings (Jorge, Gonzales-Meijome, et al., 2008). ORA CH and CRF measurements were neither clinically nor statistically comparable to ICare RBT measurements.

All measurements in this study were collected at one specific sitting and it is therefore conceivable that variation in measurement may occur from one visit to the next with or without a specific lens which limits the clinical usefulness of the results of this study. The study should be expanded to collect data over a number of consecutive visits to determine the variability of the measurements thereby validating the clinical usefulness of the results obtained in this study.

4.7 Summary of findings

- ORA CH and CRF metrics were neither clinically nor statistically comparable with ICare RBT measurements.
- ICare RBT and ORA IOPg were clinically and statistically comparable but the ICare RBT was less comparable with ORA IOPcc.
- With the high modulus Pure Vision lens *in situ* the ICare RBT overestimated ORA IOPg and IOPcc. The difference became clinically insignificant when the data for measurements with all the lenses were considered (< 0.60 mmHg).

Chapter 5

Intraocular pressure and corneal biomechanical metric measurements through soft disposable contact lenses with the ICare rebound tonometer and the Reichert ocular response analyser

5.1 Introduction

Chapter three showed that the intraobserver reliability (test-retest repeatability by the same observer) of the ICare RBT and the ORA produced repeatable and consistent results even when measurements were performed with disposable contact lenses on the eye. Interobserver reliability (test-retest repeatability between different observers) also produced repeatable and consistent results with the ICare RBT. Chapter four confirmed that the ICare RBT and ORA IOPg pressure measurements were highly correlated and comparable. Clinically the differences between the two measurements were less than 0.60 mmHg and this difference seemed not to be affected by the presence of a contact lens on the eye. ICare RBT and IOPcc pressure measurements were also correlated and comparable but to a lesser extent than ICare RBT and IOPg measurements.

Although the diagnosis of glaucoma relies on many clinical tests as well as risk factor analyses, accurate IOP measurements form an essential part of the diagnosis and treatment of glaucoma (Quigley and Addicks, 1981; Lusky et al., 1993; Cartwright and Anderson, 1998; Quigley, 2001; Maier et al., 2005; Heijl et al., 2008). In certain clinical situations it may be necessary to measure the IOP with a soft contact lens on the eye. Examples include patients wearing bandage contact lenses for the treatment of corneal injuries after corneal surgery such as LASIK, PRK, and corneal crosslinking (Arora et al., 2004; Blackmore, 2010; Markoulli et al., 2012), avoiding topical anaesthesia, to minimise trauma, and when the corneal surface is extremely irregular (Zeri et al., 2015). In situations where patients wear extended wear contact lenses and it may not be possible to remove the lenses for IOP measurement. The latter especially applies when the patient makes use of the newer ICare HOME (TA022) tonometer (Liang et al., 2009; Asrani et al., 2011; Flemmons et al., 2011). This tonometer was specifically designed for home use by glaucoma patients who need regular IOP monitoring (Tiolat, 2015). The tonometer uses the same rebound technology of ICare TAO1i, but integrates EyeSmart eye recognition and EasyPosalignment features to improve usability. IOP is determined by impact duration or deceleration of a magnetic solenoid probe directed at the central cornea, and computed from six consecutive measurements. The ICare HOME has shown good

agreement with the current reference standard Goldmann Applanation Tonometer (GAT) when used for self-measurement by adults, and by a caregiver on a child (Dabasia et al., 2015; Mudie et al., 2016). The device has also demonstrated good repeatability. Mudie et al. (2016) found that the ICare HOME and ICare TA01i (used in the this programme of research) compared well with mean differences M = 0.30, SD = 2.82 mmHg (Mudie et al., 2016).

More recent developments include the use of soft contact lenses for sustained drug delivery to the eye. The soft lenses are impregnated with the drug required for therapy which is then released into the eye over a period of time to treat a specific diseases such as glaucoma, microbial keratitis, and ocular inflammation (Braga et al., 2011; Peng and Chauhan, 2011; Gupta and Aqil, 2012; Peng et al., 2012; Tieppo, Pate, et al., 2012; Tieppo, White, et al., 2012). It is important to evaluate the accuracy and repeatability of IOP measurements with and without contact lenses using the ICare tonometer as well as the newer Reichert ORA to validate clinical decisions based on IOP measurements with these instruments.

Literature shows that various studies have been conducted on the ICare tonometer; yet in only two the Reichert ORA was used to measure IOP with contact lenses on the eye (Lam and Tse, 2014; Sapkota et al., 2014). Conversely, the ORA is essentially a noncontact tonometer and a number of studies have been conducted on the accuracy of the NCT measurement with contact lenses *in situ*. These results provided the first evidence that continued contact lens wear does not adversely affect IOP (Janoff, 1977). In Table 5.1 the findings of the different studies dealing with IOP measurement with contact lenses *in situ* using the NCT, ICare RBT and, more recently, the ORA are summarised. These findings substantiate that accurate measurement of intraocular pressure with contact lenses *in situ* was possible with a variety of instruments. However, various factors seem to affect the accuracy of the measurements including lens prescription or power, lens modulus or stiffness, lens thickness, lens anterior curvature, and lens hydration. The generally accepted tenet in the literature is that as long as the lens thickness does not exceed 0.15 mm to 0.30 mm and it is fairly new, well hydrated, and has a low prescription power the accuracy of the measurements would not significantly differ from measurements without contact lenses on the eye. It is further accepted that higher power plus lenses lead to overestimation, and higher power minus lenses to underestimation of intraocular pressure (McMonnies, 1986; Insler and Robbins, 1987; Sugimoto-Takeuchi et al., 1991; Mark et al., 1992; Scibilia et al., 1996; Schollmayer and Hawlina, 2003; Patel and Illahi, 2004; Kerautret et al.,

2008; Patel and Stevenson, 2009; Liu et al., 2011; Zeri et al., 2011; Firat et al., 2012; Ogbuehi, 2012; Anton et al., 2013; Lam and Tse, 2014).

Study	**Methods/Subjects**	**Lenses used**	**Results**
McMonnies, (1986)	NCT 5 eyes of albino rabbits	Hydrogel lathe cut lenses, -5.00 and 38% water content, CT (0.057 - 0.219 mm) Spun cast U3 & B4 (Bausch & Lomb) hydrogel lenses, CT (0.071 and 0.152 mm)	No effect on IOP as long as the CT < 0.15 mm.
Insler & Robbins, (1987)	NCT 23 subjects and 43 eyes	Plus and minus powered hydrogel lenses	Measured IOP was highly correlated with lens power. Plus lenses = higher measured IOP.
Sugimoto-Takeuchi et al. (1991)	NCT 18 subjects and 29 eyes	Plano-T & Plano B4 (Bausch & Lomb) therapeutic hydrogel lenses	No effect on IOP.
Mark et al. (1992)	TonoPen and NCT 9 cadaver eyes	Bandage hydrogel lenses on cadaver eyes	NCT accurate with and without a therapeutic contact lens. TonoPen equally inaccurate with and without a therapeutic contact lens.
Scibilia et al. (1996)	TonoPen and NCT Group A 5 subjects and 10 eyes Group B 10 subjects and 10 eyes	Hydrogel lenses, O4 (Bausch & Lomb), Acuvue (Johnson & Johnson), Permalens (Coopervision)	No statistically significant differences with or without the lenses.
Schollmayer and Hawlina (2003)	NCT 80 subjects and 120 eyes	Silicone hydrogel lenses of different power (Focus Night & Day – Ciba Vision)	Lower measured IOP over low minus lenses, but higher IOP measured with plus power lenses.
Patel and Illahi (2004)	NCT	-15.00 to +3.00 D hydrogel	With CT < 0.30 mm and

	8 subjects and 8 eyes	lenses	power < +3.00 D, accurate measurements could be obtained with NCT.
Study	**Methods/Subjects**	**Lenses used**	**Results**
Patel and Stevenson (2009)	NCT 25 subjects and 50 eyes	Low water content silicone hydrogel lenses (Focus Night & Day [Ciba Vision]) and high water content hydrogel lens (Focus Dailies [Ciba Vision]). Power varied between -7.50 to +6.00 D	Lens power, modulus, and IOP affect the accuracy of the measurement.
Zeri et al. (2011)	RBT 68 subjects and 136 eyes	Hydrogel (Acuvue 2 [Johnson & Johnson]) and silicone hydrogel (Acuvue Oasys [Johnson & Johnson])	RBT can be accurately performed over silicone hydrogel lenses. However, measurement with low power plus and hydrogel lenses was lower than without them.
Firat et al. (2012)	NCT and DCT 40 subjects and 40 eyes	Silicone hydrogel plano power lens (Focus Night & Day [Ciba Vision])	Statistically insignificant difference with NCT. Statistically significant difference with DCT.
Ogbuehi et al. (2012)	NCT 39 subjects and 39 eyes	High water content hydrogel, Dailies – nelfilcon A (Ciba Vision). 69% water content. Two powers used, +6.00 and -6.00 D with CT 0.207 and 0.085 mm respectively	Statistically significant increase in measured IOP with +6.00 D lenses (3 mmHg). Statistically significant decrease in IOP with -6.00 D lenses. Difference between two lens powers was 3.6 mmHg. Reliable estimates of IOP can be made through high water content minus lenses up to -6.00 D. CT of +0.2 mm results in unreliable estimates of IOP.
Lam and Tse (2014)	DCT and ORA CH and CRF 74 subjects and 148 eyes	Silicone hydrogel lenses' high Modulus Focus Night and Day (Ciba Vision) and	No significant difference in CH and CRF measured through the lenses. High

		low modulus Acuvue Advance (Johnson & Johnson)	modulus silicone hydrogel lenses demonstrated greater effect on IOP 95% LoA: 2.73 mmHg than low modulus lenses 95% LoA: 1.0 mmHg. DCT can be performed reliably over low modulus silicone hydrogel lenses.
Study	**Methods/Subjects**	**Lenses used**	**Results**
Sapkota et al. (2014)	ORA IOPcc and IOPg 28 subjects and 56 eyes	Silicone hydrogel one day lens (Acuvue True Eye [Johnson & Johnson]) and hydrogel one day (Daily Aqua Comfort Plus [Ciba Vision]). Power used was a -3.00 D lens on 28 subjects without ocular pathology	Both IOPg and IOPcc when measured with contact lenses were statistically lower than without contact lenses ($p < 0.05$). With True Eye IOPg and IOPcc were M = 0.88, SD = 2.04 and M = 1.55, SD = 2.16 mmHg lower respectively. With Aqua Comfort the values were M = 1.03, SD = 1.93 mmHg and M = 1.62, SD = 3.12 mmHg respectively. To measure IOP accurately with the ORA, contact lenses should be removed.
Rimayanti et al. (2014)	GAT and NCT 21 subjects and 21 eyes	Acuvue 2 (Johnson & Johnson), etafilcon A, 58% water content, 8.70 mm base curve, 14.00 mm diameter, 40 Dk/t, 0.084 mm CT, modulus 0.25 MPa, power -5.00, -0.50, and +5.00 D	GAT without lenses was similar to NCT. With higher plus powered thicker lenses NCT overestimated IOP. With higher minus powered thinner lenses NCT underestimated IOP. Differences in IOP measurement depend on lens power and the radius of ocular surface curvature affects the ocular surface displacement and IOP

			readings.
Study	**Methods/Subjects**	**Lenses used**	**Results**
Takenaka et al. 2015	NCT, GAT, ICare RBT, TonoPen XL 26 subjects and 26 eyes	Acuvue 2 (Johnson & Johnson), etafilcon A, 58% water content, 8.70 mm base curve, 14.00 mm diameter, 40 Dk/t, 0.084 mm CT, modulus 0.25 MPa, power -5.00, -0.50, and +5.00 D	GAT without lenses was used as the standard against which the measurements with lenses were tested. The authors concluded that the NCT and ICare RBT gave the most accurate IOP measurements with contact lenses *in situ.*

Table 5.1 Summary of previous studies that examined the validity of measuring IOP with contact lenses *in situ* with the NCT, ORA and RBT.(RBT = rebound tonometry; NCT = non-contact tonometry; DCT = dynamic contour tonometry)

Statistical power calculation (G*Power 3.0.10, Franz Faul, Universität Kiel, Germany) required a sample size of at least 50 subjects. Four commonly prescribed disposable soft contact lenses of different powers (range -6.00D to +6.00 D, minus lenses *n* = 32 and plus lenses *n* = 18) and different materials (hydrogel and silicone hydrogel) were used (Table 2.1). This study specifically aimed to investigate the accuracy of IOP and biomechanical metric measurement with the contact lenses *in situ* using the ICare RBT and Reichert ORA.

5.2 Subjects and methods

Chapter two presented a complete description of the subjects, materials and methodology used in this specific study. To evaluate the accuracy of IOP and corneal biomechanical measurements with the ICare RBT and ORA with contact lenses *in situ*, two experienced optometrists (DJB and GHK) took two ICare RBT measurements on every single subject enrolled in the study according to the protocol established for the study of each subject's left eye with and without each and every contact lens *in situ*. One experienced optometrist (DJB) took four ORA measurements according to the aforementioned protocol established for the study of each subjects left eye with and without each of the contact lenses *in situ*. The measurements were recorded by an experienced optometric assistant (MLG) blinding the optometrists and reducing observer bias. The measurements with and without contact lenses *in situ* were compared for both the ICare RBT as well as the Reichert ORA.

5.3 Statistical analysis

Most tonometers measure in increments of 1 mmHg (Doughty and Zaman, 2000). Interobserver repeatability of the ICare RBT varies by 2 − 3 mmHg (Proctor et al., 2010). The current study showed

that 95% of repeated measurements were within 4.39 mmHg of each other (Table 3.3), and interobserver reliability without lenses was M = 0.10, SD = 2.2 mmHg; with all measurements M = 0.40, SD = 2.1 mmHg which is considerably better than previously reported values. Observer DJB's measurements were consistently higher than those of observer GHK. Without lenses the difference was 0.09 mmHg and when all the measurements were considered, it was 0.37 mmHg which is not clinically significant. Intersessional measurements have limits of agreement between repeated readings of ±5 mmHg (Davies et al., 2006). The current study showed that 95% of the measurements were within ±3.5 mmHg (Table 3.2)). The repeatability and reproducibility of the ORA varies between 4.3 to 4.7 mmHg (Kotecha et al., 2010) which is similar to previous findings with non-contact tonometers (Tonnu et al., 2005). This current study showed the intraobserver reliability of the measurements with the ORA was 2.86 mmHg for CH; 3.44 mmHg for CRF; 4.94 mmHg for IOPcc; and 3.75 mmHg for IOPg (Table 3.4). Clinically IOP variation within 3 mmHg is considered acceptable (Mackie et al., 1996; Choudhari et al., 2009; Lam and Tse, 2014). Differences ≥ 1 mmHg were considered clinically significant.

Data were analysed using the statistical package SPSS v. 22.0 and Microsoft Excel (Microsoft Corporation, Redmond, WA) with Analyse-it v 4.10.2 (Analyse-it Software, Ltd.). Researchers recommend the Shapiro-Wilk test as the best choice for testing the normality of the data (Ghasemi and Zahediasl, 2012). This test confirms a normal distribution of the data (Appendix 6).

The Paired *t*-tests were performed to test the hypothesis that measurements with the ICare RBT and ORA and K-readings without and with contact lenses *in situ* were equal. The *t*-test is the easiest way to compare two means; it estimates both the means and SD which introduces a dependency on sample size. However, Norman and Streiner (2008) advise this test is not appropriate when there are more than two groups or when individuals in one group are matched to individuals in another group (Norman and Streiner, 2008). $p < 0.05$ was considered significant. Bland Altman plots were used to assess the differences in IOP reading without and with every kind of contact lens as function of IOP value. The differences between the two measurements were plotted against the mean of the two measurements. The mean of the differences and the standard deviation of the differences were also calculated. The closer the mean of the differences was to zero and the smaller the value of the standard deviation of the differences the better the agreement between measures. Also calculated were 95% limits of agreement as well as 95% confidence intervals for these limits of agreement were also calculated (Bland and Altman, 1986).

5.4 Results

Figures 2.1 and 2.2, show the range and frequency distribution of the mean spherical equivalent refractive error (MSE) and corneal astigmatism in the study population. Twenty-six (26) subjects had cylindrical refractive errors (M = -0.94D, SD = 0.58, range -0.25 to -2.50D). Tables 5.2 to 5.4, show the means, SD, and *p*-values for the ICare and ORA measurements with and without contact lenses for the entire sample as well as minus and plus lenses separately. Table 2.2 gives the descriptive statistics for all the variables measured.

No data was forthcoming from the manufactures on the lens thickness for the different lens powers used in the study. However, the Scheimpflug corneal tomography system (Pentacam) was used to measure not only the combined cornea contact lens thickness but also the combined cornea contact lens curvature. Although Scheimpflug photography provides images of the anterior segment with minimal distortion, the distortion of the cornea and lens itself distort the image. Therefore biometrical measurements in the anterior segment such as corneal curvature, changes in lens curvature during accommodation, depth of anterior chamber angle, always have to be corrected by specific algorithms. The amount of correction depends on the depth of the layer in question, meaning that each refractive zone adds a small amount of distortion to the path of the light rays (Wegener and Laser-Junga, 2009). The combined cornea contact lens thickness and curvature measured in this study could conceivably be affected by introduced distortion which is not corrected by the pre-pre-programmed algorithms. The mean CCT without lenses was M = 531.46, SD = 35.51 µm and K was M = 7.80, SD = 0.28 mm.

Although the corneal curvature (K) was expected to change with the contact lenses on the cornea the changes were neither clinically nor statistically significant. When analysing the data for the entire sample (plus and minus lenses), the results were:

- K with the Pure Vision lens was M = 7.79, SD = 0.42 mm, and the difference between the K without the lens was M = 0.01, SD = 0.40 mm (95% CI [-0.183 to 0.122]), $t = 0.285$, $p = 0.777$.
- With the Frequency XC lens the K was M = 7.93, SD = 0.44 mm and the mean difference between K without the lens was M = -0.13, SD = 0.41 mm (95% CI [-0.242 to -0.001]), $t = -2.01$, $p = 0.050$.
- With the Acuvue 1-Day Moist lens K was M = 7.88, SD = 0.39 mm and the mean difference between K without the lens was M = -0.082, SD = 0.35 mm (95% CI [-0.181 to 0.016]), $t = -1.53$, $p = 0.133$.

- Lastly with the Acuvue Oasys lens K was M = 7.90, SD = 0.43 mm and the mean difference between K without the lens was M = -0.102, SD = 0.407 mm (95% CI [-0.218 to 0.0132]), *t* = -1.652, *p* = 0.105.

Splitting the data between plus and minus lenses it was apparent that the K-readings with the plus lenses were steeper (M = 7.60, SD = 0.45 [95% CI 7.494 to 7.704] mm) than the measurements without the lenses in the plus lens group (M = 7.93, SD = 0.45 [95% CI 7.79 to 8.06] mm), and with the minus lenses flatter (M = 8.03, SD = 0.31 [95% CI 7.954 to 8.104] mm) than the measurements without the lenses in the minus lens group (M = 7.73, SD = 0.26 [95% CI 7.63 to 7.82] mm) (Figures 5.1 and 5.2). The mean difference between the K-readings with plus and minus lenses were M = -0.43, SD = 0.52 (95% CI -0.522 to -0.307) mm which is significant *t* = 6.98, *p* < 0.0001.

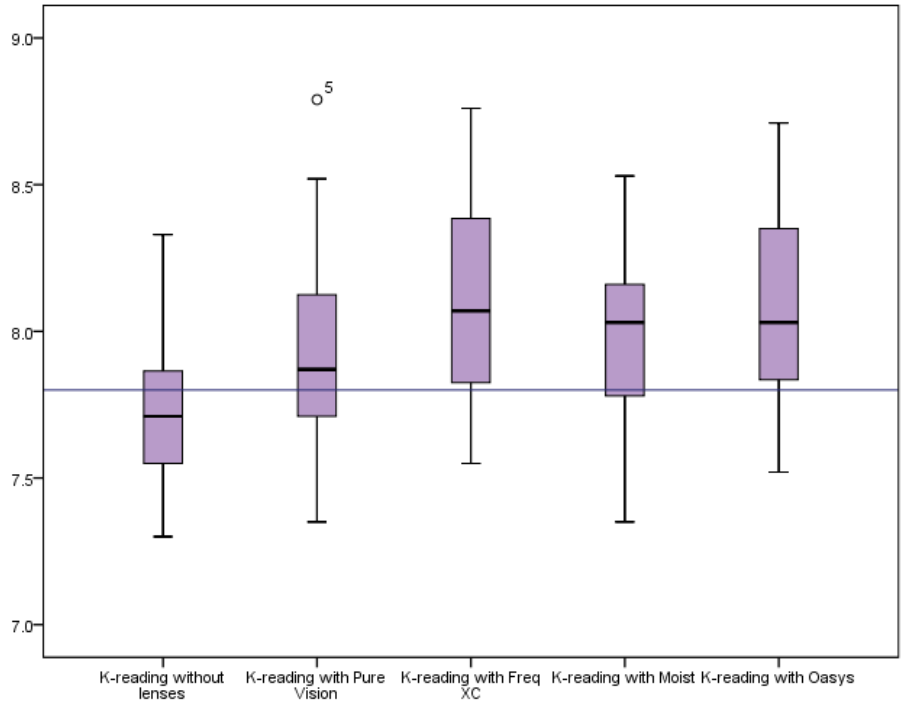


Figure 5.1 Corneal curvature (K) without and with minus powered contact lenses *in situ* – blue line indicates mean K without lenses

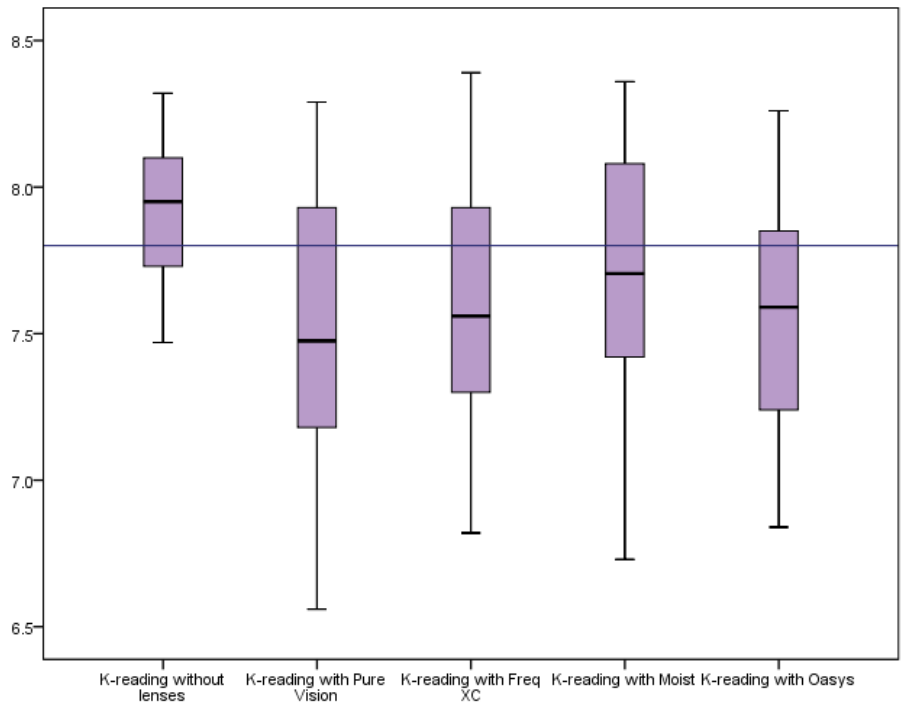


Figure 5.2 Corneal curvature (K) without and with plus powered contact lenses *in situ* – blue line indicates mean K without lenses

The published parameters (based on a -3.00 D lens) for the centre thickness of the four lenses used in the study were: 90 µm for the Pure Vision lens; 75 µm for the Frequency XC lens; 84 µm for the Acuvue 1-Day Moist lens; and 70 µm for the Acuvue Oasys lens (Table 2.1). Published thickness for the pre-corneal tear film was 3 µm (King-Smith et al., 2000). Therefore the expected CCT with each of the lenses on the eye should be the baseline measured CCT without lenses + contact lens CT + pre-corneal tear film thickness. Considering the data for both plus and minus lenses, the following was expected: for the Pure Vision lens the expected CCT should be M = 624.46, SD = 35.51; for the Frequency XC it should be M = 609.46, SD = 35.51; for the Acuvue 1-Day Moist the expected CCT should be M = 618.46, SD = 35.51; and for the Acuvue Oasys it should be M = 604.46, SD = 35.51. This relates to a difference of M = 55.3, SD = 28.1 µm (95% CI [47.33 to 63.31]) between the measured CCT with the Pure Vision lens *in situ* compared to the expected CCT. With the Frequency XC the difference was M = 9.5, SD = 38.8 µm (95% CI [-1.54 to 20.50]); with the Acuvue 1-Day Moist M = 66.5, SD = 22.9 µm (95% CI [60.3 to 73.05]); and for Acuvue Oasys M = 13.5, SD = 30.3 µm (95% CI [4.93 to 22.15]).

In all cases the measured CCT with lenses *in situ* was lower than expected, significantly so with the Pure Vision and the Acuvue 1-Day Moist lenses. Reasons for this could be that the published CT was for -3.00 D lenses only and that this sample included lenses ranging in power from -6.00 to +6.00 D (M = -0.95, SD = 2.69D) as well as the measurement technique employed. However, splitting the data into plus and minus lenses (Figures 5.3 and 5.4) it was apparent that the measured CCT was significantly higher with plus power (particularly Frequency XC and Acuvue Oasys) lenses than minus lenses. With the plus power lenses *in situ* the CCT was M = 607.03, SD = 49.31 (95% CI 595.4 to 618.6) µm and with the minus powered lenses M = 564.0, SD = 46.5 (95% CI 553.0 to 574.90) µm. The mean difference between the CCT with plus and minus power lenses was M = 43.1, SD = 74.2 (95% CI 25.6 to 60.5) µm which is significant t = -4.93, p < 0.001.

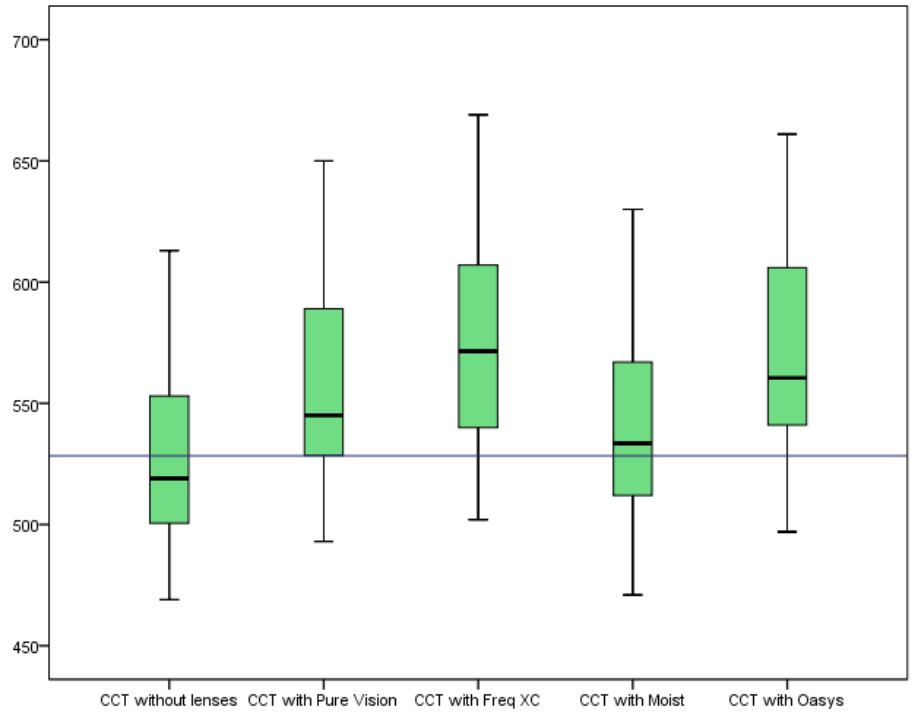


Figure 5.3 Central corneal thickness (CCT) without and with the different minus powered contact lenses in situ – blue line indicates mean CCT without lenses

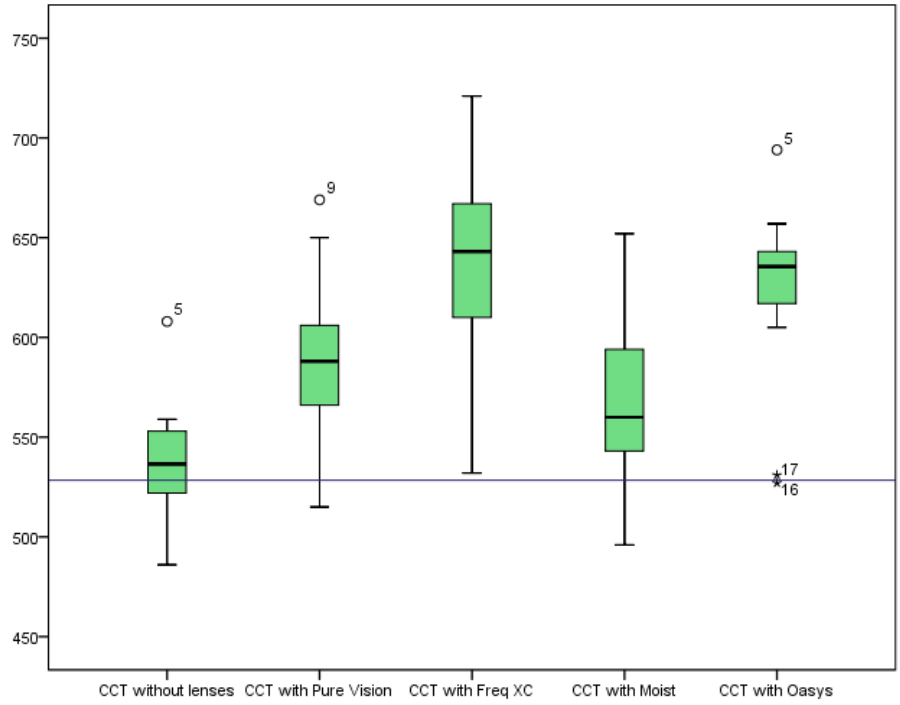


Figure 5.4 Central corneal thickness (CCT) without and with plus powered contact lenses *in situ* – blue line indicates mean CCT without lenses

Considering the data for the entire cohort, all ICare RBT and ORA measurements were significantly affected by the presence of a contact lens on the eye, with the exception of the two ORA metrics CH and CRF which were not significantly affected by the presence of the Acuvue 1-Day Moist (CH p = 0.160) and Frequency XC (CRF p = 0.757) lenses. This was confirmed by the Bland-Altman plots which showed it was possible to accurately measure IOP with ICare RBT while wearing Frequency XC and Oasys lenses as well as ORA CH and CRF with the Frequency XC, Acuvue 1-Day Moist, and Oasys lenses. This, however, was not the case with ORA IOPcc and ORA IOPg which were significantly underestimated with all of the lenses on the eye. Looking at the data for the minus lenses only, all the measurements with the ICare RBT and ORA were significantly affected with the exception of RBT with the Frequency XC lens (p = 0.093); ORA CH with the Acuvue 1-Day Moist lens (p = 0.622); and ORA IOPg with the pure Vision lens (p = 0.492). With the plus powered lenses on the eye, ICare RBT was not significantly affected by the presence of Frequency XC (p = 0.229) and Acuvue Oasys lenses (p = 0.128). This was not true for ORA CH with Acuvue 1-Day Moist (p = 0.086), IOPcc and IOPg with Frequency XC (IOPcc [p = 0.291]; IOPg [p = 0.455]) as well as Acuvue 1-Day Moist lenses (IOPcc [p = 0.668]; IOPg [p = 0.965]). IOPg with plus powered Acuvue Oasys lenses was not statistically different to measurement without the lenses (p = 0.792). With the Pure Vision lenses on the eye, ICare RBT

significantly overestimated IOP M = 3.97, SD = 4.12 mmHg (95% CI [2.799 to 5.140]). This was even more evident with the plus powered Pure Vision lenses M = 5.85, SD = 6.01 mmHg (95% CI [2.859 to 8.836]). ICare RBT significantly underestimated IOP with both minus and plus power Acuvue 1-Day Moist lenses in that the means were: M = -1.22, SD = 1.91 mmHg (95% CI [-1.90 to-0.53]) and M = -1.89, SD = 2.09 mmHg (95% CI [2.93 to-0.85]) respectively.

ORA IOPcc and IOPg were significantly underestimated in the entire cohort irrespective of lens power (Table 5.5, page 150). ORA IOPcc measurements with the Pure Vision lenses fared the worst underestimating IOPcc by M = -4.30, SD = 2.34 mmHg (95% CI [-4.964 to -3.637]). This was also the case with the ORA biomechanical metric measurements with Pure Vision, overestimating CH by M = 4.89, SD = 3.29 mmHg (95% CI [3.953 to 5.822]) and CRF by M = 4.65, SD =3.18 mmHg (95% CI [3.746 to 5.555]). ORA CH and CRF were also significantly overestimated with plus powered silicone lenses, especially Pure Vision CH: M =7.65, SD = 3.89 mmHg (95% CI [5.920 to 9.386]), CRF: M = 7.48, SD = 3.74 mmHg (95% CI [5.623 to 9.346]) and, to a lesser extent, Acuvue Oasys CH: M = 1.96, SD = 1.01 mmHg (95% CI [1.457 to 2.465]), CRF: M = 1.68, SD = 1.60 mmHg (95% CI [0.886 to 2.478]).

	Without CL (mmHg)	**Pure Vision (mmHg)**	**Frequency XL (mmHg)**	**Acuvue 1-day Moist (mmHg)**	**Acuvue Oasys (mmHg)**
	Entire sample (*n* = 50)	**All powers**	**All powers**	**All powers**	**All powers**
RBT	**M = 14.58, SD = 3.38**	M = 18.49, SD = 5.43 Difference = 3.91 *p* = 0.000	M = 14.09, SD = 3.15* Difference = -0.49 *p* = 0.036	M = 13.12, SD = 3.11 Difference = -1.46 *p* = 0.000	M = 13.74, SD = 3.24* Difference = -0.84 *p* = 0.004
ORA CH	**M = 9.68, SD = 1.4**	M = 14.56, SD = 3.38 Difference = 4.88 *p* = 0.000	M = 10.08, SD = 1.34* Difference = 0.40 *p* = 0.002	M = 9.81, SD = 1.39** Difference = 0.13 *p* = 0.160	M = 10.59, SD = 1.64* Difference = 0.91 *p* = 0.000
ORA CRF	**M = 9.57, SD =1.65**	M = 14.22, SD = 3.40 Difference = 4.65 *p* = 0.000	M = 9.60, SD = 1.65** Difference = 0.03 *p* = 0.757	M = 9.34, SD = 1.53* Difference = -0.23 *p* = 0.033	M = 9.99, SD = 2.05* Difference = 0.42 *p* = 0.034
ORA IOPcc	**M = 16.02, SD = 3.50**	M = 11.72, SD =3.18 Difference = - 4.30 *p* = 0.000	M = 14.82, SD = 3.09 Difference = -1.2 *p* = 0.000	M = 15.06, SD = 2.61* Difference = -0.96 *p* = 0.004	M = 14.00, SD = 2.68 Difference = -2.02 *p* = 0.000
ORA IOPg	**M = 14.64, SD = 3.58**	M = 15.79, SD = 3.75 Difference = 1.15 *p* = 0.007	M = 13.55, SD = 3.48 Difference = -1.09 *p* = 0.003	M = 13.62, SD = 2.86 Difference = -1.02 *p* = 0.002	M = 13.48, SD = 3.33 Difference = -1.10 *p* = 0.000

Table 5.2 Means, standard deviations and p values (*n* = 50) of the ICare RBT and ORA metrics measured with and without the different contact lenses on the eye.(* Differences < 1 mmHg considered clinically insignificant. ** Differences < 1 mmHg and *p* < 0.05 are considered statistically and clinically insignificant. Shaded cells represent differences > 1 mmHg from the non-lens condition.) (RBT = rebound tonometery; CH = corneal hysteresis; CRF = corneal resistance factor; IOPcc = cornea corrected IOP; IOPg = Goldman equivalent IOP)

	Without CL (mmHg)	Pure Vision (mmHg)	Frequency XL (mmHg)	Acuvue 1-day Moist (mmHg)	Acuvue Oasys (mmHg)
	-VE only (*n* = 32)	-VE	-VE	-VE	-VE
RBT	**M = 13.88, SD = 3.19**	M = 16.70, SD = 3.79 Difference = 2.81 *p* = 0.000	M = 13.40, SD = 3.03** Difference = -0.48 *p* = 0.093	M = 12.66, SD = 3.16 Difference = -1.22 *p* = 0.001	M = 13.06, SD = 3.13* Difference = -0.82 *p* = 0.015
ORA CH	**M = 9.74, SD = 1.48**	M = 13.07, SD = 2.06 Difference = 3.33 *p* = 0.000	M = 10.04, SD = 1.44* Difference = 0.26 *p* = 0.038	M = 9.80, SD = 1.42** Difference = 0.059 *p* = 0.622	M = 10.07, SD = 1.49* Difference = 0.33 *p* = 0.004
ORA CRF	**M = 9.52, SD = 1.59**	M = 12.58, SD = 1.56 Difference = 3.05 *p* = 0.000	M = 9.27, SD = 1.52* Difference = -0.26 *p* = 0.016	M = 9.13, SD = 1.50* Difference = -0.39 *p* = 0.001	M = 9.24, SD = 1.67* Difference = -0.28 *p* = 0.000
ORA IOPcc	**M = 15.72, SD = 3.23**	M = 11.71, SD = 3.03 Difference = -4.00 *p* = 0.000	M = 14.20, SD = 2.87 Difference = -1.52 *p* = 0.000	M = 14.37, SD = 2.43 Difference = -1.35 *p* = 0.000	M = 13.79, SD = 2.73 Difference =-1.95 *p* = 0.000
ORA IOPg	**M = 15.72, SD = 3.23**	M = 14.28, SD = 2.72** Difference = -0.17 *p* = 0.492	M = 12.54, SD = 2.82 Difference = -1.92 *p* = 0.000	M = 12.84, SD = 2.61 Difference = -1.61 *p* = 0.000	M = 12.54, SD = 2.94 Difference = -1.92 *p* = 0.000

Table 5.3 Means, standard deviations and p values (*n* = 32) of the ICare RBT and ORA metrics measured with and without the different minus contact lenses on the eye (range -0.50 to -6.00 D).(* Differences < 1 mmHg considered clinically insignificant. ** Differences < 1 mmHg and *p* < 0.05 were considered statistically and clinically insignificant. Shaded cells represent differences > 1 mmHg from the non-lens condition.) (–VE = negative power lenses; RBT = rebound tonometery; CH = corneal hysteresis; CRF = corneal resistance factor; IOPcc = cornea corrected IOP; IOPg = Goldman equivalent IOP; M = Mean; SD = Standard deviation)

	Without CL (mmHg)	Pure Vision (mmHg)	Frequency XL (mmHg)	Acuvue 1-day Moist(mmHg)	Acuvue Oasys (mmHg)
	+VE only (*n* = 18)	+VE	+VE	+VE	+VE
RBT	**M = 15.82, SD = 3.45**	M = 21.67, SD = 6.48 Difference = 5.85 *p* = 0.001	M = 15.31, SD = 3.06** Difference = -0.51 *p* = 0.229	M = 13.93, SD = 2.93 Difference = -1.89 *p* = 0.001	M = 14.94, SD = 3.15** Difference = -0.88 p = 0.128
ORA CH	**M = 9.56, SD = 1.34**	M = 17.21, SD = 3.69 Difference = 7.65 *p* = 0.000	M = 10.22, SD = 1.16* Difference = 0.66 *p* = 0.023	M = 9.82, SD = 1.38** Difference = 0.26 *p* = 0.086	M = 11.52, SD = 1.52 Difference = 1.96 p = 0.000
ORA CRF	**M = 9.64, SD = 1.79**	M = 17.13, SD = 3.84 Difference = 7.48 *p* = 0.000	M = 10.21, SD = 1.72* Difference = 0.56 *p* = 0.042	M = 9.72, SD = 1.57** Difference = 0.17 *p* = 0.495	M = 11.33, SD = 2.02 Difference = 1.68 *p* = 0.000
ORA IOPcc	**M = 16.57, SD = 3.99**	M = 11.74, SD = 3.51 Difference = -4.83 *P* = 0.000	M =15.94, SD = 3.22** Difference =- 0.63 *p* = 0.291	M = 16.28, SD = 2.55** Difference = -0.28 *p* = 0.668	M = 14.37, SD = 2.62 Difference = -2.2 *p* = 0.001
ORA IOPg	**M = 14.97, SD = 4.18**	M = 18.47, SD = 3.88 Difference = 3.49 *p* = 0.000	M = 15.35, SD = 3.88** Difference = 0.38 *p* = 0.455	M = 15.00, SD = 2.83** Difference = 0.028 *p* = 0.965	M = 15.14, SD = 3.41** Difference = 0.17 *p* = 0.792

Table 5.4 Means, standard deviations and p values (*n* = 18) of the ICare RBT and ORA metrics measured with and without the different plus contact lenses on the eye (range +0.50 to +6.00 D).(* Differences < 1 mmHg considered clinically insignificant. ** Differences < 1 mmHg and *p* < 0.05 were considered statistically and clinically insignificant. Shaded cells represent differences > 1 mmHg from the non-lens condition.) (+VE = positive power lenses; RBT = rebound tonometery; CH = corneal hysteresis; CRF = corneal resistance factor; IOPcc = cornea corrected IOP; IOPg = Goldman equivalent IOP; M = Mean; SD = Standard deviation)

Comparison: without and with lenses	**Mean difference (M) and Standard deviation (SD) mmHg**			**95% CI**		
	Total sample: (*n* = 50)	Minus lenses: (*n* = 32)	Plus lenses: (*n* = 18)	Total sample:	Minus lenses:	Plus lenses:
$RBT_{Without}$. $RBT_{Pure\ Vision}$	M = 3.97, SD = 4.12*	M = 2.81, SD = 1.83*	M = 5.85, SD = 6.01*	2.80 to 5.14	2.15 to 3.47	2.86 to 8.84
$RBT_{Without}$. $RBT_{Frequency\ XC}$	M = -0.43, SD = 1.65	M = -0.48, SD = 1.58	M = -0.51, SD = 1.75	-0.90 to 0.031	-1.06 to 0.09	-1.38 to 0.36
$RBT_{Without}$. $RBT_{1\text{-}Day\ Moist}$	M = -1.40, SD = 1.96*	M =-1.22, SD = 1.91*	M = -1.89, SD = 2.09*	-1.95 to 0.83	-1.90 to -0.53	-2.93 to -0.85
$RBT_{Without}$. RBT_{Oasys}	M = -0.78, SD = 1.98	M = -0.82, SD = 1.81	M = -0.88, SD = 2.32*	-1.34 to 0.21	-1.47 to -0.17	-2.03 to 0.28
$CH_{Without}$. $CH_{Pure\ Vision}$	M = 4.89, SD = 3.29*	M = 3.33, SD = 1.87*	M = 7.65, SD = 3.89*	3.95 to 5.82	2.66 to 4.01	5.92 to 9.39
$CH_{Without}$. $CH_{Frequency\ XC}$	M = 0.41, SD = 0.88	M = 0.26, SD = 0.69	M = 0.67, SD = 1.13	0.16 to 0.66	0.01 to 0.51	0.11 to 1.23
$CH_{Without}$. $CH_{1\text{-}Day\ Moist}$	M = 0.13, SD = 0.65	M = 0.06, SD = 0.67	M = 0.26, SD = 0.60	-0.05 to 0.32	-0.18 to 0.30	-0.04 to 0.56
$CH_{Without}$. CH_{Oasys}	M = 0.92, SD = 1.10	M = 0.33, SD = 0.60	M = 1.96, SD = 1.01*	0.61 to 1.23	0.11 to 0.55	1.46 to 2.47
$CRF_{Without}$. $CRF_{Pure\ Vision}$	M = 4.65, SD = 3.18*	M = 3.06, SD = 1.01*	M = 7.48, SD = 3.74*	3.75 to 5.56	2.69 to 3.42	5.62 to 9.35
$CRF_{Without}$. $CRF_{Frequency\ XC}$	M = 0.04, SD = 0.88	M = -0.26, SD = 0.57	M = 0.56, SD = 1.08	-0.21 to 0.29	-0.46 to -0.05	0.02 to 1.10
$CRF_{Without}$. $CRF_{1\text{-}Day\ Moist}$	M = -0.23, SD = 0.72	M =-0.39, SD = 0.57	M = 0.08, SD = 0.87	-0.43 to -0.02	-0.60 to -0.19	-0.36 to 0.51
$CRF_{Without}$. CRF_{Oasys}	M = 0.42, SD = 1.38	M = -0.28, SD = 0.40	M = 1.68, SD = 1.60*	0.03 to 0.82	-0.43 to -0.14	0.89 to 2.48
$IOPcc_{Without}$. $IOPcc_{Pure\ Vision}$	M = -4.30, SD = 2.34*	M = -4.00, SD = 1.83*	M = -4.83, SD = 3.03*	-4.96 to -3.63	-4.66 to -3.34	-6.33 to -3.33
$IOPcc_{Withou}$. $IOPcc_{Frequency\ XC}$	M = -1.20, SD = 2.05*	M = -1.52, SD = 1.76*	M = -0.63, SD = 2.45	-1.78 to -0.62	-2.16 to -0.89	-1.84 to 0.59
$IOPcc_{Without}$. $IOPcc_{1\text{-}Day\ Moist}$	M = -0.97, SD = 2.51*	M = -1.35, SD = 1.83*	M = -0.29, SD = 2.77	-1.61 to -0.33	-2.01 to -0.69	-1.67 to 1.10

Comparison: without and with lenses	Mean difference (M) and standard deviation (SD) mmHg			95% CI		
$IOPcc_{Without}$. $IOPcc_{Oasys}$	M = -2.02, SD = 1.99*	M = -1.93, SD = 1.79*	M = -2.20, SD = 2.35*	-2.59 to -1.46	-2.57 to -1.28	-3.37 to -1.03
$IOPg_{Without}$. $IOPg_{Pure\ Vision}$	M = 1.15, SD = 2.86*	M = -0.17, SD = 1.42	M = 3.49, SD = 3.29*	0.33 to 1.96	-0.69 to 0.34	1.86 to 5.13
$IOPg_{Without}$. $IOPg_{Frequency\ XC}$	M = -1.09, SD = 2.49*	M = -1.91, SD = 2.32*	M = 0.38, SD = 2.11	-1.79 to -0.38	-2.75 to -1.07	-0.67 to 1.43
$IOPg_{Without}$. $IOPg_{1\text{-}Day\ Moist}$	M = -1.02, SD = 2.18*	M = -1.61, SD = 1.65*	M = 0.03, SD = 2.64	-1.64 to -0.40	-2.21 to -1.02	-1.29 to 1.34
$IOPg_{Without}$. $IOPg_{Oaysys}$	M = -1.17, SD = 2.20*	M = -1.92, SD = 1.44*	M = 0.17, SD = 2.68	-1.79 to -0.54	-2.43 to -1.40	-1.17 to 1.50

Table 5.5 Bland-Altman analysis of the differences between measurements with and without lenses plotted against the arithmetic mean of the measurements with and without lenses for both ICare RBT and ORA instruments.(Values are indicated for the total sample as well as for minus and plus lenses separately. Negative values indicate the measurement with the contact lenses on the eye was lower than the measurement without the lenses on the eye. * = Clinically significant differences. Shaded blocks indicate differences of ±2.00 mmHg or more.) (RBT = rebound tonometery; CH = corneal hysteresis; CRF = corneal resistance factor; IOPcc = cornea corrected IOP; IOPg = Goldman equivalent IOP)

5.5 Discussion

Previous studies posit that measurement of IOP using the ICare rebound tonometer and NCT is possible with contact lenses *in situ* (Table 5.1). However, although the principles of the ORA are based on those of the noncontact tonometer (Luce, 2005; Kotecha, 2007; Kniestedt et al., 2008), it measures instrument-specific corneal biomechanics as well as IOPcc and IOPg. It is important to consider that the biomechanical properties CH and CRF measured by the ORA characterise the structural response of the eye to this specific measurement device; therefore, they cannot be seen as intrinsic elastic or viscoelastic properties of the cornea (Jorge, Gonzales-Meijome, et al., 2008; Lau and Pye, 2011). Currently Young's modulus of elasticity of the cornea can only be measured *ex vivo* (Kerautret et al., 2008; Lau and Pye, 2011). The purpose of this study was to compare IOP measurements with the ICare and ORA tonometers with four commonly used disposable soft contact lenses *in situ* to IOP measurements with these instruments without lenses on the same eyes of a group contact lens wearers (*n* = 50).

The rebound response of the ICare RBT reflects the viscoelastic properties of the cornea (Chihara, 2008; Jorge, Gonzales-Meijome, et al., 2008). Although the CCT and corneal curvature can affect the ICare IOP accuracy, it seems that the biomechanical properties (in this study represented by CH and CRF) have the greatest influence on the instrument's IOP measurement (Chui et al., 2008). Although

research shows the accuracy of IOP measurement with ICare RBT and NCT was not affected by corneal astigmatism (De Moraes et al., 2008; Johannesson et al., 2008; Hamilton-Maxwell, 2014; Townsend and McSoley, 2015), subjects with more than 2.50 Dioptres of corneal astigmatism were nonetheless excluded from this study.

IOP measurements are significantly higher when the corneal modulus of elasticity is increased and the corneal curvature and CCT remains constant (Liu and Roberts, 2005). Measuring IOP with contact lenses *in situ* should therefore affect the measurement accuracy considerably. Wearing contact lenses during NCT tonometry alters the ocular surface behaviour (changes the amount of deformation) and therefore the IOP readings (Rimayanti et al., 2014). It is likely that the viscoelastic properties of the contact lenses and lens thickness affect the rebound response of the ICare RBT. Lower modulus softer lenses seem to absorb more energy leading to lower IOP measurements while higher modulus stiffer lenses lead to overestimation of the IOP. The Bland-Altman analyses clearly indicate that, with both the ICare RBT as well as the ORA, IOP measurements with and without the higher modulus Pure Vision lenses were statistically and clinically significantly different (Table 5.5).

Splitting the data into plus and minus lenses, the differences became much more pronounced with the plus powered thicker higher modulus Pure Vision lenses having the greatest effect on the measurement accuracy. With the lower modulus Frequency XC, Acuvue 1-Day Moist, and Acuvue Oasys the ICare RBT underestimated the IOP when compared to the measurements without lenses. This underestimation was possibly due to the energy of the probe being absorbed by the low modulus material. In contrast to the findings of Zeri et al. (2011) that the ICare RBT underestimated IOP over moderate plus power hydrogel lenses (Zeri et al., 2011), the findings of the current study showed that ICare RBT underestimated IOP with minus as well as plus powered contact lenses of moderate modulus of elasticity. Zeri et al. (2015) measured the IOP with and without a +2.00 and a +6.00 D etafilcon A hydrogel lens *in situ* and found the ICare RBT significantly underestimated IOP with the lenses (Zeri et al., 2015). These authors speculate that the reasons for the lower IOP measurements with the lenses could be attributed to the lower resistance to deformation of the high water content etafilcon A material. They therefore concluded that the corneal thickness (combined lens and corneal thickness) did not affect the value of the IOP measured with the ICare RBT (Zeri et al., 2015). With the low modulus of elasticity hydrogel Acuvue 1-Day Moist lenses the difference was statistically as well as clinically significant (> 1 mmHg). With both plus and minus powered high modulus of elasticity silicone Pure Vision lenses, ICare RBT significantly overestimated IOP (> 1

mmHg) (Table 5.5). These findings are similar to those of previous research conducted with the NCT (McMonnies, 1986; Insler and Robbins, 1987; Schollmayer and Hawlina, 2003; Patel and Illahi, 2004; Touboul, 2008; Patel and Stevenson, 2009; Liu et al., 2011).

In the current study the cornea/lens thickness was significantly thicker with the plus power lenses than with minus power lenses (70.33 and 33.32 µm respectively) than measurement of CCT without lenses and the corneal curvature was steeper (M = 7.60, SD = 0.45 mm compared to M = 7.93, SD = 0.27 mm without lenses) with the plus power lenses and flatter (M = 8.03, SD = 0.31 mm compared to M = 7.73, SD = 0.26 mm without lenses) with the minus power lenses. Liu and Roberts (2005) found that IOP measurements were affected by CCT (lower with thinner corneas and higher with thicker corneas), corneal curvature (lower with flatter corneas and higher with steeper corneas), and Young's modulus (Liu and Roberts, 2005). Although the results of the current study support these results, the contact lens modulus of elasticity seem to play a more significant role in the accuracy of IOP measurement with contact lenses *in situ* with the ICare RBT and ORA.

The ORA corneal hysteresis (CH) measurement was significantly higher with the silicone lenses (specifically with the thicker plus lenses) compared to the measurement without lenses. The corneal resistance factor (CRF) was also significantly higher with the silicone Pure Vision lenses. These findings contradicted those of Lam and Tse (2014) which indicated the measurement of the two biomechanical metrics were not affected by the presence of a silicone hydrogel lens on the eye (Lam and Tse, 2014). The modulus of elasticity of the Pure Vision and Acuvue Oasys lenses was 1.1 and 0.75 MPa respectively. This differs from that of the Focus Night & Day's 1.5 MPa (Ciba Vision) and Acuvue Advance's 0.43 MPa (Johnson & Johnson) that Lam and Tse (2014) used in their study. Other differences between the two studies include the use of only -3.00 D lenses compared to lens powers ranging between -6.00D to +6.00D, difference in lens thickness across the power range, and the use of an ORA WS score of three-and-a-half compared to the six-score used in this study. The low WS may affect the influence of the ocular pulse amplitude on the measurements (Lam and Tse, 2014).

Of further interest is that the ORA IOPcc with Pure Vision as well as Frequency XC, Acuvue 1-Day Moist, and Acuvue Oasys measurements were significantly lower (irrespective of lens power) than the instrument-measured IOPcc without lenses (Tables 5.2 to 5.5). In the case of ORA IOPg, the measurement was significantly lower for the minus power Frequency XC, Acuvue 1-Day Moist, and Acuvue Oasys lenses and significantly higher for the Pure Vision plus lenses, but no significant difference was observed with any of the other brands of plus lenses (Tables 5.2 to 5.5, and Figure

4.9). The IOPcc, and to a lesser extent the IOPg calculation, takes corneal viscoelastic properties into consideration (Lau and Pye, 2011). As expected, these measurements were influenced by a contact lens which alters ocular surface behaviour, apparent corneal thickness, corneal curvature, and viscoelastic corneal properties; therefore altering the time needed to achieve maximal light detection in NCT (Liu et al., 2011). In the case of IOPcc, the measurements in this study were lower with lenses *in situ* than without the lenses; with IOPg lower measurements with minus lenses and significantly higher measurements with thicker plus lenses were seen. These findings concur with those of Sapkota et al. (2014), namely, that ORA IOPcc and IOPg measurements were lower with -3.00 low and moderate modulus (0.66 and 0.89 MPa) daily wear contact lenses on the eye. IOPcc was highly affected and underestimated by more than 3 mmHg in 36% of their subjects (Sapkota et al., 2014). In the current study IOPcc was underestimated by more than 3 mmHg with only the Pure Vision lenses in all subjects. Young's modulus of the human cornea has been reported as M = 0.29, SD = 0.06 MPa (Hamilton and Pye, 2008) which, in this study, was similar to the modulus of Frequency XC and Acuvue 1-Day Moist lenses, but significantly lower than the modulus of Pure Vision and Acuvue Oasys lenses (Table 2.1).

Other than the influence of the lenses on the biomechanical properties of the cornea/lens combination (Table 1.7), factors such as anterior corneal and lens curvature; central corneal thickness; lens water content; central lens thickness; oxygen transmissibility of the lenses; combined lens corneal thickness; and hydration may influence the accuracy of the measurements with lenses *in situ.* The effects of these factors need further study.

All measurements in this study were collected at one specific sitting and it is therefore conceivable that variation in measurements may occur from one visit to the next with a specific lens, limiting the clinical usefulness of the results of this particular study. Hence, the study should be expanded and additional research be undertaken to collect data over a number of consecutive visits to determine the variability of the measurements validating the clinical usefulness of the results obtained in this study.

5.6 Conclusion

ICare RBT and ORA IOPg tonometry is possible with low minus power, moderate modulus of elasticity, thin silicone hydrogel (Acuvue Oasys) and hydrogel (Frequency XC, Acuvue 1-Day Moist) disposable soft contact lenses *in situ*. With the advent of "therapeutic" contact lenses for sustained

drug delivery to the eye as well as ICare HOME IOP measurements, this information will aid manufactures and clinicians in deciding which materials, centre thickness, water content, and power contact lenses can be used that will augment the accuracy of IOP measurements with the lenses *in situ*.

5.7 Summary of findings

- In the case of ORA IOPcc, the IOP measurements were lower with lenses *in situ* than without the lenses, and with ORA IOPg the IOP measurements were lower with minus lenses and significantly higher with thicker and stiffer plus lenses *in situ.*
- The ICare RBT underestimated IOP measurements with low modulus plus and minus lenses and overestimated IOP with thicker high modulus plus lenses *in situ.*
- The ORA CH and CRF metrics were overestimated with thicker high modulus plus lenses *in situ.*
- Accurate ICare RBT and ORA IOPg tonometry was possible with low minus power, moderate modulus of elasticity, thin silicone hydrogel, and hydrogel disposable soft contact lenses *in situ.*

Chapter 6

Physiological and physical factors and their impact on ICare RBT and ORA IOP measurements in a population of normal subjects with and without contact lenses *in situ.*

6.1 Introduction

Chapter three showed that the intraobserver reliability (test-retest repeatability by the same observer) of the ICare RBT and the ORA produced repeatable and consistent results even when measurements were performed with disposable contact lenses on the eye. Interobserver reliability (test-retest repeatability between different observers) also produced repeatable and consistent results with the ICare RBT. Chapter four confirmed that the ICare RBT and ORA IOPg pressure measurements were highly correlated and comparable. Clinically the differences between the two measurements were less than 0.60 mmHg and this difference seemed not to be affected by the presence of a contact lens on the eye. ICare RBT and IOPcc pressure measurements were also correlated and comparable but to a lesser extent than ICare RBT and IOPg measurements. Chapter five showed that ICare RBT and ORA tonometry was possible with low minus power (range -0.50 to -6.00 D), and low modulus of elasticity (0.26 to 0.75 MPa) silicone hydrogel and hydrogel disposable soft contact lenses *in situ.* However, it is clear that further analysis of the data was needed to individually examine the effects of the different corneal, refractive and contact lens characteristics on the accuracy of the ICare and ORA measurements in more detail.

From the literature reviewed in Chapter one it is evident that numerous physiological as well as physical factors affect the accuracy of the IOP measurements made with any commercially available tonometer. Although not all the factors discussed previously were measured during this study, care was taken to eliminate some of them by means of the study methodology which was carefully designed to exclude specific factors, namely, diurnal variation; ocular pulse amplitude,; accommodation; operator bias and technique; calibration issues; Valsalva manoeuvre; nervousness or forced eyelid closure; as well as the influence of the pre-corneal tear film (Bao et al., 2015).

Although NCT is affected by the same ocular sources of error including CCT, scleral rigidity, corneal curvature; and corneal biomechanics; and ocular surface behaviour (Kniestedt et al., 2008; Rimayanti et al., 2014), data have been presented showing it is more influenced by CCT than applanation

tonometry (Graf, 1991). Factors influencing the CH and CRF include diurnal variation; tear film (a dry cornea leads to false CH values); IOP (the higher the IOP the lower the CH and higher the CRF); age (CH and CRF decrease by between 0.24 to 0.28 mmHg and 0.31 mmHg per decade respectively); corneal curvature (flatter corneas have lower CH and CRF values); and corneal swelling (corneal thickness increases but CH decreases due to the modified matrix viscosity and reduced dampening capacity of the cornea) (Moreno-Montanes et al., 2008; Sullivan-Mee et al., 2009; Kotecha et al., 2010; Terai et al., 2012; Wang et al., 2013). As mentioned, CH is dependent on IOP and measured IOP is dependent on CH. CH can be seen as a dynamic corneal property indicating how much energy the cornea can absorb under stress. A 2013 study suggest that along with IOP it is the only other known modifiable risk factor for glaucoma progression manifested as visual field changes and ONH damage with age (Medeiros et al., 2013). Xu et al. (2008) found that long-term soft contact lens wear leads to changes in corneal viscoelastic properties. Lower CH and CRF was apparent the first day after contact lens removal as well as two weeks after discontinuing contact lens wear while CCT remained constant (Xu et al., 2008).

Although GAT IOP has a significant association with CCT, as expected IOPcc produced by the ORA was found to have no significant association with ocular variables such as CCT, corneal curvature, and axial length (Medeiros and Weinreb, 2006; ElMallah and Asrani, 2008). Studies of the ORA have produced conflicting results: two studies showed promising results with the ORA IOPcc seeming to compensate for corneal factors (Kotecha et al., 2006; Medeiros and Weinreb, 2006). In the second study of glaucoma patients undergoing therapy with topical medication, the ORA IOPcc and IOPg consistently overestimated GAT IOP by 8.3 mmHg and 7.2 mmHg respectively. In second study group of patients the ORA IOP (both IOPcc and IOPg) measurements were not independent of CCT (Martinez-de-la-Casa, Garcia-Feijoo, Fernandez-Vidal, et al., 2006). Medeiros and Weinreb (2006) reported a difference of M = 0.068, SD = 2.77 mmHg between ORA IOPcc and GAT. The difference was significantly influenced by CCT. Thicker CCT resulted in higher GAT compared to ORA IOPcc and thinner CCT resulted in lower GAT compared to ORA IOPcc (Medeiros and Weinreb, 2006).

ICare RBT is affected by the same physical properties of the eye that affect GAT. These properties include CCT, corneal curvature, corneal biomechanics as well as refractive error with ICare RBT overestimating GAT IOP in myopic eyes. ICare is not influenced by the OPA (Detry-Morel et al., 2006; Lopez-Caballero et al., 2007; Avitabile et al., 2010; Hohmann et al., 2012; Rao et al., 2012). It has been shown that ICare RBT may be more sensitive to CCT than GAT and that a CCT change of 10 µm

can result in a measurement deviation of 0.7 mmHg (Brusini et al., 2006; Nakamura et al., 2006; Sahin, Niyaz, et al., 2007; Avitabile et al., 2010). Salvetat et al. (2011) also found CCT in subjects with normal corneas significantly affected IOP measurements with GAT and RBT. An increase of 0.41 mmHg (GAT) and 0.50 mmHg (RBT) for every 10 µm increase in CCT was observed. These authors further found although corneal curvature did not seem to influence GAT, it significantly affected RBT. RBT tends to underestimate IOP in healthy steep corneas and overestimate IOP in healthy flat corneas by 0.76 mmHg per 1.00 D change in corneal curvature. Steep corneas may therefore hypothetically decrease the probe velocity leading to the underestimation of the IOP (Salvetat et al., 2011).

Chui et al. (2008) found other biomechanical "corneal" (ORA specific) properties such as CH and CRF were more important than CCT in influencing IOP measurements with the ICare RBT (Chui et al., 2008). Although this study considered the influence of CCT, CH and CRF on IOP measured with the RBT, it did not report or comment on the correlation between the RBT IOP, GAT IOP (IOPg), and the corneal corrected IOP (IOPcc) measured with the ORA (Chui et al., 2008). In a 2008 study by Jorge et al. (2008), the influence of CCT and corneal biomechanical properties of the cornea (measured by the ORA) on ICare tonometry was evaluated. In the study ICare tonometry and ultrasound pachymetry was measured centrally, nasally and peripherally and the ICare IOP measurements were correlated with corneal thickness as well as ORA CH, CRF, IOPg, and IOPcc (Jorge, Gonzales-Meijome, et al., 2008). Jorge et al. (2008) found although CCT plays a role in the accuracy of RBT measurements, the elastic and viscous properties of the cornea seem to play a more significant role in the interaction of the tonometer probe with the ocular surface. CRF showed a higher correlation with ICare RBT than CCT or CH (Jorge, Gonzales-Meijome, et al., 2008). There was also a high correlation between ICare RBT and IOPg but a lower correlation with IOPcc which suggests that ICare RBT measurements are affected not only by the actual IOP, but also by corneal properties including viscosity and viscoelasticity (Jorge, Gonzales-Meijome, et al., 2008).

It was the aim of this chapter to identify and consider the essentially important measured intrinsic and extrinsic variables (corneal and contact lens properties) which may affect the measurements of IOP with the ICare RBT and the ORA tonometer.

6.2 Subjects and methods

Chapter two gave a complete description of the subjects, materials and methodology used in this specific study. To establish which intrinsic and extrinsic factors affect the accuracy of the ICare RBT

and ORA, two experienced optometrists (DJB and GHK) took two ICare RBT measurements on every one of the subjects enrolled in the study. The measurements were taken according to the protocol established for the study of each subject's left eye with and without each and every contact lens *in situ*. One experienced optometrist (DJB) took four ORA measurements according to the protocol established for the study of each subject's left eye with and without the contact lenses *in situ*. The measurements were recorded by and experienced optometric assistant (MLG) blinding the optometrists and reducing observer bias. Additionally, a recently calibrated Oculus Pentacam corneal analysis system was used on each patient to screen for corneal pathology (corneal ectasia, scarring, and prior surgery), the amount and presence of corneal astigmatism, and to record central corneal thickness at the thinnest location on the corneal thickness map as well as RM corneal curvature (RM – arithmetic mean of the simulated Ks) with and without contact lenses *in situ*. The Pentacam measurements were taken by one experienced optometrist (DJB) and was recorded by the optometric assistant (MLG) if the Pentacam QS (quality score) was acceptable. All the variables recorded as well as those inherent to the different contact lenses were analysed to establish their effect on the IOP measurement accuracy with the ICare RBT and Reichert ORA.

6.3 Statistics

In order to evaluate the effects of corneal thickness, corneal curvature, and refractive error on ICare RBT and Reichert ORA measurements, regression analysis was used with ICare IOP and ORA metrics designated as the dependent or response variables and corneal curvature, corneal thickness, and refractive error the independent or predictor variables. Pearson's *r* as well as standard errors between variables was used to estimate the strength of the relationship between the dependent and the predictor variables and regression lines were used to predict the response variable from the predictor variables. The Pearson correlation coefficients were used to assess if a linear relationship existed between the variables and regression analyses to determine the value of one variable in terms of another (McAlinden et al., 2011). Significance levels were evaluated by the paired 2-tailed *t*-test and $p < 0.05$ was considered statistically significant (Armstrong et al., 2011; McAlinden et al., 2011).

Multiple scatter plots for measurements without and with lenses were used to display the relationships between the variables stated in the graphical matrix. To further determine the linear relationship between one dependent variable (ICare RBT, or ORA CH, CRF, IOPcc and IOPg) and multiple independent variables (age, Rx, CCT, CH, CRF, corneal curvature (K), lens modulus, Dk/t, CT,

and water content) multiple linear regression models were used. A linear equation involving the independent variables predicting the dependent variable was constructed and the goodness of fit of the multiple regression to the data points was carried out using ANOVA tests. Multiple regression analysis assumes that the predictor variables are independent of each other which is rare a rare situation in practice. Multiple regression should account for at least half of the variance in the data, in other words the multiple correlation coefficient (R) should be at least 0.7 (Coefficient of determination, $R^2 \geq 0.49$). Finally, multiple regression is probably best used in an exploratory context, identifying variables that might be examined by more detailed studies (Armstrong and Eperjesi, 2007). Stepwise regression was performed to identify the strongest correlated independent variables. The maximum allowable *p*-value for an independent variable to be included with the stepwise algorithm was set at 0.05. If at any step a variables *p*-value went above 0.05, it was removed.

It is impossible to estimate regression coefficients before doing the research and data collection study; hence, power studies are not really relevant. As a rule of thumb the number of data points (i.e., observations or cases) should be considerably more than 5 to 10 times the number of variables (Kleinbaum et al., 1988; Norman and Streiner, 2008). The number of observations recorded in the current study was 1 750 and the number of variables for the regression analysis 10. In order to perform a multiple regression analysis it is important to consider which variables are significant to include in the model based on previous studies. In the case of the ICare RBT the literature shows that corneal biomechanical properties, represented here by the metrics CH and CRF, play a major role in the accuracy of the IOP measurements, more so than CCT (Chui et al., 2008; Jorge, Gonzales-Meijome, et al., 2008; Salvetat et al., 2011).

Other variables that necessitate consideration include CCT, corneal curvature, and refractive error (Detry-Morel et al., 2006; Lopez-Caballero et al., 2007; Avitabile et al., 2010; Salvetat et al., 2011; Hohmann et al., 2012; Rao et al., 2012; Rimayanti et al., 2014). With regard to the ORA, many of the same variables influence the accuracy of the measurements. Age, corneal curvature, CCT, and corneal biomechanics are important variables to include in the analysis (Luce, 2005; Kotecha et al., 2006; Kniestedt et al., 2008; Kotecha et al., 2010). Previous studies determined that CRF is closely associated with CCT but not with IOPcc. IOPg is also closely associated with CCT, corneal curvature as well as axial length (Moreno-Montanes et al., 2008; Sullivan-Mee et al., 2009; Kotecha et al., 2010; Terai et al., 2012; Wang et al., 2013).

6.4 Results

Regarding the correlation between ICare RBT and ORA measurements (Table 6.1), stronger correlations were found between IOPg (r = 0.854, p = 0.000) than IOPcc (r = 0.717, p = 0.000). In terms of the biomechanical metrics CRF was also strongly correlated (r = 0.629, p = 0.000) but CH was not (r = 0.131, p = 0.366). Although CCT showed a strong correlation (r = 0.561, p = 0.000), corneal curvature did not (r = 0.129, p = 0.372). Multiple regression analyses showed that CRF significantly affects ICare RBT β = 2.329 (95 % CI [1.725 to 2.932]), p < 0.0001. CH also affects ICare RBT but less significantly β = -1.949 (95% CI [-2.542 to -1.357]), p < 0.0001. Furthermore, corneal curvature also affects the ICare RBT measurement β = 1.097 (95% CI [-1.021 to 3.215]), p = 0.3020); but this effect is not statistically significant (Figures 6.1 to 6.5). Stepwise regression (R^2 = 0.72) confirmed that CRF significantly affects RBT β = 2.268 (95% CI [1.676 to 2.861]), p = 0.0000. CH also affects RBT but less significantly β = -2.001 (95% CI [-2.574 to -1.427]), p = 0.0000. Although CCT had an effect it was not as significant as that of CRF and CH, β = 0.0232 (95% CI [0.0016 to 0.045]), p = 0.0000.

	Pearson correlation coefficient ***r***	**Statistical significance (2-tailed)** ***p*-values**
RBT vs		
CH	0.131	0.366
CRF	0.629**	0.000
K	0.129	0.372
CCT	0.561**	0.000
IOPcc	0.717**	0.000
IOPg	0.854**	0.000
CRF vs		
CCT	0.725**	0.000
IOPg	0.636**	0.000
IOPcc	0.259	0.070
K	-0.147	0.308
CH	0.760**	0.000
CH vs		
CCT	0.562**	0.000
IOPg	0.022	0.880
IOPcc	-0.406**	0.003
Rx vs		
K	0.319*	0.024

Table 6.1 Significant correlation of biomechanical properties measured by ORA and parameters measured by ICare RBT and Oculus Pentacam.(Pearson correlation coefficients as well as statistical significance are indicated. * = Correlation is significant at p = 0.05 level (2-tailed), ** = correlation is significant at the p = 0.01 level (2-tailed), *n* = 50.) (K = corneal curvature, RBT = rebound tonometry, CCT = central corneal thickness, CH = corneal hysteresis, CRF = corneal resistance factor, Rx = MSE or mean spherical equivalent refractive error, IOPg = Goldmann equivalent IOP, and IOPcc = corneal compensated IOP)

The ORA metric CRF is strongly correlated with CH (r = 0.760, p = 0.000), CCT (r = 0.725, p = 0.000), and IOPg (r = 0.636, p = 0.000) (Table 6.1). Multiple regression analyses confirmed the effect of CCT β = 0.024 (95% CI [0.01815 to 0.03452]), $p < 0.0001$ and corneal curvature β = -1.135 (95% CI [-2.255 to -0.01558]), p = 0.0470 on CRF. Stepwise regression (R^2 = 0.96) showed that CH significantly affects CRF β = 0.868 (95% CI [0.803 to 0.933]), p = 0.0000. IOPg also affects CRF but less significantly β = 0.285 (95% CI [0.259 to 0.311]), p = 0.0000. The metric CH was correlated to CCT (r = 0.562, p = 0.000, IOPcc r = -0.406, p = 0.003) as well as CRF (strongest correlation) as previously shown in Figure 6.2 (page 162). Multiple regression analyses confirmed the effect of CCT β = 0.029 (95% CI [0.01815 to 0.03995]), $p < 0.0001$ and IOPg β = -0.189 (95% CI [-0.0366 to -0.01234]), p =0.0366 on CH (Figures

6.1 to 6.5). Stepwise regression (R^2 = 0.94) confirmed that CRF significantly affects CH β = 1.078 (95% CI [0.997 to 1.158]), *p* = 0.0000. IOPg also affects CH but less significantly β = -0.307 (95% CI [-0.344 to -0.269]), *p* = 0.0000.

As shown before IOPcc was strongly correlated with ICare RBT and CH. Multiple regression analyses confirmed the strong effects of ICare RBT β = 0.210 (95% CI [0.06073 to 0.3588]), *p* = 0.0069, CRF β = 2.229 (95% CI [1.776 to 2.683]), *p* < 0.0001, and CH β = -3.121 (95% CI [-3.530 to -2.713]), *p* <0.0001 on IOPcc. Stepwise regression (R^2 = 0.94) showed that CH significantly affects IOPcc β = -3.142 (95% CI [-3.519 to -2.766]), *p* = 0.0000. CRF also affects IOPcc but less significantly β = 2.351 (95% CI [1.936 to 2.767]), *p* = 0.0000. Finally RBT also affects IOPcc β = 0.1899 (95% CI [0.059 to 0.321]), *p* = 0.0045. As previously noted, IOPg was strongly correlated with ICare RBT and CRF. Multiple regression analyses confirmed the strong effects of ICare RBT β = 0.2312 (95% CI [0.06252 to 0.4000]), *p* = 0.0084), CRF β = 2.473 (95% CI [1.960 to 2.987]), *p* < 0.0001, and CH β = -2.782 (95% CI [-2.782 to -1.857]), *p* <0.0001 on IOPg. Stepwise regression (R^2 = 0.75) showed that RBT significantly affects IOPg β = 0.914 (95% CI [0.762 to 1.066]), *p* = 0.0000. Rx also affects IOPg but less significantly β = -0.226 (95% CI [-0.402 to -0.045]), *p* = 0.01205. Multiple scatter plots of the different variables and their correlations are shown in Figures 6.6 and 6.7.

N	50
Equation	RBT = -7.62 + 0.0118 AGE + 0.1307 Rx + 0.01849 CCT + 1.097 K - 1.949 CH + 2.329 CRF
R^2	0.743
R^2 adjusted	0.707
SE of fit (RMSE)	1.8564

Parameter	Estimate	95% CI	SE	VIF	t	DF	p-value
Constant	-7.620	-26.29 to 11.05	9.2573	-	-0.82	43	0.4149 [1]
AGE	0.01180	-0.04814 to 0.07174	0.029724	1.07	0.40	43	0.6933 [1]
Rx	0.1307	-0.06162 to 0.3231	0.095387	1.13	1.37	43	0.1776 [1]
CCT	0.01849	-0.004301 to 0.04129	0.011303	2.29	1.64	43	0.1091 [1]
K	1.097	-1.021 to 3.215	1.0501	1.22	1.04	43	0.3020 [1]
CH	-1.949	-2.542 to -1.357	0.29388	2.47	-6.63	43	<0.0001 [2]
CRF	2.329	1.725 to 2.932	0.29914	3.46	7.78	43	<0.0001 [2]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Do not reject the null hypothesis at the 5% significance level.
[2] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.

Figure 6.1 This model predicts that the ICare RBT variable is significantly affected by the CH and CRF variables, p < 0.0001.R^2 and R^2 adjusted are > 0.70 indicating that the model has good predictive value. The K variable has less effect on the RBT variable and age, CCT, and Rx variables seem to have very little effect on the RBT variable. The ƒ statistic was 20.72, p < 0.0001 which also indicates that the model has good statistic predictive value. (RBT = rebound tonometry, Rx = MSE refractive error, CCT = central corneal thickness, K = corneal curvature, CH = corneal hysteresis, and CRF = corneal resistance factor. R^2 = coeffiecient of determination).

N	50
Equation	CRF = 3.371 - 0.01811 AGE + 0.01555 Rx + 0.02442 CCT - 1.135 K + 0.07664 RBT + 0.1147 IOPg
R^2	0.667
R^2 adjusted	0.621
SE of fit (RMSE)	1.01559

Parameter	Estimate	95% CI	SE	VIF	t	DF	p-value
Constant	3.371	-6.840 to 13.58	5.0633	-	0.67	43	0.5091 [1]
AGE	-0.01811	-0.05050 to 0.01429	0.016063	1.04	-1.13	43	0.2658 [1]
Rx	0.01555	-0.09520 to 0.1263	0.054915	1.26	0.28	43	0.7784 [1]
CCT	0.02442	0.01433 to 0.03452	5.0062 E-03	1.50	4.88	43	<0.0001 [2]
K	-1.135	-2.255 to -0.01558	0.55531	1.14	-2.04	43	0.0470 [2]
RBT	0.07664	-0.1047 to 0.2580	0.089930	4.52	0.85	43	0.3988 [1]
IOPg	0.1147	-0.04895 to 0.2784	0.081160	4.02	1.41	43	0.1647 [1]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Do not reject the null hypothesis at the 5% significance level.
[2] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.

Figure 6.2 This model predicts that the CRF variable is significantly affected by the CCT and K variables, *p* < 0.0001 and *p* = 0.0470 respectively.R^2 and R^2 adjusted are < 0.70 indicating that the model has fairly good predictive value. The IOPg variable has less effect on the CRF variable and age, as well as Rx variables seem to have very little effect on the CRF variable. The ƒ statistic was 14.36, *p* < 0.0001 which also indicates that the model has good statistic predictive value. (RBT= rebound tonometry, Rx = MSE refractive error, CCT = central corneal thickness, K = corneal curvature, CH = corneal hysteresis, IOPg = Goldmann equivalent IOP, IOPcc = corneal compensated IOP, and CRF = corneal resistance factor. R^2 = coeffiecient of determination).

N	50
Equation	CH = 6.21 - 0.0238 AGE - 0.0006502 Rx + 0.02905 CCT - 1.198 K + 0.07328 RBT - 0.189 IOPg
R^2	0.476
R^2 adjusted	0.402
SE of fit (RMSE)	1.09618

Parameter	Estimate	95% CI	SE	VIF	t	DF	p-value
Constant	6.210	-4.811 to 17.23	5.4651	-	1.14	43	0.2621 [1]
AGE	-0.02380	-0.05877 to 0.01116	0.017338	1.04	-1.37	43	0.1769 [1]
Rx	-6.502 E-04	-0.1202 to 0.1189	0.059273	1.26	-0.01	43	0.9913 [1]
CCT	0.02905	0.01815 to 0.03995	5.4034 E-03	1.50	5.38	43	<0.0001 [2]
K	-1.198	-2.407 to 0.01091	0.59938	1.14	-2.00	43	0.0520 [1]
RBT	0.07328	-0.1225 to 0.2690	0.097066	4.52	0.75	43	0.4544 [1]
IOPg	-0.1890	-0.3657 to -0.01234	0.087600	4.02	-2.16	43	0.0366 [2]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Do not reject the null hypothesis at the 5% significance level.
[2] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.

Figure 6.3 This model predicts that the CH variable is significantly affected by the CCT and IOPg variables, *p* < 0.0001 and *p* = 0.0366 respectively.R^2 and R^2 adjusted are < 0.70 indicating that the model has poor predictive value. The K variable has less effect on the CH variable and age, as well as Rx variables seem to have very little effect on the CH variable. The ƒ statistic was 6.5, *p* < 0.0001 which also indicates that the model has poor statistic predictive value. (RBT = rebound tonometry, Rx = MSE refractive error, CCT = central corneal thickness, K = corneal curvature, CH = corneal hysteresis,

IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP, and CRF = corneal resistance factor. R^2 = coeffiecient of determination).

N	50
Equation	IOPcc = 20.77 - 0.01423 AGE - 0.06146 Rx + 0.005306 CCT - 0.1597 K + 0.2098 RBT - 3.121 CH + 2.229 CRF
R^2	0.943
R^2 adjusted	0.934
SE of fit (RMSE)	0.89907

Parameter	Estimate	95% CI	SE	VIF	t	DF	p-value
Constant	20.77	11.65 to 29.89	4.5186	-	4.60	42	<0.0001 [1]
AGE	-0.01423	-0.04334 to 0.01487	0.014422	1.07	-0.99	42	0.3293 [2]
Rx	-0.06146	-0.1567 to 0.03379	0.047195	1.18	-1.30	42	0.2000 [2]
CCT	0.005306	-0.006080 to 0.01669	5.6420 E-03	2.43	0.94	42	0.3523 [2]
K	-0.1597	-1.199 to 0.8796	0.51497	1.25	-0.31	42	0.7581 [2]
RBT	0.2098	0.06073 to 0.3588	0.073857	3.89	2.84	42	0.0069 [1]
CH	-3.121	-3.530 to -2.713	0.20245	5.00	-15.42	42	<0.0001 [1]
CRF	2.229	1.776 to 2.683	0.22488	8.33	9.91	42	<0.0001 [1]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.
[2] Do not reject the null hypothesis at the 5% significance level.

Figure 6.4 This model predicts that the IOPcc variable is significantly affected by the CH, CRF, and RBT variables *p* < 0.0001 for CH and CRF and *p* = 0.0069 for RBT.R^2 and R^2 adjusted are > 0.70 indicating that the model has excellent predictive value. The K variable has less effect on the IOPcc variable and the age, CCT, and Rx variables seem to have very little effect on the IOPcc variable. The ƒ statistic was 99.79, *p* < 0.0001 which also indicates that the model has excellent statistic predictive value. (RBT = rebound tonometry, Rx = MSE refractive error, CCT = central corneal thickness, K = corneal curvature, CH = corneal hysteresis, IOPcc = corneal compensated IOP, and CRF = corneal resistance factor. R^2 = coeffiecient of determination).

N	50
Equation	IOPg = 7.228 - 0.01516 AGE - 0.09807 Rx + 0.0079 CCT - 0.1103 K + 0.2312 RBT - 2.32 CH + 2.473 CRF
R^2	0.931
R^2 adjusted	0.919
SE of fit (RMSE)	1.01772

Parameter	Estimate	95% CI	SE	VIF	t	DF	p-value
Constant	7.228	-3.094 to 17.55	5.1149	-	1.41	42	0.1650 [1]
AGE	-0.01516	-0.04811 to 0.01778	0.016325	1.07	-0.93	42	0.3584 [1]
Rx	-0.09807	-0.2059 to 0.009745	0.053424	1.18	-1.84	42	0.0735 [1]
CCT	0.007900	-0.004989 to 0.02079	6.3866 E-03	2.43	1.24	42	0.2230 [1]
K	-0.1103	-1.287 to 1.066	0.58293	1.25	-0.19	42	0.8509 [1]
RBT	0.2312	0.06252 to 0.4000	0.083604	3.89	2.77	42	0.0084 [2]
CH	-2.320	-2.782 to -1.857	0.22917	5.00	-10.12	42	<0.0001 [2]
CRF	2.473	1.960 to 2.987	0.25455	8.33	9.72	42	<0.0001 [2]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Do not reject the null hypothesis at the 5% significance level.
[2] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.

Figure 6.5 This model predicts that the IOPg variable is significantly affected by the CH and CRF variables, $p < 0.0001$ for both as well as the RBT variable, $p = 0.0084$.R^2 and R^2 adjusted are > 0.70 indicating that the model has excellent predictive value. The K variable has less effect on the IOPg and age variables, and CCT, and Rx variables seem to have very little effect on the IOPg variable. The ƒ statistic was 80.78, $p < 0.0001$ which also indicates that the model has excellent statistic predictive value. (RBT = rebound tonometry, Rx = MSE refractive error, CCT = central corneal thickness, K = corneal curvature, CH = corneal hysteresis, IOPg = Goldmann equivalent IOP, and CRF = corneal resistance factor. R^2 = coeffiecient of determination).

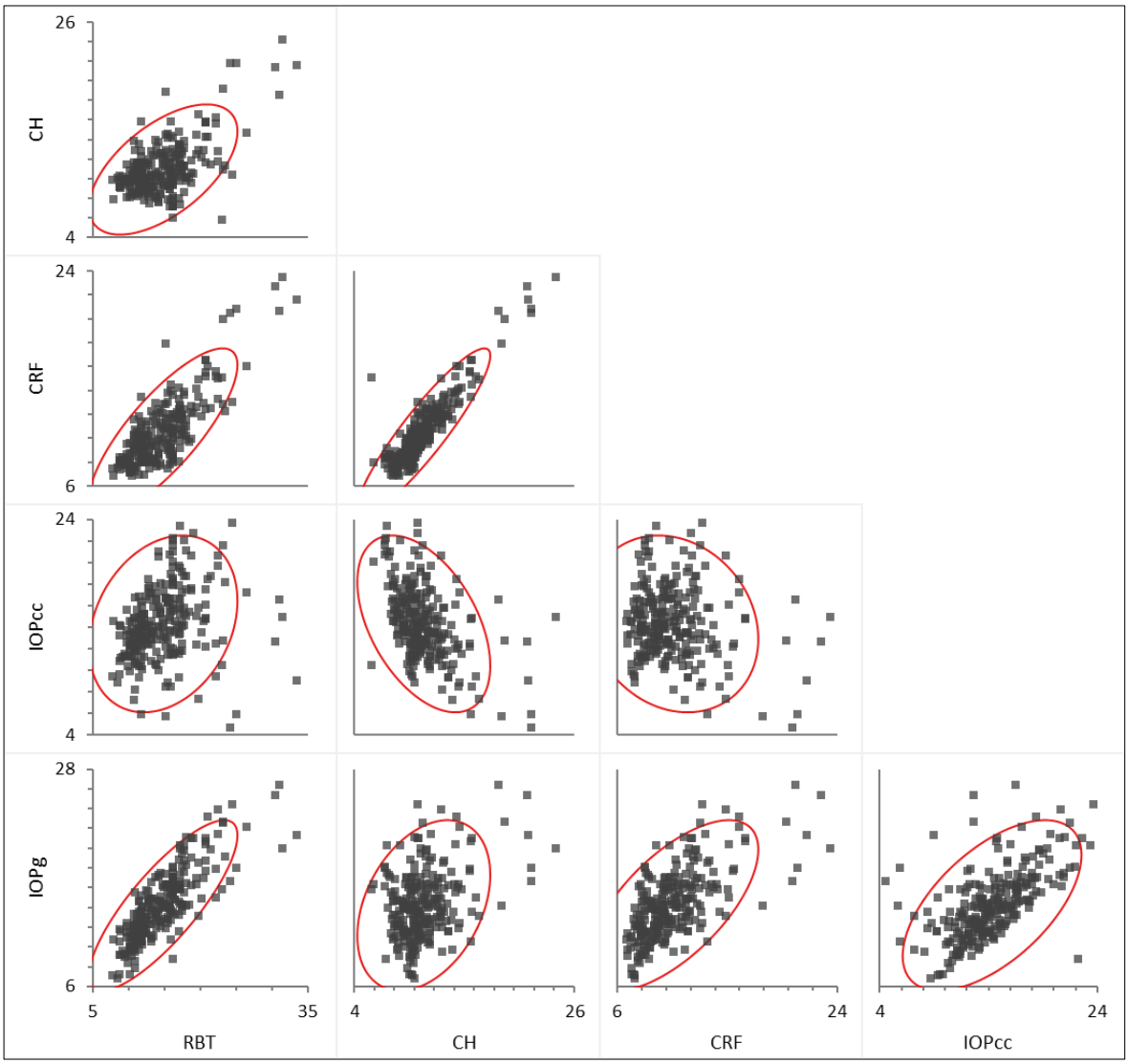


Figure 6.6 Multiple scatter plots of the correlation of all ICare RBT and ORA measurements with and without lenses.ICare RBT is strongly correlated with ORA IOPg and CRF. The correlation with ORA IOPcc and CH is weaker. (CH = corneal hysteresis, CRF = corneal resistance factor, RBT = rebound tonometry, IOPg = Goldmann equivalent IOP, IOPcc = cornea compensated IOP).

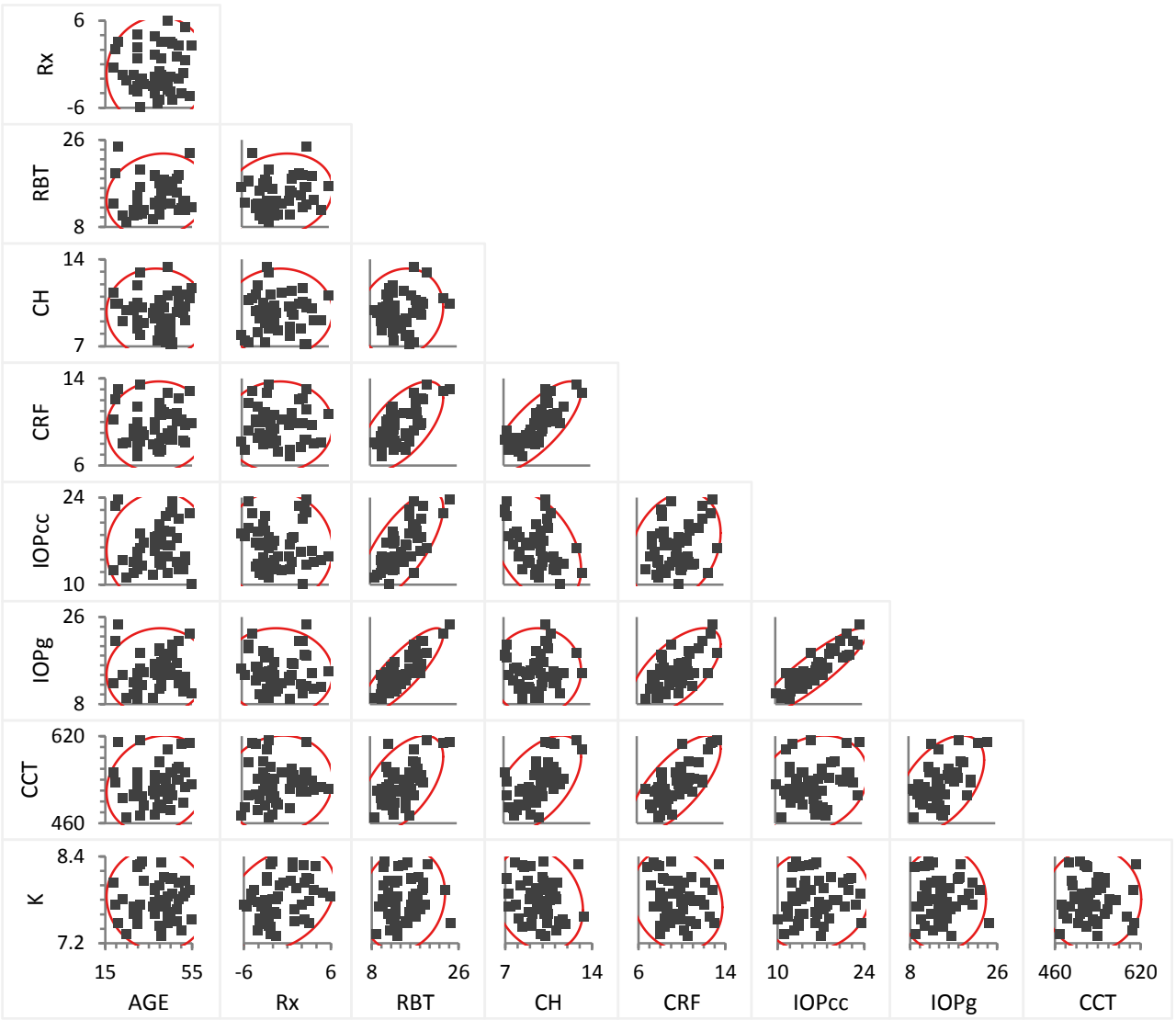


Figure 6.7 Multiple scatter plots of the different variables displaying relationships from the multiple linear regression model.

From the above it is evident that RBT had strong relationships with CRF, IOPcc, IOPg, and less strong with CCT. CH had strong relationships with CCT, and CRF. CRF had strong relationships with RBT, CCT, IOPg, and less strong with IOPcc. IOPcc had strong relationships with RBT and IOPg while IOPg had strong relationships with CRF, IOPcc, and less strong with CH. CCT had strong relationships with CH, CRF, and less strong with IOPg. K does not seem to have had strong relationships with these variables. (RBT = rebound tonometry, Rx =MSE Refractive error, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP, CCT = central corneal thickness, and K =corneal curvature

With contact lenses *in situ* multiple regression analyses confirmed the strong predictive effects of CH and CRF on ICare RBT as well as ORA IOPg and IOPcc with the four different lenses *in situ*.

For ICare RBT with the Pure Vision (A) lens R^2 = 0.78 and R^2 adjusted = 0.75, f = 25.93, p < 0.0001 indicating good predictability with the model including age, Rx, CHA, CRFA, CCTA, and KA as predicting variables. Both CHA and CRFA had significant predictive ability β = -0.59, p = 0.026 (95% CI [-1.098 to -0.076]), and β = 2.14, p < 0.0001 (95% CI [1.55 to 2.73]), respectively. Stepwise regression (R^2 = 0.77) showed that KA significantly affects RBTA β = 2.239 (95% CI [0.007 to 4,470]), p = 0.0493. CRFA also affects RBTA but less significantly β = 2.096 (95% CI [1.634 to 2.557]), p = 0.0000. CHA's effect on RBTA was the least significant β = -0.692 (95% CI [-1.165 to -0.219]), p = 0.0041. For the Frequency XC (B) lens R^2 = 0.79 and R^2 adjusted = 0.76, f = 27.15, p < 0.0001 and the predictive values of CHB and CRFB were β = -1.6, p < 0.0001 (95% CI [-2.15 to -1.05]), and β = 2.42, p < 0.0001 (95 % CI [1.904 to 2.934]), respectively. Stepwise regression (R^2 = 0.77) showed that CRFB significantly affects RBTB β = 2.473 (95% CI [2.047 to 2.899]), p = 0.0000. CHB also affects RBTB but less significantly β = -1.547 (95% CI [-2.070 to -1.024]), p = 0.0000. For the Acuvue 1-Day Moist (C) lens R^2 = 0.80 and R^2 adjusted = 0.77, f = 28.06, p < 0.0001 and the predictive values of CHC and CRFC were β = -1.99, p < 0.0001 (95% CI [-2.603 to -1.383]) and β = 2.896, p < 0.0001 (95 % CI [2.338 to 3.454]) respectively. Stepwise regression (R^2 = 0.78) showed that CRFC significantly affects RBTC β = 2.904 (95% CI [2.446 to 3.362]), p = 0.0000. CHC also affects RBTC but less significantly β = -1.982 (95% CI [-2.486 to -1.478]), p = 0.0000. For the Acuvue Oasys (D) lens R^2 = 0.80 and R^2 adjusted = 0.77, f = 28.01, p < 0.0001 and the predictive values of CHD and CRFD were β = -1.890, p < 0.0001 (95 % CI [-2.541 to -1.239]) and β = 2.651, p < 0.0001 (95% CI [2.028 to 3.274]) respectively. Stepwise regression (R^2 = 0.78) showed that CRFD significantly affects RBTD β = 2.774 (95% CI [2.299 to 3.249]), p = 0.0000. CHD also affects RBTD but less significantly β = -2.038 (95% CI [-2.623 to -1.455]), p = 0.0000. Finally Rx also had an effect on RBTD β = -0.225 (95% CI [-0.397 to -0.052]), p = 0.01080. (Figures 6.8 to 6.11).

N	50
Equation	RBTA = -19.85 + 0.03051 AGE - 0.2782 Rx - 0.5868 CHA + 2.138 CRFA + 0.0008741 CCTA + 1.867 KA
R^2	0.783
R^2 adjusted	0.753
SE of fit (RMSE)	2.6958

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	-19.85	-42.68 to 2.982	11.321	-	0.0867 [1]
AGE	0.03051	-0.05722 to 0.1182	0.043501	1.09	0.4868 [1]
Rx	-0.2782	-0.7030 to 0.1465	0.21061	2.62	0.1934 [1]
CHA	-0.5868	-1.098 to -0.07584	0.25337	4.96	0.0254 [2]
CRFA	2.138	1.549 to 2.727	0.29205	6.63	<0.0001 [2]
CCTA	8.741 E-04	-0.02336 to 0.02511	0.012015	1.88	0.9423 [1]
KA	1.867	-0.5183 to 4.251	1.1826	1.70	0.1218 [1]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Do not reject the null hypothesis at the 5% significance level.
[2] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.

Figure 6.8 For ICare RBT with the Pure Vision lens (designated A) R^2 = 0.783 and R^2 adjusted = 0.753, f = 25.93, p < 0.0001 indicating good predictability with the model including age, Rx, CHA, CRFA, CCTA, and KA as predicting variables.Both CHA and CRFA had significant predictive ability with β =-0.59, p = 0.026, and β = 2.14, p < 0.0001 respectively. (RBT = rebound tonometry, Rx =MSE Refractive error, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP, CCT = central corneal thickness, and K =corneal curvature, R^2 = coeffiecient of determination)

N	50
Equation	RBTB = -6.201 + 0.008511 AGE - 0.03079 Rx - 1.6 CHB + 2.419 CRFB + 0.006886 CCTB + 1.097 KB
R^2	0.791
R^2 adjusted	0.762
SE of fit (RMSE)	1.5370

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	-6.201	-19.01 to 6.609	6.3522	-	0.3344 [1]
AGE	0.008511	-0.04193 to 0.05895	0.025012	1.11	0.7353 [1]
Rx	-0.03079	-0.2673 to 0.2057	0.11726	2.50	0.7942 [1]
CHB	-1.600	-2.151 to -1.049	0.27309	2.78	<0.0001 [2]
CRFB	2.419	1.904 to 2.934	0.25523	3.65	<0.0001 [2]
CCTB	0.006886	-0.006806 to 0.02058	6.7892 E-03	3.01	0.3162 [1]
KB	1.097	-0.2882 to 2.482	0.68693	1.90	0.1176 [1]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Do not reject the null hypothesis at the 5% significance level.
[2] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.

Figure 6.9 For the Frequency XC lens (designated B) R^2 = 0.791 and R^2 adjusted = 0.762, f = 27.15, p < 0.0001 indicating good predictability of the model.The predictive values of CHB and CRFB were β =-1.6, p < 0.0001, and β =2 .42, p < 0.0001 respectively. (RBT = rebound tonometry, Rx = MSE Refractive error, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP, CCT = central corneal thickness, and K = corneal curvature, R^2 = coeffiecient of determination).

N	50
Equation	RBTC = 2.286 + 0.01341 AGE - 0.1115 Rx - 1.993 CHC + 2.896 CRFC + 0.003555 CCTC + 0.09399 KC
R^2	0.797
R^2 adjusted	0.768
SE of fit (RMSE)	1.4978

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	2.286	-12.29 to 16.87	7.2293	-	0.7533 [1]
AGE	0.01341	-0.03849 to 0.06531	0.025735	1.23	0.6050 [1]
Rx	-0.1115	-0.2854 to 0.06233	0.086202	1.42	0.2027 [1]
CHC	-1.993	-2.603 to -1.384	0.30234	3.88	<0.0001 [2]
CRFC	2.896	2.338 to 3.454	0.27679	3.93	<0.0001 [2]
CCTC	0.003555	-0.01201 to 0.01912	7.7198 E-03	2.21	0.6475 [1]
KC	0.09399	-1.276 to 1.464	0.67925	1.55	0.8906 [1]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Do not reject the null hypothesis at the 5% significance level.
[2] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.

Figure 6.10 For the Acuvue 1-Day Moist lens (designated C) R^2 = 0.797 and R^2 adjusted = 0.768, f = 28.06, p < 0.0001 indicating good predictability of the model.The predictive values of CHC and CRFC were β = -1.99, p < 0.0001 and β = 2.896, p < 0.0001 respectively. (RBT = rebound tonometry, Rx = MSE Refractive error, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP, CCT = central corneal thickness, and K =corneal curvature, R^2 = coeffiecient of determination).

N	50
Equation	RBTD = -0.7285 + 0.02476 AGE - 0.155 Rx - 1.89 CHD + 2.651 CRFD + 0.001149 CCTD + 0.7871 KD
R^2	0.796
R^2 adjusted	0.768
SE of fit (RMSE)	1.5605

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	-0.7285	-16.50 to 15.04	7.8207	-	0.9262 [1]
AGE	0.02476	-0.02788 to 0.07741	0.026104	1.17	0.3481 [1]
Rx	-0.1550	-0.3870 to 0.07706	0.11506	2.34	0.1851 [1]
CHD	-1.890	-2.541 to -1.240	0.32274	5.67	<0.0001 [2]
CRFD	2.651	2.028 to 3.274	0.30890	8.06	<0.0001 [2]
CCTD	0.001149	-0.01659 to 0.01889	8.7950 E-03	3.81	0.8967 [1]
KD	0.7871	-0.7473 to 2.321	0.76083	2.13	0.3067 [1]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Do not reject the null hypothesis at the 5% significance level.
[2] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.

Figure 6.11 For the Acuvue Oasys lens (designated D) R^2 = 0.796 and R^2 adjusted = 0.768, f= 28.01, p < 0.0001 indicating good predictability of the model.The predictive values of CHD and CRFD were β =-1.890, p < 0.0001 and β = 2.651, p < 0.0001 respectively. (RBT = rebound tonometry, Rx = MSE Refractive error, CH = corneal hysteresis, CRF= corneal resistance factor, IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP, CCT = central corneal thickness, and K = corneal curvature, R^2 = coeffiecient of determination).

ORA IOPg with the Pure Vision (A) lens R^2 = 0.72 and R^2 adjusted = 0.68, f = 18.42, p < 0.0001 indicating good predictability with the model including age, Rx, CHA, CRFA, CCTA, and KA as predicting variables. Both CHA and CRFA had significant predictive ability β = -0.725, p = 0.0007 (95% CI [-1.126 to -0.323]) and β = 1,399, p < 0.0001 (95% CI [0.936 to 1.861]) respectively. Stepwise regression (R^2 = 0.68) showed that KA significantly affects IOPgA β = 1.994 (95% CI [0.168 to 3.821]), p = 0.0324. CRFA also affects IOPgA but less significantly β = 1.545 (95% CI [1.167 to 1.923]), p = 0.0000. Finally CHA also had an effect on IOPgA β = -0.685 (95% CI [-1.072 to -0.2984]), p = 0.00052. For the Frequency XC (B) lens R^2 = 0.87 and R^2 adjusted = 0.85, f = 46.75, p < 0.0001 indicating good predictive value values. Both CHB and CRFB had significant predictive ability β = -2.002, p < 0.0001 (95% CI [-2.488 to -1.517]) and β = 2.802, p < 0.0001 (95% CI [2.348 to 3.256]) respectively. Stepwise regression (R^2 = 0.86) showed that CRFB significantly affects IOPgB β = 2.969 (95% CI [2.600 to 3.234]), p = 0.0000. CHB also affects IOPgB but less significantly β = -2.041 (95% CI [-2.494 to -1.588]), p = 0.0000. For the Acuvue 1-Day Moist (C) lens R^2 = 0.97 and R^2 adjusted = 0.97, f = 261.10, p < 0.0001 and the predictive values of CHC and CRFC were β = -2.336, p < 0.0001 (95% CI [-2.539 to -

2.133]) and β = 2.989, p < 0.0001 (95% CI [2.803 to 3.175]) respectively. Stepwise regression (R^2 = 0.97) showed that CRFC significantly affects IOPgC β = 3.011 (95% CI [2.853 to 3.169]), p = 0.0000. Rx also affects IOPgC but less significantly β = 0.069 (95% CI [0.021 to 0.118]), p = 0.00504. Finally CHC also had an effect on IOPgC β = -2.338 (95% CI [-2.508 to -2.168]), p =0.0000. For the Acuvue Oasys (D) lens R^2 = 0.97 and R^2 adjusted = 0.97, f = 248.90, p < 0.0001 and the predictive values of CHD and CRFD were β = -2.795, p < 0.0001 (95% CI [-3.043 to -2.547]) and β = 3.253, p < 0.0001 (95 % CI [3.015 to 3.490]) respectively. Stepwise regression (R^2 = 0.97) showed that CRFD significantly affects IOPgD β = 3.223 (95% CI [3.042 to 3.404]), p = 0.0000. CHD also affects IOPgD but less significantly β = -2.759 (95% CI [-2.985 to -2.533]), p = 0.0000. (Figures 6.12 to 6.15).

N	50
Equation	IOPgA = -13.84 + 0.05898 AGE + 0.3119 Rx - 0.7247 CHA + 1.399 CRFA - 0.001488 CCTA + 2.457 KA
R^2	0.720
R^2 adjusted	0.681
SE of fit (RMSE)	2.1173

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	-13.84	-31.77 to 4.092	8.8921	-	0.1269 [1]
AGE	0.05898	-0.009922 to 0.1279	0.034167	1.09	0.0915 [1]
Rx	0.3119	-0.02165 to 0.6456	0.16542	2.62	0.0661 [1]
CHA	-0.7247	-1.126 to -0.3233	0.19901	4.96	0.0007 [2]
CRFA	1.399	0.9362 to 1.861	0.22939	6.63	<0.0001 [2]
CCTA	-0.001488	-0.02052 to 0.01754	9.4371 E-03	1.88	0.8755 [1]
KA	2.457	0.5838 to 4.330	0.92882	1.70	0.0114 [2]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Do not reject the null hypothesis at the 5% significance level.
[2] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.

Figure 6.12 ORA IOPg with the Pure Vision lens (designated A) R^2 = 0.720 and R^2 adjusted = 0.681, f = 18.42, p < 0.0001 indicating good predictability with the model including age, Rx, CHA, CRFA, CCTA, and KA as predicting variables.Both CHA and CRFA had significant predictive ability with β = -0.725, p = 0.0007 (95 % CI [-1.126 to -0.323]) and β = 1,399, p < 0.0001 (95 % CI [0.936 to 1.861]) respectively. (RBT = rebound tonometry, Rx = MSE Refractive error, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP, CCT = central corneal thickness, and K = corneal curvature, R^2 = coeffiecient of determination).

N	50
Equation	IOPgB = 7.807 - 0.001966 AGE + 0.03644 Rx - 2.002 CHB + 2.802 CRFB + 0.004083 CCTB - 0.4177 KB
R^2	0.867
R^2 adjusted	0.848
SE of fit (RMSE)	1.3550

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	7.807	-3.486 to 19.10	5.5999	-	0.1704 [1]
AGE	-0.001966	-0.04643 to 0.04250	0.022049	1.11	0.9294 [1]
Rx	0.03644	-0.1720 to 0.2449	0.10337	2.50	0.7262 [1]
CHB	-2.002	-2.488 to -1.517	0.24075	2.78	<0.0001 [2]
CRFB	2.802	2.348 to 3.256	0.22500	3.65	<0.0001 [2]
CCTB	0.004083	-0.007987 to 0.01615	5.9852 E-03	3.01	0.4987 [1]
KB	-0.4177	-1.639 to 0.8035	0.60558	1.90	0.4940 [1]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Do not reject the null hypothesis at the 5% significance level.
[2] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.

Figure 6.13 For the Frequency XC lens (designated B) R^2 = 0.867 and R^2 adjusted = 0.849, f = 46.75, p < 0.0001 indicating good predictive value values.Both CHB and CRFB had significant predictive ability with β = -2.002, p < 0.0001 (95 % CI [-2.488 to -1.517]) and β = 2.802, p < 0.0001 (95 % CI [2.348 to 3.256]) respectively. (RBT = rebound tonometry, Rx = Refractive error, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP, CCT = central corneal thickness, and K =corneal curvature, R^2 = coeffiecient of determination).

N	50
Equation	IOPgC = 9.663 + 0.007589 AGE + 0.0558 Rx - 2.336 CHC + 2.989 CRFC + 0.0005615 CCTC - 0.2034 KC
R^2	0.973
R^2 adjusted	0.970
SE of fit (RMSE)	0.4991

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	9.663	4.805 to 14.52	2.4088	-	0.0002 [1]
AGE	0.007589	-0.009704 to 0.02488	8.5748 E-03	1.23	0.3811 [2]
Rx	0.05580	-0.002127 to 0.1137	0.028723	1.42	0.0586 [2]
CHC	-2.336	-2.539 to -2.133	0.10074	3.88	<0.0001 [1]
CRFC	2.989	2.803 to 3.175	0.092225	3.93	<0.0001 [1]
CCTC	5.615 E-04	-0.004626 to 0.005749	2.5722 E-03	2.21	0.8282 [2]
KC	-0.2034	-0.6598 to 0.2530	0.22633	1.55	0.3738 [2]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.
[2] Do not reject the null hypothesis at the 5% significance level.

Figure 6.14 For the Acuvue 1-Day Moist lens (designated C) R^2 = 0.973 and R^2 adjusted = 0.970, f = 261.10, p < 0.0001 and the predictive values of CHC and CRFC were β = -2.336, p < 0.0001 (95% CI [-2.539 to -2.133]) and β = 2.989, p < 0.0001 (95 % CI [2.803 to 3.175]), respectively.(RBT = rebound tonometry, Rx = Refractive error, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP, CCT = central corneal thickness, and K = corneal curvature, R^2 = coeffiecient of determination).

N	50
Equation	IOPgD = 9.731 - 0.01418 AGE - 0.06135 Rx - 2.795 CHD + 3.253 CRFD + 0.00245 CCTD - 0.01192 KD
R^2	0.972
R^2 adjusted	0.968
SE of fit (RMSE)	0.5949

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	9.731	3.718 to 15.74	2.9814	-	0.0022 [1]
AGE	-0.01418	-0.03425 to 0.005884	9.9513 E-03	1.17	0.1613 [2]
Rx	-0.06135	-0.1498 to 0.02711	0.043864	2.34	0.1691 [2]
CHD	-2.795	-3.043 to -2.547	0.12303	5.67	<0.0001 [1]
CRFD	3.253	3.015 to 3.490	0.11776	8.06	<0.0001 [1]
CCTD	0.002450	-0.004311 to 0.009212	3.3528 E-03	3.81	0.4689 [2]
KD	-0.01192	-0.5968 to 0.5730	0.29004	2.13	0.9674 [2]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.
[2] Do not reject the null hypothesis at the 5% significance level.

Figure 6.15 For the Acuvue Oasys lens (designated D) R^2 = 0.972 and R^2 adjusted = 0.968, *f* = 248.90, *p* <0.0001 and the predictive values of CHD and CRFD were β =-2.795, *p* < 0.0001 (95 % CI [-3.043 to -2.547]) and β = 3.253, *p* < 0.0001 (95% CI [3.015 to 3.490]) respectively.(RBT = rebound tonometry, Rx = Refractive error, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP, CCT = central corneal thickness, and K = corneal curvature, R^2 = coeffiecient of determination).

ORA IOPcc with the Pure Vision (A) lens R^2 = 0.40 and R^2 adjusted = 0.31, *f* = 4.70, *p* = 0.0009 indicating poor predictability with the model including age, Rx, CHA, CRFA, CCTA, and KA as predicting variables. Only KA and Age had any predictive ability *β* = 3.084, *p* = 0.0107 (95% CI [0.7530 to 5.415]) and *β* = 0.1018, *p* = 0.0210 (95% CI [0.01608 to 0.1876]) respectively. Stepwise regression (R^2 = 0.24) showed that KA significantly affects IOPccA β = 2.856 (95% CI [0.985 to 4.727]), *p* = 0.00277. Age also affects IOPccA but less significantly β = 0.1139 (95% CI [0.027 to 0.200]), *p* = 0.0095. The coefficient of determination (R^2) is < 0.49 which indicates that the relationships are weak in both the multiple and stepwise regression model. For the Frequency XC (B) lens R^2 = 0.97 and R^2 adjusted = 0.97, *f* = 261.19, *p* < 0.0001 indicating good predictive value values. CHB and CRFB had a significant influence with *β* = -3.413, *p* < 0.0001 (95% CI [-3.605 to -3.220]) and *β* = 2.748, *p* < 0.0001 (95% CI [2.568 to 2.928]) respectively. Stepwise regression (R^2 = 0.96) showed that CHB significantly affects IOPccB β = -3.370 (95% CI [-3.576 to -3.164]), *p* = 0.0000. CRFB also affects IOPccB but less significantly β = 2.846 (95% CI [2.678 to 3.0149]), *p* = 0.0000. For the Acuvue 1-Day Moist (C) lens R^2 = 0.94 and R^2 adjusted = 0.93, *f* = 108.30, *p* < 0.0001 and the predictive values of CHC and CRFC were

β =-2.918, p < 0.0001 (95% CI [-3.201 to -2.635]) and β = 2.465, p < 0.0001 (95% CI [2.206 to 2.725]) respectively. Stepwise regression (R^2 = 0.94) showed that CHC significantly affects IOPccC β = -2.928 (95% CI [-3.164 to -2.693]), p = 0.0000. CRFC also affects IOPccC but less significantly β = 2.533 (95% CI [2.315 to 2.751]), p = 0.0000. Finally Rx also had an effect on IOPccC β = 0.080 (95% CI [0.014 to 0.148]), p = 0.01798. For the Acuvue Oasys (D) lens R^2 = 0.96 and R^2 adjusted = 0.96 f = 178.22, p < 0.0001 and the predictive values of CHD and CRFD were β = -3.443, p < 0.0001 (95 % CI [-3.678 to 3.209]) and β = 2.729, p < 0.0001 (95% CI [2.504 to 2.953]) respectively. Stepwise regression (R^2 = 0.09) showed that Age significantly affects IOPccD β = 0.089 (95% CI [0.012 to 0.167]), p = 0.027. The coefficient of determination (R^2) is < 0.49 which indicates that the relationship is weak (Figures 6.16 to 6.19).

N	50
Equation	IOPccA = -9.309 + 0.1018 AGE + 0.3575 Rx - 0.7601 CHA + 0.561 CRFA - 0.006194 CCTA + 3.084 KA
R^2	0.396
R^2 adjusted	0.312
SE of fit (RMSE)	2.6346

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	-9.309	-31.62 to 13.00	11.064	-	0.4048 [1]
AGE	0.1018	0.01607 to 0.1875	0.042514	1.09	0.0211 [2]
Rx	0.3575	-0.05764 to 0.7726	0.20583	2.62	0.0896 [1]
CHA	-0.7601	-1.259 to -0.2607	0.24762	4.96	0.0037 [2]
CRFA	0.5610	-0.01459 to 1.137	0.28542	6.63	0.0558 [1]
CCTA	-0.006194	-0.02988 to 0.01749	0.011743	1.88	0.6006 [1]
KA	3.084	0.7535 to 5.415	1.1557	1.70	0.0107 [2]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Do not reject the null hypothesis at the 5% significance level.
[2] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.

Figure 6.16 ORA IOPcc with the Pure Vision lens (designated A) R^2 = 0.396 and R^2 adjusted = 0.312, f = 4.70, p = 0.0009 indicating poor predictability with the model including age, Rx, CHA, CRFA, CCTA, and KA as predicting variables.Only KA and age had any predictive ability with β = 3.084, p = 0.0107 (95% CI [0.7530 to 5.415]) and β = 0.1018, p = 0.0210 (95% CI [0.01608 to 0.1876]) respectively. (RBT = rebound tonometry, Rx = Refractive error, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP, CCT = central corneal thickness, and K = corneal curvature, R^2 = coeffiecient of determination).

N	50
Equation	IOPccB = 23.22 + 0.005642 AGE - 0.1462 Rx - 3.413 CHB + 2.748 CRFB + 0.006689 CCTB - 0.5988 KB
R^2	0.973
R^2 adjusted	0.970
SE of fit (RMSE)	0.5381

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	23.22	18.73 to 27.70	2.2240	-	<0.0001 [1]
AGE	0.005642	-0.01202 to 0.02330	8.7570 E-03	1.11	0.5228 [2]
Rx	-0.1462	-0.2290 to -0.06338	0.041055	2.50	0.0009 [1]
CHB	-3.413	-3.606 to -3.220	0.095615	2.78	<0.0001 [1]
CRFB	2.748	2.568 to 2.928	0.089360	3.65	<0.0001 [1]
CCTB	0.006689	0.001895 to 0.01148	2.3770 E-03	3.01	0.0073 [1]
KB	-0.5988	-1.084 to -0.1138	0.24051	1.90	0.0167 [1]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.
[2] Do not reject the null hypothesis at the 5% significance level.

Figure 6.17 For the Frequency XC lens (designated B) R^2=0.973 and R^2 adjusted = 0.970, f = 261.19, p < 0.0001 indicating good predictive value values. CHB and CRFB had a significant influence with β = -3.413, p < 0.0001 (95 % CI [-3.605 to -3.220]) and β = 2.748, p < 0.0001 (95% CI [2.568 to 2.928]) respectively. (RBT = rebound tonometry, Rx = Refractive error, CH= corneal hysteresis, CRF= corneal resistance factor, IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP, CCT = central corneal thickness, and K = corneal curvature, R^2 = coeffiecient of determination).

N	50
Equation	IOPccC = 17.87 + 0.005586 AGE + 0.07877 Rx - 2.918 CHC + 2.465 CRFC + 0.003452 CCTC + 0.09138 KC
R^2	0.938
R^2 adjusted	0.929
SE of fit (RMSE)	0.6954

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	17.87	11.10 to 24.64	3.3563	-	<0.0001 [1]
AGE	0.005586	-0.01851 to 0.02968	0.011948	1.23	0.6425 [2]
Rx	0.07877	-0.001937 to 0.1595	0.040020	1.42	0.0555 [2]
CHC	-2.918	-3.201 to -2.635	0.14036	3.88	<0.0001 [1]
CRFC	2.465	2.206 to 2.725	0.12850	3.93	<0.0001 [1]
CCTC	0.003452	-0.003776 to 0.01068	3.5840 E-03	2.21	0.3408 [2]
KC	0.09138	-0.5446 to 0.7273	0.31535	1.55	0.7734 [2]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.
[2] Do not reject the null hypothesis at the 5% significance level.

Figure 6.18 For the Acuvue 1-Day Moist lens (designated C) R^2 = 0.938 and R^2 adjusted = 0.929, f = 108.30, p < 0.0001 and the predictive values of CHC and CRFC were β = -2.918, p < 0.0001 (95% CI [-3.201 to -2.635] 0 and β = 2.465, p < 0.0001 995% CI [2.206 to 2.725] 0 respectively. (RBT= rebound tonometry, Rx = Refractive error, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc= corneal compensated IOP, IOPg= Goldmann equivalent IOP, CCT= central corneal thickness, and K = corneal curvature, R^2 = coeffiecient of determination).

N	50
Equation	IOPccD = 22.05 - 0.01341 AGE - 0.08981 Rx - 3.444 CHD + 2.729 CRFD + 0.005149 CCTD - 0.181 KD
R^2	0.961
R^2 adjusted	0.956
SE of fit (RMSE)	0.5617

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	22.05	16.37 to 27.72	2.8149	-	<0.0001 [1]
AGE	-0.01341	-0.03236 to 0.005540	9.3957 E-03	1.17	0.1608 [2]
Rx	-0.08981	-0.1733 to -0.006291	0.041416	2.34	0.0357 [1]
CHD	-3.444	-3.678 to -3.209	0.11616	5.67	<0.0001 [1]
CRFD	2.729	2.505 to 2.953	0.11118	8.06	<0.0001 [1]
CCTD	0.005149	-0.001235 to 0.01153	3.1656 E-03	3.81	0.1112 [2]
KD	-0.1810	-0.7333 to 0.3713	0.27385	2.13	0.5122 [2]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.
[2] Do not reject the null hypothesis at the 5% significance level.

Figure 6.19 For the Acuvue Oasys lens (designated D) R^2 = 0.961 and R^2 adjusted = 0.956 f = 178.22, p < 0.0001 and the predictive values of CHD and CRFD were β = -3.443, p < 0.0001 (95% CI [-3.678 to 3.209]) and β = 2.729, p < 0.0001 (95% CI [2.504 to 2.953]) respectively. (RBT = rebound tonometry, Rx = Refractive error, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal compensated IOP, IOPg = Goldmann equivalent IOP, CCT = central corneal thickness, and K = corneal curvature, R^2 = coeffiecient of determination).

The above regression analyses included analysis of the data of all the measurements with each of the four lenses (plus and minus) *in situ*. From Chapter 5 it was evident that the K-readings with the plus lenses were steeper (M = 7.60, SD = 0.45 [95% CI 7.494 to 7.704] mm) than the measurements without the lenses in the plus lens group (M = 7.93, SD = 0.45 [95% CI 7.79 to 8.06] mm), and with the minus lenses flatter (M = 8.03, SD = 0.31 [95% CI 7.954 to 8.104] mm) than the measurements without the lenses in the minus lens group (M = 7.73, SD = 0.26 [95% CI 7.63 to 7.82] mm).(Figures 5.1 and 5.2, pages 143 and 144). The mean difference between the K-readings with plus and minus lenses were M = -0.43, SD = 0.52 (95% CI -0.522 to -0.307) mm which is significant t = 6.98, p < 0.0001. Salvetat et al. (2011) found that 1.00 D of corneal curvature change could influence IOP measurement by 0.76 mmHg. Therefore, the IOP measurements with the lenses could be affected by 1.41 mmHg and 1.25 mmHg for plus and minus lenses respectively due to the changes in corneal curvature (Salvetat et al., 2011).

Multiple regression analyses of the results of measurements with all the plus lenses confirmed the predictive effects of both CH: β = -1.46, p < 0.0001 (95% CI [-2.000 to -0.913]) and CRF: β = 2.53, p <

0.0001 (95% CI [1.998 to 3.054]); however, K: β = -0.173, *p* = 0.827 (95% CI [-1.743 to 1.397]) had little predictive effect on ICare RBT measurements. Stepwise regression (R^2 = 0.86) showed that CRF+ significantly affects RBT+ β = 2.535 (95% CI [2.061 to 3.009]), *p* = 0.0000. CH+ also affects RBT+ but less significantly β = -1.461 (95% CI [-1.955 to -0.966]), *p* = 0.0000. With IOPcc both CH: β = -3.18., *p* < 0.0001 (95% CI [-3.540 to -2.812]) and CRF: β = 2.624, *p* < 0.0001 (95% CI [2.271 to 2.978]) were strongly predictive but K: β = -0.11, *p* = 0.8330 (95% CI [-1.161 to 0.9388]) had little predictive effect. Stepwise regression (R^2 = 0.86) showed that CH+ significantly affects IOPcc+ β = -3.215 (95% CI [-3.548 to -2.880]), *p* = 0.0000. CRF+ also affects IOPcc+ but less significantly β = 2.685 (95% CI [2.365 to 3.005]), *p* = 0.0000. With IOPg both CH: β = -2.80, *p* < 0.0001 (95% CI [-2.985 to -2.609]) and CRF: β = 3.27, *p* < 0.0001 (95% CI [3.088 to 3.453]) were strongly predictive but K: β = -0.3490, *p* = 0.2036 (95% CI [-0.8916 to 0.1937]) had little predictive effect. Stepwise regression (R^2 = 0.97) showed that CRF+ significantly affects IOPg+ β = 3.263 (95% CI [3.097 to 3429]), *p* = 0.0000. CH+ also affects IOPg+ but less significantly β = -2.781 (95% CI [-2.954 to -2.607]), *p* = 0.0000.

The multiple regression analyses of the results with the minus lenses for RBT confirmed the predictive effects of CH: β = -0.76, *p* < 0.0001 (95% CI [-1.051 to -0.4605]) and CRF: β = 1.79, *p* < 0.0001 (95% CI [1.484 to 2.099]). Interestingly Age: β = 0.082, *p* = 0.0001 (95% CI [0.0404 to 0.1229]) and more importantly K: β = 2.09. *p* = 0.0002 (95% CI [1.002 to 3.185]) also had predictive effects in the model. Stepwise regression (R^2 = 0.77) showed that K- significantly affects RBT- β = 2.524 (95% CI [1.525 to 3.522]), *p* = 0.0000. CRF- also affects RBT- but less significantly β = 1.879 (95% CI [1.596 to 2.161]), *p* = 0.0000. CH- also affects RBT- β = -0.820 (95% CI [-1.108 to -0.532]), *p* = 0.0000. Finally Age also had an effect on RBT- β = 0.090 (95% CI [0.050 to 0.129]), *p* = 0.0001. With IOPcc the results were similar with CH: β = -1.18, *p* < 0.0001 (95% CI [-1.495 to -0.8624]); CRF: β = 0.57, *p* = 0.2260, (95% CI [0.2425 to 0.9005]); Age: β = 0.12, *p* < 0.0001 (95% CI [0.0745 to 0.1629]), and K: β = 1.81, *p* = 0.0027 (95% CI [0.6368 to 2.974]) also having predictive effects in the model. Stepwise regression (R^2 = 0.60) showed that K- significantly affects IOPcc- β = 1909 (95% CI [0.852 to 2.968]), *p* = 0.0040. CH- also affects RBT- but less significantly β = -1.181 (95% CI [-1.486 to -0.876]), *p* = 0.0000. CRF- also affects IOPcc- β = 0.634 (95% CI [0.335 to 0.934]), *p* = 0.0003. Finally Age also had an effect on IOPcc- β = 0.123 (95% CI [0.081 to 0.166]), *p* = 0.0000. In terms of IOPg the results were similar with CH: β = -0.82, *p* < 0.0001 (95% CI [-1.088 to -0.5576]); CRF: β = 1.39, *p* < 0.0001 (95% CI [1.116 to 1.668]); age: β = 0.095, *p* < 0.0001 (95% CI [0.0576 to 0.1317]), and K: β = 1.183, *p* = 0.0183 (95% CI [0.2035 to 2.162]) having predictive effects in the model. Stepwise regression (R^2 = 0.70) showed that K- significantly affects IOPg- β = 1,261 (95% CI [0.371 to 2.150]), *p* = 0.00548. CRF- also affects IOPg- β =

1.450 (95% CI [1.198 to 1.701]), p = 0.0000. CH- also affects IOPg- β = -0.821 (95% CI [-1.077 to -0.564]), p = 0.0000. Finally Age also had an effect on IOPg- β = 0.099 (95% CI [0.063 to 0.135]), p = 0.0000.

To establish which of the inherent properties of the contact lenses influence the accuracy of the measured IOP all the measurements were grouped together; in other words the data for age, Rx, RBT, CH, CRF, CCT, IOPcc, IOPg, CCT, K, modulus, water content, Dk/t, and CT included measurements without lenses as well as measurements with each of the lenses *in situ* (n = 250).

With ICare RBT R^2 = 0.79 and R^2 adjusted = 0.78, f = 90.39, p < 0.0001 indicating good predictability with the model including age, Rx, CH, CRF, CCT, K, modulus, water content, Dk/t, and CT as predicting variables. Both CH and CRF had significant predictive ability β = -1.198, p < 0.0001 (95% CI [-1.438 to -0.9579]), and β = 2.323, p < 0.0001 (95% CI [2.073 to 2.573]) respectively. K also had significant predictive ability and influence β = 1.368, p = 0.0003 (95 % CI [0.6313 to 2.105]) but age less so β = 0.03131, p = 0.0271 (95 % CI [0.0036 to 0.0590]). Stepwise regression (R^2 = 0.79) showed that CRF significantly affects RBT β = 2.330 (95% CI [2.115 to 2.545]), p = 0.0000. CH also affects RBT but less significantly β = -1.224 (95% CI [-1.454 to -0.994]), p = 0.0000. K affects RBT β = 1.302 (95% CI [0.640 to 1.964]), p = 0.00012. Age had a smaller effect β = 0.032 (95% CI [0.005 to 0.059]), p = 0.02236 as did CT β = -0.0087 (95% CI [-0.0167 to -0.001]), p = 0.03371. (Figure 6.20, page 181).

N	250
Equation	RBT = -8.368 + 0.03131 AGE + 0.01106 Rx - 1.198 CH + 2.323 CRF + 0.0007057 CCT + 1.368 K + 1.874 Modulus + 0.04756 Water - 0.005147 Dk/t - 0.04712 CT
R^2	0.791
R^2 adjusted	0.782
SE of fit (RMSE)	1.9621

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	-8.368	-15.66 to -1.073	3.7030	-	0.0247[1]
AGE	0.03131	0.003578 to 0.05904	0.014076	1.07	0.0271[1]
Rx	0.01106	-0.08895 to 0.1111	0.050768	1.44	0.8278[2]
CH	-1.198	-1.438 to -0.9579	0.12195	7.03	<0.0001[1]
CRF	2.323	2.073 to 2.573	0.12686	8.38	<0.0001[1]
CCT	7.057 E-04	-0.006835 to 0.008247	3.8280 E-03	2.55	0.8539[2]
K	1.368	0.6313 to 2.105	0.37413	1.43	0.0003[1]
Modulus	1.874	-1.457 to 5.205	1.6909	27.93	0.2688[2]
Water	0.04756	-0.02142 to 0.1165	0.035015	37.12	0.1757[2]
Dk/t	-0.005147	-0.01651 to 0.006212	5.7664 E-03	6.15	0.3729[2]
CT	-0.04712	-0.1050 to 0.01079	0.029398	59.81	0.1103[2]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.
[2] Do not reject the null hypothesis at the 5% significance level.

Figure 6.20 This model predicts that ICare RBT is significantly affected by CH and CRF, p<0.0001 for both as well as K, *p* = 0.0003. R^2 and R^2 adjusted are > 0.70 indicating that the model has excellent predictive value.Age has less influence on ICare RBT. The *f* statistic was 90.39, *p* < 0.0001 which also indicates that the model has excellent statistic predictive value. (RBT= rebound tonometry, Rx = refractive error, CCT = central corneal thickness, K = corneal curvature, CH = corneal hysteresis, IOPg = Goldmann equivalent IOP, CT = contact lens centre thickness, water = contact lens water content, Dk/t = oxygen transmissibility of the contact lens, modulus = modulus of elasticity of the contact lens, and CRF = corneal resistance factor, R^2 = coeffiecient of determination).

With ORA IOPg R^2 = 0.79 and R^2 adjusted = 0.76, *f* = 91.84, *p* < 0.0001 indicating good predictability with the model including age, Rx, CH, CRF, CCT, K, modulus, water content, Dk/t, and CT as predicting variables. Both CH and CRF had significant predictive ability with *β* = -1.658, *p* < 0.0001 (95 % CI [-1.857 to -1.459]), and *β* = 2.316, *p* < 0.0001 (95 % CI [2.109 to 2.523]) respectively. Lens modulus also had significant predictive ability and influence *β* = -2.953, *p* = 0.0360 (95 % CI [-5.711 to -0.1943]). Stepwise regression (R^2 = 0.78) showed that CRF significantly affects IOPg β = 2.425 (95% CI [2.249 to 2.599]), *p* = 0.0000. CH also affects IOPg but less significantly β = -1.736 (95% CI [-1.927 to -1.544]), *p* = 0.0000. Modulus also affects IOPg β = -1.604 (95% CI [-2.402 to -0807]), *p* = 0.00008 (Figure 6.21).

N	250
Equation	IOPg = 2.611 + 0.01543 AGE + 0.06474 Rx - 1.658 CH + 2.316 CRF + 0.00425 CCT + 0.4003 K - 2.953 Modulus - 0.03006 Water + 0.005425 Dk/t + 0.02344 CT
R^2	0.794
R^2 adjusted	0.785
SE of fit (RMSE)	1.62481

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	2.611	-3.430 to 8.651	3.0664	-	0.3954[1]
AGE	0.01543	-0.007537 to 0.03839	0.011656	1.07	0.1870[1]
Rx	0.06474	-0.01808 to 0.1476	0.042040	1.44	0.1249[1]
CH	-1.658	-1.857 to -1.459	0.10098	7.03	<0.0001[2]
CRF	2.316	2.109 to 2.523	0.10505	8.38	<0.0001[2]
CCT	0.004250	-0.001994 to 0.01049	3.1698 E-03	2.55	0.1813[1]
K	0.4003	-0.2100 to 1.011	0.30981	1.43	0.1976[1]
Modulus	-2.953	-5.711 to -0.1943	1.4002	27.93	0.0360[2]
Water	-0.03006	-0.08718 to 0.02706	0.028995	37.12	0.3009[1]
Dk/t	0.005425	-0.003982 to 0.01483	4.7750 E-03	6.15	0.2571[1]
CT	0.02344	-0.02452 to 0.07139	0.024344	59.81	0.3366[1]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Do not reject the null hypothesis at the 5% significance level.
[2] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.

Figure 6.21 This model predicts that ORA IOPg is significantly affected by CH and CRF, p<0.0001 for both as well as Modulus, *p* = 0.00360. R^2 and R^2 adjusted are > 0.70 indicating that the model has excellent predictive value.The *f* statistic was 91.84, *p* < 0.0001 which also indicates that the model has excellent statistic predictive value. (Rx = refractive error, CCT = central corneal thickness, K = corneal curvature, CH = corneal hysteresis, IOPg = Goldmann equivalent IOP, CT = contact lens centre thickness, water = contact lens water content, Dk/t = oxygen transmissibility of the contact lens, modulus=modulus of elasticity of the contact lens, and CRF= corneal resistance factor. R^2 = coeffiecient of determination).

With ORA IOPcc R^2 = 0.68 and R^2 adjusted = 0.67, *f* = 50.57, *p* < 0.0001 indicating good predictability with the model including age, Rx, CH, CRF, CCT, K, modulus, water content, Dk/t, and CT as predicting variables. Both CH and CRF had significant predictive ability with *β* = -2.082, *p* < 0.0001 (95 % CI [-2.318 to -1.846]), and *β* = 1.785, *p* < 0.0001 (95 % CI [1.539 to 2.031]) respectively. Lens modulus also had significant predictive ability and influence *β* = -3.311, *p* = 0.0476 (95 % CI [-6.586 to -0.0349]) but age less so *β* = 0.03065, *p* = 0.0277 (95 % CI [0.003386 to 0.05792]). Stepwise regression (R^2 = 0.69) showed that CH significantly affects IOPcc β = -2.131 (95% CI [-2.361 to -1.901]), *p* = 0.0000. CRF also affects IOPcc but less significantly β = 1.799 (95% CI [1.589 to 2.011]), *p* = 0.0000. Modulus also affects IOPcc β = -2.327 (95% CI [-3.269 to -1.386]), *p* = 0.0000. Finally Age also affects IOPcc β = 0.030 (95% CI [0.003 to 0.057]), *p* = 0.02848 (Figure 6.22).

N	250
Equation	IOPcc = 13.15 + 0.03065 AGE + 0.0797 Rx - 2.082 CH + 1.785 CRF + 0.0005199 CCT + 0.5833 K - 3.311 Modulus - 0.0008219 Water + 0.008676 Dk/t + 0.003983 CT
R^2	0.679
R^2 adjusted	0.666
SE of fit (RMSE)	1.92959

Parameter	Estimate	95% CI	SE	VIF	p-value
Constant	13.15	5.979 to 20.33	3.6416	-	0.0004[1]
AGE	0.03065	0.003386 to 0.05792	0.013843	1.07	0.0277[1]
Rx	0.07970	-0.01865 to 0.1781	0.049926	1.44	0.1117[2]
CH	-2.082	-2.318 to -1.846	0.11993	7.03	<0.0001[1]
CRF	1.785	1.539 to 2.031	0.12475	8.38	<0.0001[1]
CCT	5.199 E-04	-0.006896 to 0.007936	3.7645 E-03	2.55	0.8903[2]
K	0.5833	-0.1415 to 1.308	0.36793	1.43	0.1142[2]
Modulus	-3.311	-6.586 to -0.03487	1.6629	27.93	0.0476[1]
Water	-8.219 E-04	-0.06866 to 0.06701	0.034434	37.12	0.9810[2]
Dk/t	0.008676	-0.002495 to 0.01985	5.6707 E-03	6.15	0.1274[2]
CT	0.003983	-0.05297 to 0.06093	0.028910	59.81	0.8905[2]

H0: β = 0
The parameter is equal to 0.
H1: β ≠ 0
The parameter is not equal to 0.
[1] Reject the null hypothesis in favour of the alternative hypothesis at the 5% significance level.
[2] Do not reject the null hypothesis at the 5% significance level.

Figure 6.22 This model predicts that ORA IOPcc is significantly affected by CH and CRF, $p < 0.0001$ for both as well as Modulus, $p = 0.00476$ and less significantly by age $p = 0.0277$.R^2 and R^2 adjusted are < 0.70 indicating that the model has poor predictive value. The *f* statistic was 50.57, $p < 0.0001$ which also indicates that the model has fair statistic predictive value. (Rx = refractive error, CCT = central corneal thickness, K = corneal curvature, CH = corneal hysteresis, IOPg = Goldmann equivalent IOP, CT = contact lens centre thickness, water = contact lens water content, Dk/t = oxygen transmissibility of the contact lens, modulus = modulus of elasticity of the contact lens, and CRF = corneal resistance factor, R^2 = coeffiecient of determination).

6.5 Discussion

Biomechanical properties of the cornea have a significant impact on IOP measurement error (Liu and Roberts, 2005) which may vary depending on the instrumentation used to measure the IOP. In fact, all tonometers that measure IOP through the application of stress to the corneal tissue are subject to the effects of corneal resistance which is an 'effective' rather than an intrinsic mechanical property such as Young's modulus. Relatively recently the ORA, an *in vivo* method to measure the biomechanical properties of the cornea in the form of two metrics, CH and CRF, became available. CH can be considered a dynamic corneal property indicating how much energy the cornea absorbs and is the difference between the two pressure measurements made by the ORA. Corneal resistance is a composite characteristic which incorporates the material as well as geometric properties of the

corneal tissue (Luce, 2005; Jorge, Gonzales-Meijome, et al., 2008; Lau and Pye, 2011). Although CH and CRF represent biomechanical properties of the cornea, it is prudent to keep in mind that they are composite measures which characterise the structural response of the eye to the measurement device rather than intrinsic properties of the corneal tissue (Jorge, Gonzales-Meijome, et al., 2008; Lau and Pye, 2011). In other words, these so-called biomechanical properties represent the response of the entire corneal tissue to the measurement principle of the ORA (Jorge, Gonzales-Meijome, et al., 2008; Lau and Pye, 2011). Considering that the ORA uses the delay in corneal response after the applanation process to determine the viscoelastic properties of the cornea, it can be assumed that the absorbed energy could also delay the corneal response when an impact is applied to the cornea to measure IOP (Jorge, Gonzales-Meijome, et al., 2008). The ICare RBT should therefore be affected by the corneal biomechanical properties. Previous studies show this is indeed the case and that ICare RBT is correlated with CRF and CH (Chui et al., 2008; Jorge, Gonzales-Meijome, et al., 2008). Other studies also found correlations between ICare RBT and CCT, corneal curvature, and refractive error (Detry-Morel et al., 2006; Lopez-Caballero et al., 2007; Avitabile et al., 2010; Hohmann et al., 2012; Rao et al., 2012). The purpose of this experimental chapter was to identify from the measured, intrinsic and extrinsic variables (corneal and contact lens properties) the significant ones which may affect the measurement of IOP with the ICare RBT and the ORA tonometers with and without disposable soft contact lenses on the eye.

Multiple linear regression analyses of the results of this study showed that CRF was correlated to and significantly affected ICare RBT. This was also the case with CH and CCT although the effect was less. Although corneal curvature also affects ICare RBT, it was not statistically significant. CCT was strongly correlated to and affected CRF. CCT, IOPg and ICare RBT were strongly correlated to CH and CRF. As shown before, IOPcc was strongly correlated with and predicted ICare RBT and was affected by CH and CRF. IOPg was strongly correlated with and predicted ICare RBT and was affected by CH, CRF and Rx.

These results agreed with those of previous studies which showed that ICare RBT was strongly correlated to CRF, more so than with CCT. Although CCT was correlated with CH, CH did not demonstrate as strong a correlation with ICare RBT as CRF did (Jorge, Gonzales-Meijome, et al., 2008). Corneas with higher values of CH and CRF have a longer delay in response to stress and relaxation forces which means it absorbs more energy when impacted by the probe resulting in higher IOP measurements with the ICare RBT (Chui et al., 2008; Jorge, Gonzales-Meijome, et al.,

2008). The strong correlation between CRF and ICare RBT indicated that the RBT measurements were affected by viscoelastic properties of the cornea rather than just by CCT or elastic (CH) properties. This was in agreement with the findings of Jorge et al. (2008). Other as yet unknown and unmeasured tissue properties of the cornea may also affect the ICare RBT measurements. In contrast to previous studies (Detry-Morel et al., 2006; Lopez-Caballero et al., 2007; Avitabile et al., 2010; Hohmann et al., 2012; Rao et al., 2012), the present study did not find significant correlations between age, refractive error, and corneal curvature with the ICare RBT IOP measurements without contact lenses on the eye. Reasons for this difference may be due to the relatively narrow age range (18 to 55 years, M = 38.90, SD = 9.23 years) of the study participants and the fact that they were all Caucasian and long-term soft contact lens wearers. Although the participants removed their lenses at least 24 hours before data collection, the effects of long-term contact lens wear on the cornea − and therefore IOP measurements − cannot be ruled out (Xu et al., 2008; Hamilton-Maxwell, 2014; Mahjoob et al., 2014).

The multiple regression analyses confirmed the strong predictive effects of CH and CRF on ICare RBT as well as ORA IOPg and IOPcc with the different lenses *in situ*. For ICare RBT both CH and CRF had significant predictive ability and therefore influence with all four lenses. For ORA IOPg, both CH and CRF had significant predictive ability and influence with all four lenses. For ORA IOPcc, CH and CRF had significant predictability and influence with the four lenses tested. However, when splitting the data for the plus and minus lenses, corneal curvature (K) and age also had a small predictive effect on the IOP measurements with the three instruments in the minus lens group only. This may be due to the fact that the combined cornea/lens thickness was less with the minus lenses (M = 561.66, SD = 44.78 µm) than with the plus lenses (M = 607.03, SD = 49.31 µm) or the differences in sample size between the two groups (minus 32 subjects and plus 18 subjects).

Multiple and stepwise regression analysis of the variables including contact lens properties confirmed the significant predictive effects of CRF, CH and modulus on ICare RBT, ORA IOPg and ORA IOPcc. Corneal curvature (K) and age also had predictive ability with the ICare RBT and ORA IOPcc.

The results indicate that the biomechanical properties of the cornea/lens combination were more important in predicting or influencing the measurements of IOP with the ICare RBT and ORA IOPg and IOPcc than CCT, corneal curvature, age, and refractive error.

6.6 Conclusion

The present study showed that although central corneal thickness, age and corneal curvature had some influence on the accuracy of IOP measurements with the ICare RBT and ORA, the biomechanical properties (represented by CH and CRF) of the cornea were more important to consider as it had a greater influence on the accuracy of the measurements with these two instruments. ICare RBT was significantly influenced by the biomechanical properties and corneal curvature and to a lesser extent by age. For IOPg the results were similar in that it was significantly influenced by biomechanical properties and lens modulus. In the case of IOPcc, the most significant influence was from biomechanical properties, modulus and − to a lesser extent − from age. Modulus is a viscoelastic property of the contact lens and it is therefore not unexpected that it would have some influence on the IOP measurements, similar to that of the two biomechanical metrics CH and CRF. Although the ICare RBT and ORA IOPcc do not correlate well, it may be possible to calibrate the ICare RBT to more closely approximate the ORA IOPcc measurements rather than the ORA IOPg measurements if future studies validate that ORA IOPcc is, in fact, a more accurate representation of the "true IOP" of the eye. The ICare RBT is a versatile, cost-effective instrument which is simple to use, accurate for clinical use, and adaptable to different clinical situations.

6.7 Summary of findings

- ICare RBT was influenced by the biomechanical properties (CH and CRF), lens modulus of elasticity, corneal curvature, and age.
- ORA IOPg was influenced by the biomechanical properties (CH and CRF), lens modulus of elasticity, and ocular surface behaviour.
- ORA IOPcc was influenced by the biomechanical properties (CH and CRF), lens modulus of elasticity, and age.
- Although central corneal thickness and corneal curvature had some influence on the accuracy of IOP measurements with the ICare RBT and ORA, the biomechanical properties of the cornea and ocular surface behaviour were more important to consider; and a greater influence on the accuracy of the measurements with these two instruments was observed.

Chapter 7

Final discussion, conclusion, and recommendations for future work

This programme of research examined the reproducibility and repeatability of ICare RBT measurements and the repeatability of the ORA measurements with and without contact lenses on the eye. IOP measurements with the two instruments were clinically compared and by using four different disposable lenses (commonly used by South African practitioners) with different material and physical characteristics. The effect on the accuracy of IOP measurements with contact lenses *in situ* with both the ICare and ORA tonometers were evaluated. Additionally, the physiological as well as physical factors that influence IOP measurement with and without contact lenses on the eye when using these two instruments were examined.

7.1 Reproducibility and repeatability of the ICare RBT and repeatability of the Reichert ORA in a population of normal subjects measured with and without soft disposable contact lenses *in situ*

7.1.1 Intraobserver reliability of the ICare RBT

Without contact lenses the ICCs were 0.95 and 0.88 for DJB and GHK respectively. When considering all the measurements with and without contact lenses on the eye, the ICCs remained high: 0.94 and 0.92 for DJB and GHK respectively. In other words, taking into account Spitzer and Endicott''s criteria, the ±90% intraobserver repeatability of ICare RBT by the two experienced optometrists in this group of patients was excellent (Spitzer and Endicott, 1980). This compares well to previous published data by Asrani et al. (2011), Sahin et al. (2007), and Martinez-de-la-Casa et al. (2005) who all found that the ICare RBT produced repeatable measurements by the same examiner (Martinez-de-la-Casa et al., 2005; Sahin, Basmak, et al., 2007; Asrani et al., 2011). Bland-Altman analyses confirmed the results obtained by ICC with mean differences between measurements without lenses (M = 0.30 mmHg, SD = 1.3 mmHg and M = 0.10 mmHg, SD = 1.7 mmHg for DJB and GHK respectively).

When considering all the measurements, with and without contact lenses by the two observers the mean differences between measurements were M = -0.1 mmHg, SD = 1.5 mmHg and M = 0.1 mmHg, SD = 1.6 mmHg for DJB and GHK respectively. Clinically these small measurement differences are not significant.

In this study the measurement error for the measurements taken without contact lenses was 1.74 mmHg and 2.35 mmHg for DJB and GHK respectively. Measurement error for all the measurements was 2.12 mmHg and 2.45 mmHg for DJB and GHK respectively. This means for 95% of the measurements the true value would be expected to be less than the measurement errors indicated here. Repeatability without lenses was 2.45 mmHg and 2.98 mmHg for DJB and GHK respectively and with all measurements 2.98 mmHg and 3.19 mmHg for DJB and GHK respectively. Hence, for 95% of the measurements the difference between the two measurements would be expected to be less than these values. Compared to GAT with repeatability of 1.7 – 2.0 mmHg the ICare RBT intraobserver repeatability was poor (Thorburn, 1978; Dielemans et al., 1994; Kotecha et al., 2005). However, for clinical IOP screening purposes the intraobserver repeatability of the ICare RBT was as good if not better than comparative noncontact tonometers (Hansen, 1995; Mackie et al., 1996; Tonnu et al., 2005; Ogbuehi, 2006; Regine et al., 2006; Lafaut et al., 2007; AlMubrad and Ogbuehi, 2008; Ogbuehi and Almubrad, 2008). Intraobserver measurement repeatability was not affected by the presence of the disposable contact lenses on the eye.

7.1.2 Interobserver reliability of the ICare RBT

Without contact lenses the ICC was 0.81 and the mean difference determined by Bland-Altman analyses between observer DJB and GHK was M = 0.10 mmHg, SD = 2.2 mmHg. When all the measurements were considered the ICC was 0.88 and the mean difference by Bland-Altman analyses between observer DJB and GHK was (M = 0.4 mmHg, SD = 2.1 mmHg). Clinically, these small measurement differences were not significant. Repeatability was 4.39 mmHg without lenses and 4.12 mmHg with all measurements considered. Therefore for 95% of the measurements the difference between the two observers was expected to be < 4.39 mmHg. In this study the results showed that the interobserver measurement reliability with the ICare RBT was as good without contact lenses on the eye as it was with the four different disposable lenses on the eye. The interobserver reliability values determined in this study also compared well with previous studies for the same instrument (Martinez-de-la-Casa et al., 2005; Detry-Morel et al., 2006; Sahin, Basmak, et al., 2007; Asrani et al., 2011).

Therefore, independent experienced clinicians making IOP measurements under similar conditions with the same ICare RBT would produce repeatable and consistent results even when contact lenses are worn.

7.1.3 Intraobserver reliability of the Reichert ORA without contact lenses *in situ*

It is well known that the OPA affects the accuracy of IOP measurements with the NCT. Several studies showed that the OPA affects the intraobserver repeatability of the ORA IOPcc and IOPg measurements and to a lesser extent the instrument specific biomechanical measurements CH and CRF. In this study four measurements taken by the same observer with the ORA revealed the following results: ICCs were 0.63 for CH, 0.79 for CRF, 0.77 for IOPcc and 0.87 for IOPg. IOPg gave the best test-retest reproducibility followed by CRF, IOPcc and CH. This contrasted with the results found by Wang et al. (2013) which indicated the IOPcc had the poorest test-retest reproducibility. However, except for CH, the ORA measurements performed well considering Spitzer and Endicott's criteria (all ICCs >0.70). Bland-Altman analyses revealed the mean differences between measurements for CH ranged from Ms = 0.013 mmHg to 0.21 mmHg with SDs = 1.21 mmHg to 1.63 mmHg depending on which measurements were compared.

The measurement error for CH was calculated at ME = 2.12 mmHg and the repeatability at 2.86 mmHg. This means that for 95% of the measurements the true value would be within 2.12 mmHg and the difference between the measurements would be less than 2.86 mmHg. The mean differences between measurements for CRF ranged from Ms = 0.08 mmHg to 0.25 mmHg with SDs = 1.35 mmHg to 1.21 mmHg. The measurement error for CRF was calculated at 1.73 mmHg and the repeatability at 2.44 mmHg. This means for 95% of the measurements the true value would within 1.72 mmHg and the difference between the measurements would be less than 2.44 mmHg. These values were clinically insignificant, studies have shown that calibration errors of up to 2 mmHg are frequently encountered with GAT tonometers and measurements are made in 1 mmHg increments (Doughty and Zaman, 2000; Choudhari et al., 2009). Test-retest repeatability for the two corneal biomechanical metrics (CH and CRF) measured by the ORA was excellent.

Bland-Altman analyses revealed the mean differences between measurements for IOPcc ranged from Ms = 0.45 mmHg to 0.21 mmHg with SDs = 2.18 mmHg to 2.27 mmHg. The measurement error for IOPcc was calculated at 3.5 mmHg and the repeatability at 4.94 mmHg. This means for 95% of the measurements the true value would within 3.5 mmHg and the difference between the measurements would be less than 4.94 mmHg. Mean differences between measurements for IOPg ranged from Ms = 0.41 mmHg to 0.65 mmHg with SDs = 1.87 mmHg to 2.10 mmHg. The measurement error for IOPg was 2.65 mmHg and the repeatability 3.75 mmHg indicating that for 95% of the measurements the true value would be within 2.65 mmHg and the difference between

the measurements would be less than 3.75 mmHg. These findings agreed with those of Wang et al. (2013), Moreno-Montanes et al. (2008), and Kotecha et al. (2010) who found that the intraobserver reliability for the IOPcc and IOPg was not as good as that of the two biomechanical metrics (CH and CRF). Reasons for this difference were attributed to the OPA as well as the fact that the two IOP values were calculated from the biomechanical metrics. The repeatability of < 4.94 mmHg found in this study also compared well to the 4.3 mmHg found by Kotecha et al. (2010). Although the repeatability was not as good as that of CH and CRF the mean differences were small and therefore clinically not significant. Intraobserver reliability of the ORA can thus be considered good for all the parameters measured.

7.2 Clinical comparison of the ICare RBT and ORA with and without contact lenses *in situ*

Intraocular pressure measurements with the rebound tonometer (ICare) and the Reichert ocular response analyser (ORA) were compared in this population of healthy subjects with and without contact lenses on the eye.

In the case of the ICare RBT, the literature as well as this study showed that corneal biomechanical properties (CH and CRF) play a major role in the accuracy of the IOP measurements, more so than CCT (Chui et al., 2008; Jorge, Gonzales-Meijome, et al., 2008; Salvetat et al., 2011). The other variables important to consider include CCT, corneal curvature, and refractive error (Detry-Morel et al., 2006; Lopez-Caballero et al., 2007; Avitabile et al., 2010; Salvetat et al., 2011; Hohmann et al., 2012; Rao et al., 2012). With regard to the ORA, many of the same variables influenced the accuracy of the measurements but not all of them influenced each one of the four measurements. Age, corneal curvature, CCT, and corneal biomechanics are important variables which can affect the accuracy of the ORA measurements (Luce, 2005; Kotecha et al., 2006; Kniestedt et al., 2008; Kotecha et al., 2010).

Individually different measurements are affected differently by the variables; CRF is closely associated with CCT; IOPcc is not significantly associated with CCT; and IOPg is associated with CCT, corneal curvature, ocular surface behaviour as well as axial length (Moreno-Montanes et al., 2008; Sullivan-Mee et al., 2009; Kotecha et al., 2010; Terai et al., 2012; Wang et al., 2013; Rimayanti et al., 2014). The ORA employs the same principles as the NCT and is therefore significantly affected by the OPA while the ICare RBT is not affected by the OPA (Moreno-Montanes et al., 2008; Sullivan-Mee et al., 2009; Kotecha et al., 2010; Wang et al., 2013). Jorge et al. (2008) evaluated the correlations

between the corneal biomechanical properties with the IOP obtained with the ICare RBT. They found the ICare RBT displayed higher and more variable results than the ORA with IOPg and IOPcc being more reliable. ICare RBT had a strong positive correlation with IOPg, less so with IOPcc and CRF and a poor correlation with CH. From their results they postulated that the strong correlation with CRF indicated that ICare RBT has a higher correlation with the biomechanical properties of the cornea than with CCT (Jorge, Gonzales-Meijome, et al., 2008). The present study showed that although CCT and K had some influence on the accuracy of IOP measurements with the ICare RBT and ORA, the biomechanical properties of the cornea were more important to consider since it had a greater influence on the accuracy of the IOP measurements with these two instruments.

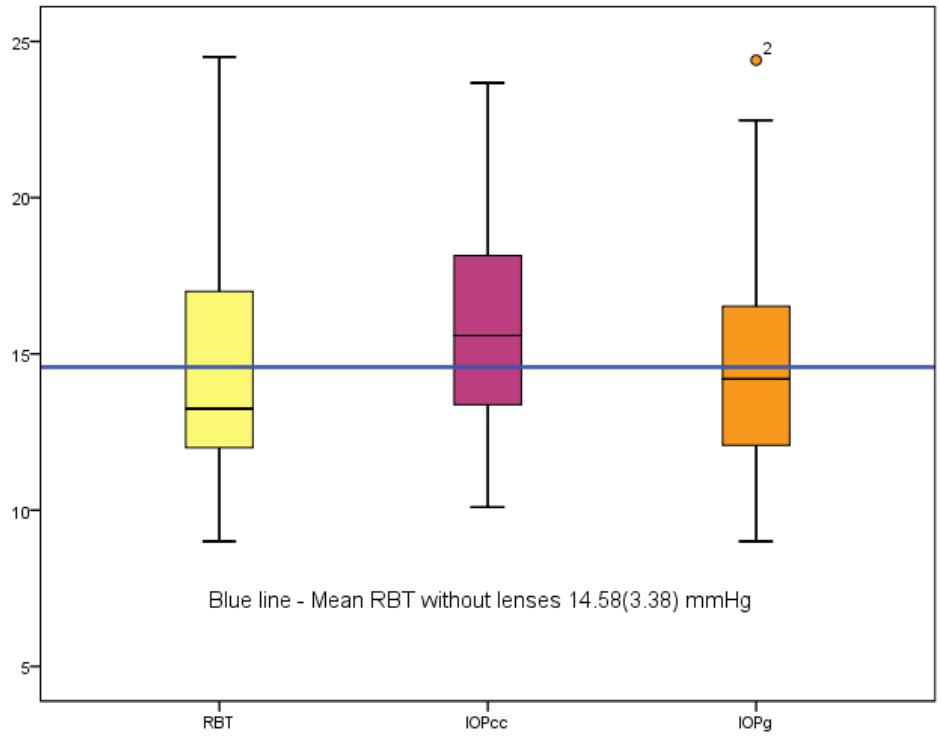


Figure 7.1 Comparison between ICare RBT and ORA IOPcc and IOPg measurements without lenses. RBT and IOPg measurements were well correlated and comparable.(Yellow = RBT, purple = IOPcc, and orange = IOPg).

The results of this study further showed that ICare RBT and ORA IOPg measurements were comparable (Figure 7.1). For the purposes of this study differences of more than 1mmHg were considered clinically significant as most tonometers measure in increments of 1mmHg. Without lenses the mean RBT measurement were M = 14.58, SD = 3.35 mmHg and IOPg M = 14.64, SD = 3.58 mmHg. The mean difference between the two measurements, according to the Bland-Altman

analyses was M = -0.06, SD = 0.59 mmHg and a strong linear relationship existed between the two measurements: r = 0.854. The ANOVA and t-tests confirmed the hypothesis that the two measurements were the same t = -0.04, p = 0.956. With the Pure Vision lenses the ICare RBT and ORA metrics did not compare well at all and the RBT significantly overestimated the IOP compared to the ORA. Pure Vision has a high modulus of elasticity (1.1 MPa) which may have affected the biomechanics of the cornea/lens combination and therefore the ICare RBT measurements.

With the Frequency XC lens the mean ICare RBT measurement was M = 14.09, SD = 3.15 mmHg and IOPg M = 13.55, SD = 3.48 mmHg. Although the ANOVA showed that the RBT and ORA metrics were not comparable, the t-tests showed that the RBT and IOPg values were comparable (t = 2.06, p = 0.0449) with the differences between them clinically and statistically insignificant. Although the hypothesis that ICare RBT and IOPcc were comparable was rejected, and the difference between the means were statistically significant it was not clinically significant (RBT M =14.09, SD = 3.15 mmHg and IOPcc M = 14.83, SD = 3.09 mmHg) (Table 4.3).

With the Acuvue 1-Day Moist lens the mean ICare RBT measurement was M = 13.62, SD = 2.86 mmHg and IOPg M = 13.12, SD = 3.11 mmHg. The ANOVA showed that RBT and IOPg values were comparable (f = 1.44, p = 0.2365), but the t-tests rejected this hypothesis (t = -2.47, p < 0.017). However, despite the fact that the difference between the means was statistically significant, clinically it was not significant (Table 4.3).

With the Acuvue Oasys lens the mean RBT measurement was M = 13.74, SD = 3.24 mmHg, IOPcc M = 14.00, SD = 2.68 mmHg, and IOPg M = 13.48, SD = 3.33 mmHg. The ANOVA confirmed the hypothesis that the RBT, IOPcc and IOPg measurements were comparable (f = 1.17, p = 0.2841 for IOPcc and f = 1.72, p = 0.1957 for IOPg). This hypothesis was further confirmed by the t-tests which indicated that the RBT and ORA IOPcc and IOPg measurements were statistically and clinically comparable (t = -1.08, p = 0.2841 for IOPcc and t = 1.31, p < 0.1957 for IOPg). Finally, the Bland-Altman analyses of all the measurements with as well as without lenses indicated that the mean differences between RBT and IOPcc was M = 0.48, SD = 4.63 mmHg with a weak linear correlation r = 0.262 between the two measurements. The difference was not clinically significant. The mean differences between RBT and IOPg were M = 0.59, SD = 2.39 mmHg with a strong linear correlation between the two measurements. The difference was neither clinically nor statistically significant.

In conclusion, this study confirmed that the ICare RBT and ORA IOPg pressure measurements were highly correlated and comparable. Clinically the difference between the two measurements was less than 0.60 mmHg and this difference seemed not to be affected by the presence of a contact lens on the eye. ICare RBT and IOPcc pressure measurements were also correlated and comparable but to a lesser extent than ICare RBT and IOPg measurements. Clinically, when compared to the ICare RBT measurements, the ORA IOPcc measurements showed a difference larger than 1 mmHg. This overestimation was not unexpected. However, when the measurements with contact lenses were included in the analysis the difference became clinically insignificant (0.50 mmHg). This may be due to the contact lens induced biomechanical differences and their effects on the ICare RBT measurements. The lower correlation with ORA IOPcc also suggests that the ICare RBT measurements were affected by corneal biomechanical properties and not only the IOP or CCT of the eye. The aforementioned confirms previously reported results by Jorge, Gonzales-Meijome, et al. (2008) as well as those of this study. The ORA CH and CRF were neither clinically nor statistically comparable to ICare RBT measurements.

7.3 Accuracy of the ICare RBT and ORA with disposable silicone hydrogel and hydrogel lenses *in situ*

The primary goal of this study was to evaluate the accuracy of intraocular pressure measurement with the ICare RBT and the ORA with four commonly used soft disposable contact lenses *in situ*, and to establish whether it is at all feasible to measure intraocular pressure with lenses *in situ* during a normal clinical ophthalmic evaluation. Although contact lenses are normally removed during a comprehensive ophthalmological examination and therefore tonometry, certain circumstances may require measurement of IOP with the lenses remaining on the eye. These circumstances include situations where contact lenses are used in the treatment of corneal injuries; post surgically and, more recently, as drug delivery devices to the cornea and anterior segment of the eye for the treatment of diseases such as chronic glaucoma, anterior segment inflammation, recurrent corneal erosions and keratoconjunctivitis sicca. It is therefore important to know how and which of the physical characteristics of the contact lens influence the accuracy of IOP measurements with these two instruments commonly used in clinical practice.

The rebound response of the ICare RBT reflects the viscoelastic properties of the cornea (Chihara, 2008; Jorge, Gonzales-Meijome, et al., 2008). Although the CCT and corneal curvature can affect the ICare IOP accuracy, it is apparent that the biomechanical properties (in this study represented by CH

and CRF) have the greatest influence on the instrument's IOP measurements (Chui et al., 2008). IOP measurements are significantly increased when the corneal modulus of elasticity is increased and the corneal curvature and CCT remains constant (Liu and Roberts, 2005). Measuring IOP with contact lenses *in situ* should therefore affect the measurement accuracy considerably. It is likely that the viscoelastic properties, lens thickness and water content of the contact lenses affect the rebound response of the ICare RBT. Lower modulus, thinner, and/or softer lenses seem to absorb more energy leading to lower IOP measurements while higher modulus, thicker, and/or stiffer lower water content lenses lead to overestimation of the IOP. The Bland-Altman analysis clearly indicated that with both the ICare RBT as well as the ORA, IOP measurements with and without the higher modulus Pure Vision lenses were statistically and clinically significantly different.

Splitting the data into plus and minus lenses, the differences became much more pronounced with the plus powered Pure Vision lenses having the greatest effect on the measurement accuracy. With the lower modulus Frequency XC, Acuvue 1-Day Moist, and Acuvue Oasys, the ICare RBT underestimated the IOP when compared to the measurements without lenses. This underestimation was possibly due to the energy of the probe being absorbed by the low modulus material. In contrast to the findings of Zeri et al. (2011, 2015) that the ICare RBT underestimated IOP over moderate plus power hydrogel lenses, the results of this study showed that ICare RBT underestimated IOP with minus as well as plus powered contact lenses of moderate modulus of elasticity (Zeri et al., 2011; Zeri et al., 2015). With the low modulus of elasticity hydrogel Acuvue 1-Day Moist lenses, the differences were statistically as well as clinically significant (> 1 mmHg). With both plus and minus powered high modulus of elasticity silicone Pure Vision lenses, ICare RBT significantly overestimated IOP (> 1 mmHg). These findings were similar to those of previous research conducted with the NCT (McMonnies, 1986; Insler and Robbins, 1987; Schollmayer and Hawlina, 2003; Patel and Illahi, 2004; Touboul, 2008; Patel and Stevenson, 2009; Liu et al., 2011).

The ORA corneal hysteresis (CH) measurement was significantly higher with the silicone hydrogel lenses, (specifically with the plus lenses) when compared to the measurements without lenses. The corneal resistance factor (CRF) was also significantly higher with the silicone hydrogel Pure Vision lenses. These current results contrast with those of Lam and Tse (2014) which indicated the measurement of the two biomechanical metrics were not affected by the presence of a silicone hydrogel lens on the eye (Lam and Tse, 2014). The modulus of elasticity of the Pure Vision and Acuvue Oasys lenses were 1.1 and 0.75 MPa respectively. This differed from that of the Focus Night

& Day's 1.5 MPa (Ciba Vision) and Acuvue Advance's 0.43 MPa (Johnson and Johnson) used by Lam and Tse (2014) in their study. Other differences between the two studies included the use of only -3.00 D lenses compared lens powers that ranged between -6.00 to +6.00 D in this study, and the use of an ORA WS score of 3.5 compared to the 6 used in this study. The low WS may have affected the influence of the ocular pulse amplitude on the measurements (Lam and Tse, 2014).

Of further interest is that ORA IOPcc with Pure Vision as well as Frequency XC, Acuvue 1-Day Moist, and Acuvue Oasys measurements were significantly lower (irrespective of lens power) than the instrument-measured IOPcc without lenses. In the case of ORA IOPg, the measurement was significantly lower for the minus power Frequency XC, Acuvue 1-Day Moist, and Acuvue Oasys lenses and significantly higher for the Pure Vision plus lenses, but no significant difference was observed with any of the other brands of plus lenses. The IOPcc, and to a lesser extent the IOPg calculation, takes corneal viscoelastic properties into consideration (Lau and Pye, 2011). As expected, these measurements were influenced by a contact lens which altered ocular surface behaviour (Rimayanti et al., 2014) and viscoelastic corneal properties; therefore, altering the time needed to achieve maximal light detection in NCT (Liu et al., 2011). In the case of IOPcc, the measurements were lower with lenses *in situ* than without the lenses, and with IOPg lower measurements with minus lenses and significantly higher measurements with plus lenses were seen. These results concur with those of Sapkota et al. (2014), namely, that ORA IOPcc and IOPg measurements were lower with a -3.00 D, moderate modulus (0.66 and 0.89 MPa) daily wear contact lens on the eye. IOPcc was highly affected and underestimated by more than 3 mmHg in 36% of their subjects (Sapkota et al., 2014). In the current study IOPcc was underestimated by more than 3 mmHg only with the Pure Vision lenses in all subjects. It seems the closer the lens modulus of elasticity is to the corneal modulus of elasticity, the less the effect is on the measurements of IOP with the lens *in situ*.

Other than the influence of the lenses on the biomechanical properties of the cornea/lens combination, factors such as anterior corneal and lens curvature; central corneal thickness; lens water content; central lens thickness; oxygen transmissibility of the lenses; and hydration may influence the accuracy of the measurements with lenses *in situ* (Table 1.7).

7.4 Impact of corneal and contact lens characteristics on the measurement of IOP with the ICare RBT and ORA

The effect of corneal thickness, corneal curvature, and refractive error on the intraocular pressure measurements with the ICare RBT and Reichert ORA in a population of normal subjects with and

without contact lenses on the eye was examined. By using the contact lenses to change the corneal thickness, corneal curvature, and corneal biomechanics this study examined the role of corneal characteristics as well as the contact lens modulus of elasticity, power, transmissibility (Dk/t), water content, and centre thickness on the accuracy of the intraocular pressure measurements with the ICare RBT and the ORA.

Biomechanical properties of the cornea have a significant impact on IOP measurement errors (Liu and Roberts, 2005) which may vary depending on the instrumentation used to measure the IOP. All tonometers that measure IOP through the application of stress to the corneal tissue are subject to the effects of corneal resistance which is an 'effective' rather than an intrinsic mechanical property such as Young's modulus. Corneal resistance is a composite characteristic that incorporates material as well as geometric properties of the corneal tissue (Luce, 2005; Jorge, Gonzales-Meijome, et al., 2008). Relatively recently an *in vivo* method in the form of the ORA has become available to measure the biomechanical properties of the cornea in the form of two metrics, CH and CRF (Luce, 2005). Both CH and CRF are influenced by viscoelastic properties because they are both linear combinations of inward and outward applanation pressure signals in ORA measurement. CH describes the damping nature of the cornea (e.g. collagen structure, hydration state) or the corneal dynamic resistance component. CRF emphasises inward applanation pressure and is influenced more heavily by elasticity (Jorge, Gonzales-Meijome, et al., 2008). In other words, these so-called biomechanical properties represent the response of the entire corneal tissue to the measurement principal of the ORA (Jorge, Gonzales-Meijome, et al., 2008).

Considering that the ORA uses the delay in corneal response after the applanation process to determine the viscoelastic properties of the cornea, it can be assumed that the absorbed energy could also delay the corneal response when an impact is applied to the cornea to measure IOP (Jorge, Gonzales-Meijome, et al., 2008). The ICare RBT could therefore be affected by the corneal biomechanical properties. In fact, some previous studies confirmed the aforementioned in that ICare RBT correlated with CRF and CH (Chui et al., 2008; Jorge, Gonzales-Meijome, et al., 2008). Other studies found correlations between ICare RBT and CCT, corneal curvature, and refractive error (Detry-Morel et al., 2006; Lopez-Caballero et al., 2007; Avitabile et al., 2010; Hohmann et al., 2012; Rao et al., 2012).

Multiple linear regression analyses of the results of the current study showed that CRF was correlated to and significantly affected ICare RBT as well as CH; although not as strongly. Corneal

curvature also seemed to affect ICare RBT; yet, it was not statistically significant. CCT was strongly correlated to and affected CRF. Central corneal thickness (CCT), IOPg and ICare RBT were strongly correlated to and was affected by CH and CRF. As shown before IOPcc was strongly correlated with and predicted ICare RBT and was affected by CH. IOPg was strongly correlated with and predicted ICare RBT and was affected by CH and CRF.

The above confirmed previous study results which showed that ICare RBT was strongly correlated to CRF, more so than with CCT. Although CCT was correlated with CH, CH did not demonstrate as strong a correlation with ICare RBT as CRF did (Jorge, Gonzales-Meijome, et al., 2008). Corneas with higher values of CH and CRF have a longer delay in response to stress and relaxation forces which means it absorbs more energy when impacted by the probe resulting in higher IOP measurements with the ICare RBT (Jorge, Gonzales-Meijome, et al., 2008). The strong correlation between CRF and ICare RBT signifies that the RBT measurements were affected by viscoelastic properties of the cornea rather than just by CCT or elastic (CH) properties, which agrees with the results of Jorge et al. (2008).

Other as yet unknown and unmeasured tissue properties of the cornea may also affect the ICare RBT measurements. In contrast to previous studies (Detry-Morel et al., 2006; Lopez-Caballero et al., 2007; Avitabile et al., 2010; Hohmann et al., 2012; Rao et al., 2012; Rimayanti et al., 2014), the present study did not find significant correlations between age, refractive error, and corneal curvature with the ICare RBT IOP measurements without contact lenses on the eye. Reasons for this difference may be due to the relatively narrow age range (18 to 55 years, M = 38.90, SD = 9.23 years) of the study participants and the fact that the participants were all Caucasian and long-term soft contact lens wearers. Although the participants removed their lenses at least 24 hours before data collection, the effects of long-term contact lens wear on the cornea and therefore IOP measurements cannot be ruled out (Xu et al., 2008; Hamilton-Maxwell, 2014; Mahjoob et al., 2014).

The CCT and corneal curvature can be changed by fitting disposable contact lenses on the eye. Measurements of the new parameters and IOP with the lenses *in situ* will theoretically make it possible to study the effects of these changes on the measured IOP with the ICare RBT as well as the ORA. The results of this study show with the contact lenses on the eye the CCT was statistically and clinically significantly thicker than without the lenses on the eye. Logically and according to the literature it is expected that the measured IOP should be accordingly higher due to the increase in CCT.

However, it was interesting to note that the predicted changes in CCT, calculated from the $CCT_{Without\ lenses}$ +published contact lens thickness +3 µm tear film thickness, was also significantly higher than the CCT measured with each of the lenses on the eye. In all instances the measured CCT with lenses *in situ* was lower than expected, significantly so with the Pure Vision and the Acuvue 1-Day Moist lenses. Reasons for this could be that the published CT was for -3.00 D lenses only and that this sample included lenses ranging in power from -6.00 to +6.00 D (M = -0.95, SD = 2.69 D) as well as the Scheimplug measurement technique employed. Although Scheimpflug photography provides images of the anterior segment with minimal distortion, the distortion of the cornea and lens itself distort the image. Therefore biometrical measurements in the anterior segment such as corneal curvature, changes in lens curvature during accommodation, depth of anterior chamber angle, always have to be corrected by specific algorithms. The amount of correction depends on the depth of the layer in question, meaning that each refractive zone adds a small amount of distortion to the path of the light rays (Wegener and Laser-Junga, 2009).

Splitting the data into plus and minus lenses (Figures 5.3 and 5.4), the measured CCT was significantly higher with the plus powered (particularly Frequency XC and Acuvue Oasys) lenses than minus lenses. With the plus powered lenses *in situ* the CCT was M = 607.03, SD = 49.31 µm and with the minus powered lenses M = 561.66, SD = 44.78 µm. This is equal to a difference of +70.03 µm and +33.32 µm without lenses for the plus and minus lenses respectively.

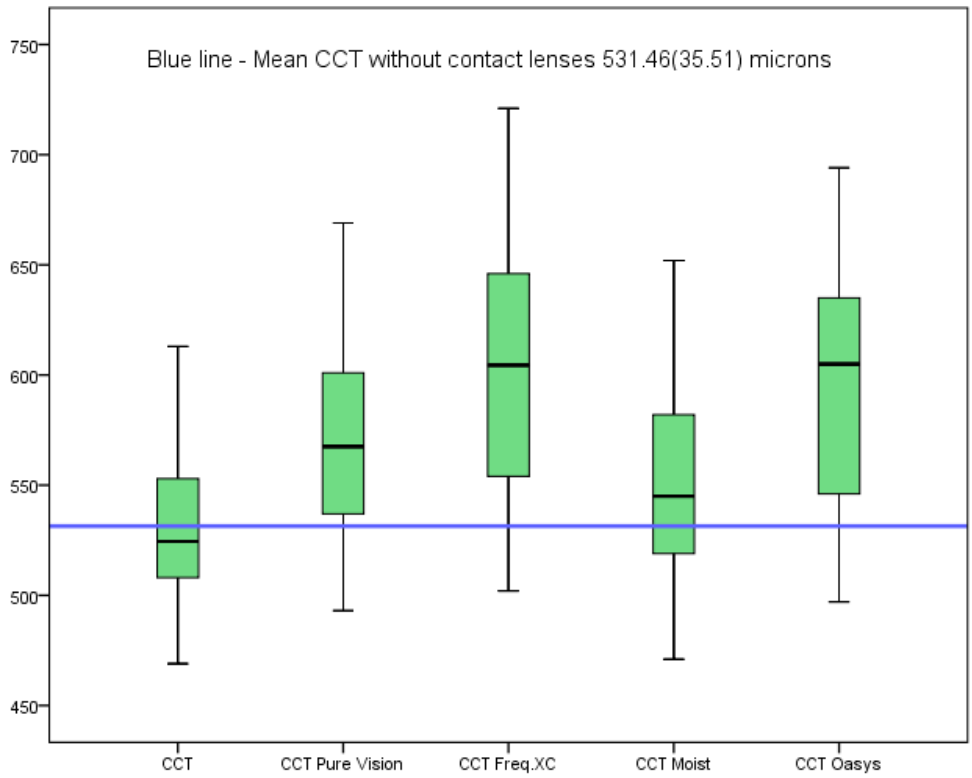


Figure 7.2 Differences in CCT measured without and with the four different contact lenses on the eye.CCT is significantly higher with the Pure Vision, Frequency XC, and Acuvue Oasys lenses *in situ*. CCT = central corneal thickness

Although the corneal curvature (K) is also expected to change due to the presence of the lenses on the eye, it was found in this study that these changes were neither clinically nor statistically significant. On the other hand, when considering the data for plus and minus powered lenses separately, two readings were notable: the K-reading with the plus lenses was steeper (M = 7.60, SD = 0.45 mm) than the K-reading measured without lenses (M = 7.93, SD = 0.27 mm) and with the minus lenses flatter (M = 8.03, SD = 0.31 mm) than that measured without the lenses (M = 7.73, SD = 0.26 mm) (Figures 5.1 and 5.2). This equates to a difference of -0.33 mm and +0.30 mm for plus and minus lenses respectively which may influence the IOP measurements with the two instruments.

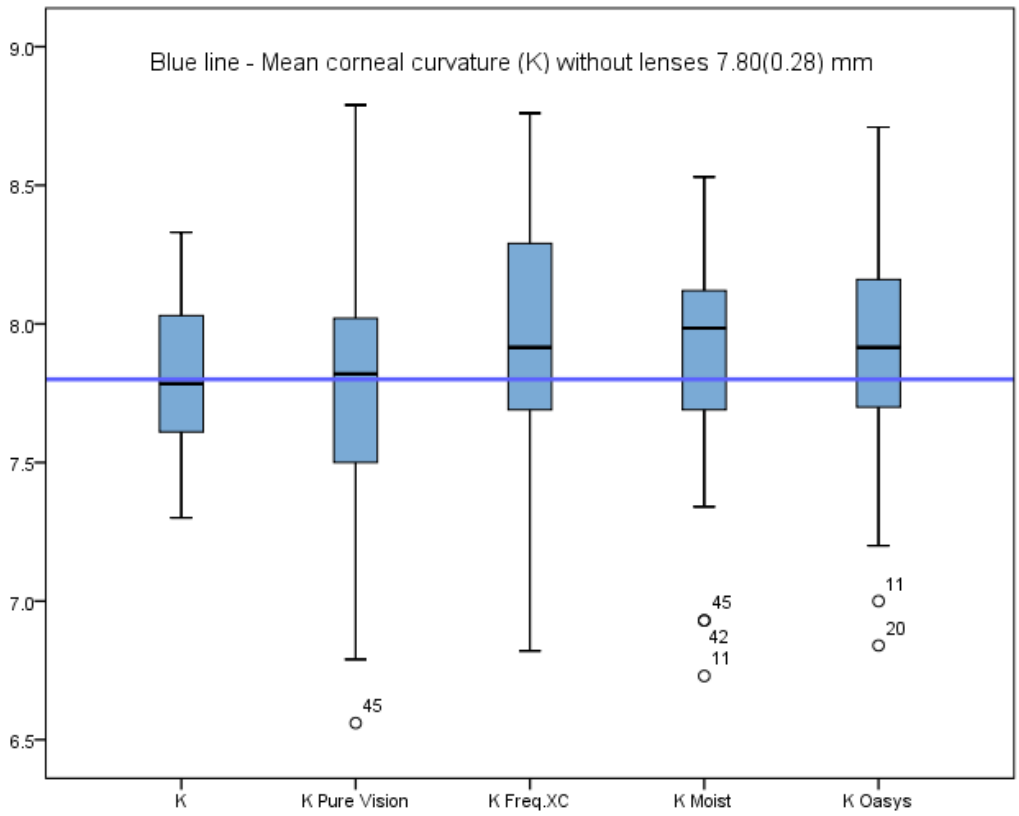


Figure 7.3 Corneal curvature with and without the four different lenses on the cornea.K = corneal curvature

Using multiple linear regression models the relationship between the dependent variables ICare RBT, ORA IOPcc and IOPg, and multiple independent variables (age, Rx, CCT, CH, CRF, and K) were used to determine which of the variables influenced the dependent variable the most. The multiple regression analyses confirmed the strong predictive effects of CH and CRF on ICare RBT as well as ORA IOPg and IOPcc with the different lenses *in situ*. For the ICare RBT both CH and CRF had significant predictive ability and therefore influence with all four lenses and, similarly, for the ORA IOPg both the CH and CRF had significant predictive ability and influence with all four lenses. For the ORA IOPcc CH and CRF had significant predictability and influence with the four lenses tested. These results seem to indicate that the biomechanical properties of the cornea/lens combination were more important in predicting or influencing the measurements of IOP with the ICare RBT and ORA IOPg and IOPcc than CCT, corneal curvature, age, and refractive error.

Further multiple linear regression analyses including all the data as well as the contact lens specific parameters revealed that ICare RBT was significantly influenced by CH, CRF, K and − to a lesser extent − by age. For IOPcc the results were similar in that it was significantly influenced by CH, CRF, and lens modulus. In the case of IOPg significant influence was from CH, CRF, modulus and to a lesser extent

from age. Modulus is an elastic property of the contact lens and it is therefore not unexpected that it would have some influence on the IOP measurements similar to that of the two biomechanical metrics CH and CRF.

In conclusion, the present study showed that although CCT and K do have some influence on the accuracy of IOP measurements with the ICare RBT and ORA, the biomechanical properties of the cornea are more important to consider and have a greater influence on the accuracy of the IOP measurements with these two instruments. This finding differs with that of Rimayanti et al. (2014) who found that the radius of ocular surface curvature is associated with changes in ocular surface displacement and therefore NCT IOP readings with contact lenses *in situ* (Rimayanti et al., 2014). Although the ICare RBT and ORA IOPcc do not correlate well, it may be possible to calibrate the ICare RBT to more closely approximate the ORA IOPcc measurements rather than the ORA IOPg measurements if future studies validate that ORA IOPcc do, in fact, provide an accurate representation of the "True IOP" of the eye. The ICare RBT is a versatile cost-effective instrument which is simple to use, accurate for clinical use, and highly adaptable to different clinical situations.

7.5 Limitations of this study

Several limitations were associated with this study. It comprised of a moderate yet adequate sample size and the investigation was performed using only Caucasian subjects with good general health and no ocular pathology. For this reason it was not possible to assess the influence of ethnicity and the effects of maladies such as glaucoma, corneal abnormalities or other eye disease on the results.

In addition, although the subjects all removed their lenses one day prior to the data collection, they were, however, all long-term soft contact lens users. This means the effects of long-term lens wear on the cornea which can affect the accuracy of IOP measurements cannot be ignored. It is well known that age affects corneal biomechanics with corneas becoming stiffer as the years advance. Due to ethical constraints the age of the subjects in this study ranged from 18 to 55 years (M = 38.90, SD = 9.23 years), which means there is a lack of evidence-based data on the effects of natural corneal biomechanical changes for subjects older than 55 years. Future studies should include subjects older than 55 years to study the effects of natural corneal biomechanical changes on the results.

All measurements in this study were collected at one specific sitting and it is therefore conceivable that variations in measurements may occur from one visit to the next with a specific lens, limiting the clinical usefulness of the results of the study. The study should be expanded to collect data over a

number of consecutive visits to determine the variability of the measurements validating the clinical usefulness of the results obtained in this study.

According to the International Standards Organization (2001), GAT corrected for CCT remains the reference instrument for clinical measurements of IOP; in other words, the gold standard for tonometry (ISO, 2001). The IOP measurements with both instruments used in this study were compared to the gold standard and these studies as well as their results are listed in Tables 1.4 and 1.5 (pages 25 and 41). GAT with contact lenses *in situ* was not investigated. This limitation might elicit interest in researchers to explore GAT with contact lenses *in situ*.

Finally, therapeutic (bandage) contact lenses and lenses designed specifically for drug delivery to the eye differ significantly (Chapter 1) from contact lenses used to correct refractive error. Similar studies using these specific lenses need to be conducted to examine the effects on IOP measurement with theses lenses *in situ*.

7.6 Importance of this work

Although therapeutic contact lenses have been used for many years to treat corneal injuries, post surgically and in keratoconjunctivitis sicca, their use as drug delivery systems to the diseased eye is in its infancy. The ocular surface is readily available for the administration of drugs making the preferred route it to treat ocular disorders, however the use of eye drops as a dosage form suffer from some major limitations. These limitations include the short residence time in the cornea due to its rapid clearance and dilution by the tears, and the fact that most of the drug is drained through the nasolacrimal ducts leading to unwanted systemic absorption and adverse effects (Kompella et al., 2010). Consequently topical drugs have a low bioavailability (< 5%) and reduced residence time in the tear film (< 3 minutes) (Kearns and Williams, 2009; Gaudana et al., 2010). This necessitates frequent high doses to achieve therapeutic levels in the eye. The stance of Stone et al. (2009) is that the lack of manual dexterity in the geriatric population and noncompliance with eye drop treatment regimens are two major limitations in eye drop administration (Stone et al., 2009).

To overcome the limitations of eye drops as a dosage form, various strategies have been employed which include permeation enhancers; viscous and adhesive polymers; collagen shields; nanoparticles; colloidal carriers; ocular implants; and contact lenses (Carvalho et al., 2015). Several studies have demonstrated that contact lenses can be used as drug delivery systems for the treatment of chronic and acute eye disease (Morgan, 1971; Maddox and Bernstein, 1972; Maurice, 1972).

The present study as well as other research studies has shown it is possible to accurately measure IOP through soft disposable lenses. However, more work is needed to understand which specific lens characteristics affect the accuracy of the IOP measurements and contemporary-specific studies need to be conducted on the modified medicated contact lenses which would include vitamin E-sustained release lenses, imprinted medicated lenses, and medicated lenses with nanoparticles. Lens designers and manufactures can then make use of the information to manufacture medicated therapeutic lenses specifically designed not to interfere with IOP measurements while delivering the active drug to the eye as required.

Since the 1950s when Goldmann first described the current the gold standard for intraocular pressure (IOP) measurements, it has been recognised that the biomechanical characteristics of the cornea, especially central corneal thickness (CCT), play a role in the accuracy of IOP measurements. In 2002 particularly, when the Ocular Hypertension Treatment Study (OHTS) (Gordon et al., 2002) once again drew attention to CCT, research studies and ophthalmic discourse once again turned to the role that CCT has on the risk for glaucoma development or progression (Medeiros, Sample, Zangwill, et al., 2003; Chauhan et al., 2005; Congdon et al., 2006; Hong et al., 2007; Rogers et al., 2007). A central issue imbedded in these speculations was that the biomechanical characteristics of the cornea might somehow reflect vulnerability of the optic nerve head to glaucoma while a further aspect generating interest was the well-described discrepancies between measured and true IOP (Wells et al., 2008).

Corneal tissue properties may or may not be directly related to lamina cribrosa tissue properties given that their embryological derivation is different, but there are also plausible connections. Firstly, corneal thickness may be associated with structural characteristics of the sclera and adjacent tissues as well as the optic disc (Pakravan et al., 2007). According to these authors, there does seem to be a correlation between thinner corneas and larger optic discs (Pakravan et al., 2007). Larger optic disc diameters may be associated with increased vulnerability to pressure-induced deformation (Sigal et al., 2004). Secondly, the corneal tissue characteristics themselves, for example their ability to resist deformation, may reflect the constitution of the extracellular matrix (ECM) (Pakravan et al., 2007). Confirming the aforementioned are suggestions that corneal hysteresis (CH) is lower in patients with Marfan syndrome, keratoconus, Fuchs endothelial dystrophy, high myopia and in pregnancy which has hormonally mediated systemic effects on connective tissues (Luce, 2005; Kotecha, 2007; Ortiz et al., 2007; Shen et al., 2008). Given that the cornea, sclera, peripapillary ring, and lamina cribrosa in

an individual eye are essentially made from ECM constituents coded for by the same genes, it is plausible, but as yet unproven, that their biomechanical characteristics may be similar. It has been surmised that an eye with a more deformable cornea, or one with less viscous damping, may also have an optic disc that is more vulnerable to glaucoma damage from raised IOP (Wells et al., 2008). Both the cornea and the lamina cribrosa tend to become more rigid with age and therefore stiffer, less resilient structures (Albon et al., 2000; Kotecha et al., 2006). Age related stiffening of connective tissues is possibly similar in the cornea and lamina cribrosa, and, because CH declines with age, (Kotecha et al., 2006) it is possible that the lamina cribrosa and peripapillary sclera behave similarly.

In the biomechanical paradigm of glaucomatous optic neuropathy, IOP acts on the tissues of the eye, producing stress, deformations and strain within these tissues which eventually leads to an IOP-related cascade of cellular events that culminate in damage to the RGC (retinal ganglion cell) axons (Burgoyne et al., 2005). This mechanical response is a function of the individual eye's anatomy (geometry) and composition (mechanical properties) which therefore contribute to determine the individual's susceptibility to IOP. The mechanical and vascular mechanisms of glaucomatous injury are inseparably intertwined: IOP-related mechanics determine the biomechanical environment within the ONH via mediating blood flow and cellular responses through various pathways. Reciprocally, the biomechanics depend on tissue anatomy and composition which are subject to change through cellular activities such as remodelling (Burgoyne et al., 2005).

The current study adds to the understanding of corneal biomechanics, its accurate *in vivo* measurement and its role in glaucoma diagnosis and effect on IOP measurement.

7.7 Recommendations for future work

Sigal et al. (2005) identified the five most important determinants of ONH biomechanics as follows: the compliance of the sclera; the size of the eye; IOP; the compliance of the lamina cribrosa; and the thickness of the sclera. The Sigal et al. (2005) study was the first to quantify the important role of scleral properties on ONH biomechanics.

Results from a study by Wells et al. (2008) suggest that optic disc surface compliance may have a relationship with corneal hysteresis, a parameter of ocular biomechanics that is easily and noninvasively measurable at the front of the eye with the ORA. These authors did not find that optic disc compliance was associated with CCT (Wells et al., 2008). If optic disc compliance, as measured by the amount of deepening of the optic cup during an acute rise in pressure, is associated with

increased risk for glaucoma, it is possible that CH might provide further information about glaucoma risk and pathogenesis. It is possible that CH had a relationship to change in mean optic disc depth in this study because it represents properties of the rest of the eye rather than just the cornea (Wells et al., 2008). In a clinic-based retrospective observational study, Congdon et al. (2006) found lower CH values were associated with progression of glaucomatous visual fields independent of CCT (Congdon et al., 2006).

The importance of measureable biomechanical properties of the cornea, such as CH and CRF, and their relationship to the biomechanics of the sclera and the lamina cribosa, needs further investigation. The morphological signal or waveform produced by the Ocular Response Analyser is a unique "signature" for the eye being measured. The waveform signal is complex and stores considerably more information than just the interrelation of the inward and outward applanation pressure conveyed by CH and CRF (Galletti et al., 2015). The ORA software provides 37 additional descriptors that further describe each signal (Mikielewicz et al., 2011). Multivariate waveform and descriptor analysis can and should be used to improve not only the diagnostic capability of the ORA, but also to improve our understanding of corneal and ocular biomechanics. Furthermore the use and adaptation of existing technology such as the ICare RBT to measure not only IOP but also biomechanical properties of the cornea deserves further exploration and study.

More work needs to be done to investigate the accuracy of IOP measurements with specialised therapeutic contact lenses (bandage lenses and lenses designed for drug delivery to the eye) *in situ*, not only at one sitting but during multiple visits to validate the clinical significance of the measurements. Studies should be larger with more diverse ethnicity and include subjects with known eye diseases such as glaucoma and corneal diseases in order to examine the effects of these factors on the accuracy of IOP measurements with the different instruments used in this study.

Finally, future studies should include measurements with GAT which is considered the gold standard reference instrument for tonometry.

7.8 Conclusion

The biomechanical properties of the cornea (viscoelasticity and elasticity) are influenced by corneal geometric parameters such as CCT, corneal diameter, corneal curvature, and astigmatism (Bao et al., 2015). It is also influenced by age [stiffness increases with age (Elsheikh et al., 2007)], corneal

hydration, disease (such as keratoconus, Fuch's endothelial dystrophy, glaucoma, and high myopia), and intraocular pressure. Following a period in which attention has been limited to the importance of CCT when measuring IOP, there is currently growing appreciation and renewed interest among researchers regarding the role of corneal biomechanics in IOP measurements. It seems there is a widespread realisation that corneal stiffness or biomechanics more than the parameters affecting it should be considered when improving the accuracy of IOP measurements.

The main purpose of the current programme of research was to determine whether it would be possible to accurately measure IOP with soft contact lenses *in situ.* The results showed that IOP could be measured accurately (within 2 mmHg) with thin minus power, low or moderate modulus of elasticity hydrogel and silicone hydrogel lenses while the subjects were wearing the lenses. Further analyses of the data revealed that although CCT and corneal curvature had some influence on the IOP measurements with the ICare RBT and ORA, the biomechanical properties of the cornea and ocular surface behaviour were more important to consider and have a greater influence on the accuracy of the IOP measurements with these two instruments. Furthermore, neither the ICare RBT nor the ORA could measure IOP with high plus (≥ +12.00 D), high modulus of elasticity, thick (0.32 to 0.49 mm) silicone aphakic lenses (Silsoft – etafilcon A [Bausch & Lomb]) *in situ*.

The results of the research further showed that the ICare RBT and ORA IOPg measurements were clinically as well as statistically comparable (differences < 0.6 mmHg) but the difference seemed not to be affected by the presence of a contact lens on the eye. Although the test-retest reliability of the ICare RBT was not as good as that reported for GAT, it compared favourably with noncontact tonometers. It was also determined that the OPA does affect the test-retest reliability of the ORA IOPcc and IOPg, but the CH and CRF repeatability was excellent. Finally, repeated measurements by independent experienced clinicians with the same ICare RBT produced repeatable and consistent results.

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Appendix

Appendix 1

Ethics approvals

Aston University Ethics Committee
Aston University
Aston Triangle
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Telephone +44 (0)121 204 3000
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Chairperson: Ms Nichola Seare

Secretary: Mr John Walter

23rd August 2013

Dr Amy Sheppard

School of Life and Health Sciences

Dear Amy

Study Title: 'Tonometry and Biomechanics of the Cornea in Contact Lens Wear'

REC Reference: Ethics Application 529

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 (September 30 2016) 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
Consent Form	One	23/04/2013
Proof of Indemnity Insurance Document	One	23/04/2013
Information and Consent Form	v2.0 Prepared May 2013	03/06/2013
Consent Form: Tonometry and Biomechanics of the cornea in contact lens wear	One	20/08/2013
Research Project Protocol: Tonometry and Biomechanics of the Cornea in Contact Lens Wear	One	20/08/2013

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 529**
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

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22 May 2014

FAXED

Mr DJ Booysen
PO Box 339
Paardekraal
1752

Fax: 011 9541000

Dear Mr Booysen

PROTOCOL: 529
TONOMETRY AND BIOMECHANICS OF THE CONRNEA IN CONTACT LENS WEAR
RE: ASSESSORS QUERIES
REFERENCE NO: 14055646
MEETING DATE: 08 May 2014

This is to certify that the above-mentioned trial was reviewed and conditionally approved by Pharma-Ethics Independent Research Ethics Committee. The approval is subject to the conditions listed below.

Please would you be so kind as to respond to the following queries raised regarding the Participant Information Sheet and Informed Consent (PIC):

1. All references to "Subject" must be replaced with participant.
2. Page 1 - WHAT IS THE PURPOSE OF THE STUDY: The information provided in this paragraph is somewhat complex and must be simplified to a grade 6 level of understanding. Furthermore terminology such as "Glaucoma, intraocular pressure, corneal biomechanics, viscoelsatic properties" must be defined or explained.

   - A simple explanation must be provided of how the device works and what it's function is.
3. Page 2 - WHAT WILL HAPPEN TO ME: Please explain what a Oculus Pentacam is.
4. Page 2 - POTENTIAL RISKS: Please simplify the information provided in this paragraph as it is very technical and complex.

Yours sincerely

MRS MARZELLE HASKINS
For and on behalf of Pharma-Ethics

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Appendix 3

Data collection table

Px Ref	Gender	Age	C/l brand	Power	ICare Sc A	ICare Sc B	ICare Cc A	ICare Cc B	CH Sc	CH Cc	CRF Sc	CRF Cc	IOPcc Sc	IOPcc Cc	IOPg Sc	IOPg Cc	Cct Sc	Cct Cc	K-read Sc	K-read Cc
Clinician A. DJB B. GHK Observer MLG			No lens																	
			A																	
			B																	
			C																	
			D																	

Table 8.1 Study data collection sheet indicating clinicians and observer information.ICare – rebound tonometry, CH – Corneal hysteresis, CRF – corneal resistance factor, IOPcc – corneal corrected IOP, IOPg – Goldmann equivalent IOP, CCT – central corneal thickness, K-Read – corneal curvature, Sc – without contact lenses, Cc – with contact lenses, C/L – contact lens, A – Pure Vision, B – Frequency XC, C – Acuvue 1-Day Moist, D – Acuvue Oasys, Px – Patient reference

Appendix 4

Consent form

Invitation.
You are invited to take part in a research study. This document is needed to help you to decide if you would like to participate. Before you decide, it is important for you to understand, why the research is being done and what it will involve. If you have any questions that are not fully explained in this document, do not hesitate to ask the Mr Dirk Booysen the principal researcher. You should not agree to take part unless you are completely happy about all the procedures involved and possible risks. Please take time to read the following information carefully.

Research project title.
Tonometry and Biomechanics of the Cornea in Contact Lens Wear.

Research workers, school and subject area responsible.
Dr Amy Sheppard, Life &Health Sciences, Vision Sciences, Aston University. A.sheppard@aston.ac.uk
Dr Leon Davies, Life &Health Sciences, Vision Sciences, Aston University. L.n.davies@aston.ac.uk
Mr Dirk J. Booysen, Life & Health Sciences, Vision Sciences, Aston University. dirk@dirkbooysen.co.za

What is the purpose of the study?
Glaucoma is a potentially blinding eye disease; early diagnosis relies on effective screening for the disease in a variety of clinical settings. One popular method of screening involves the measurement of intraocular pressure with a device called a tonometer.
The purpose of this study is to investigate if intraocular pressure can be accurately measured in a subject wearing soft disposable contact lenses with the ICare® rebound tonometer and the Ocular Response Analyser (ORA®). The ICare® tonometer is a portable, clinically approved, simple, safe to operate and effective screening device to measure the intraocular pressure. The ORA® is a clinically approved non-contact tonometer, which is safe to operate and an effective device to measure intraocular pressure as well as corneal biomechanics (viscoelastic properties) of the eye. Although other types of tonometer's accuracy have been evaluated in subjects wearing soft disposable contact lenses, the ICare® tonometer and ORA® accuracy and factors that may influence their accuracy still needs further evaluation. This research study aims to address this.

Where will the study be conducted?
The study will be entirely conducted at the Dirk Booysen Eye Care Centre™, located at 248 Voortrekker road, Monument, Krugersdorp, South Africa.

Why have I been chosen?
You have been chosen to take part in the research project because you have normal healthy eyes and are a successful disposable contact lens wearer aged between 18 to 55 years.

What will happen to me if I take part?
The ICare® rebound tonometer and the Reichert Ocular Response Analyser (ORA®) will be used to measure the intraocular pressure on each of your eyes. In addition to the intraocular pressure measurement, Oculus Pentacam® corneal analysis will be carried out on each of your eyes. All procedures will first be done with the contact lenses in your the eyes, and then repeated directly after contact lens removal. Four (4) different soft disposable lenses will be used. The information recorded will include the type of disposable lens, its prescription, the intraocular pressure, corneal curvature, corneal thickness, corneal hysteresis, and corneal resistance factor, with and without the lenses on the eye for each eye separately. Your gender, age, and contact lens prescription will also be recorded. All the information will be recorded in a single clinical session which will take approximately 30 minutes per research participant.

What is the procedure if a medical problem is discovered while participating in the study?
In the event discovering a medical condition affecting the eye such as glaucoma during the course of the study, you will immediately be referred to an appropriate medical specialist for evaluation and treatment. The information recorded as part of the study procedures will not be used but kept anonymous and stored on site in a secure database.

Are there any potential risks in taking part in the study?
All the clinical procedures forming part of this study are clinically approved and routinely performed in eye care practice. ICare® tonometry is routinely performed to measure the intraocular pressure. No topical anaesthesia is required. Six measurements are taken at 0.1s intervals with the amount of force applied by the probe so minimal that it does not elicit the blink response. The Ocular Response Analyser (ORA®) developed by Reichert, measures the cornea's response to indentation by a rapid air pulse. The principles of the ORA® are based on those of the non-contact tonometer. With the ORA® a metered air pulse is directed at the cornea until an applanation event is reached. The ORA® makes four measurements of the corneal response to the pulse of air, corneal hysteresis (CH), corneal resistance factor (CRF), Goldmann intraocular pressure (IOPg), and corneal corrected intraocular pressure (IOPcc). The Oculus Pentacam® is a non-contact corneal analysis system that makes use of Scheimpflug photography to analyse various corneal characteristics such as corneal thickness and topography.
I do not anticipate that you will have any physical or other discomfort during the procedures which should not take more than 30 minutes to complete.

Do I have to take part?
Your participation is totally voluntary and you can refuse to participate or you can stop at any time without stating any reasons whatsoever. Your refusal to participate in or your withdrawal from this clinical trial will not affect your access to other medical or eye care. The principal researcher (Mr Dirk Booysen), however, retains the right to withdraw you from the study if it is considered to be in your best interest, in which event reasons will be provided for withdrawing you from the study.

Will I have any additional expenses or be remunerated for participation?
Other than routine screening of intraocular pressure and corneal characteristics, you will receive no direct benefit from this research project. There will be no costs to you or your medical scheme for the procedures performed during this study and you will not be remunerated to take part in the study.

Insurance and compensation?

In the unlikely event of study related injuries adequate insurance for you and the principal researcher has been obtained. The researcher assumes no obligation to pay for the medical treatment of other injuries or illnesses not related to the studies. Further detailed information on the payment of medical treatment and compensation due to injury can be obtained from Mr Dirk Booysen should you wish to review it.

Will my taking part in the study be kept confidential?

Your participation in the research project will be fully confidential. Mr Dirk Booysen will be personally responsible for maintaining your privacy and confidentiality. A slight risk of breaching privacy and confidentiality in terms of clinical results will be minimised by keeping your information anonymous and stored on site in a secure database. There will be no way to link any research information to any individual participant. All information (digital and hard copies) will be permanently deleted and disposed of 12 months after completion of the study. Data that may be reported in scientific journals will not include any information that identifies you as a patient in this research study. However, in connection with this study it may be important for domestic and foreign health authorities, such as the Department of Health, the National Health Research Ethics Council, the Food and Drug Administration of the USA, the South African Medical Association Research Ethics Committee (SAMAREC), the Medicines Control Council (MCC), Aston University's School of Life & Health Sciences Research Ethics Committee (AOREC), as well as other authorised persons to be able to review your records pertaining to this trial. Therefore, by signing this document, you authorise Mr Dirk Booysen to release your records in appropriate circumstances to the appropriate authorities mentioned above. You understand that these records will be used within reason by these authorities only in connection with carrying out their obligations relating to this research study.

The information collected during this study may also be added to research databases and used in the future to develop a better understanding of the procedures used in this study, and to improve the efficiency, study design and study methods of future research. Such information will not identify you by name.

Finally, although privacy and confidentiality will be protected vigorously to the extent permissible by law, we cannot, however, absolutely guarantee privacy or confidentiality.

What will happen to the results of the research project?

We intend to present and publish the findings of this study at meetings and in academic and professional journals. Only anonymous information will be used for analysis and publication protecting your privacy and confidentiality. A copy of the published research findings will be available at our practice as soon as the project is completed.

Who is organising and funding the research?

Dr Amy Sheppard assisted by Dr Leon Davies will lead the research project, which constitutes part of Mr Dirk Booysen's postgraduate research. Mr Booysen is a qualified optometrist currently enrolled in the Ophthalmic Doctorate programme at Aston University (UK).

There is no funding for the research project.

Who has reviewed and granted ethics approval for the research study?

The protocol of this research study was submitted to Aston University's School of Life & Health Sciences Research Ethics Committee (AOREC) in the United Kingdom, as well as to the South African Medical Association Research Ethics Committee (SAMAREC), a research ethics committee registered with the National Health Research Ethics Council. Written approval has been granted by both AOREC and SAMAREC for the conduct of the research study. The study has been structured in accordance with the Guidelines on Clinical Trials and Ethics in Health Research, published by the

Department of Health and the Declaration of Helsinki (last updated October 2008), adopted by the World Medical Association (WMA), which deals with the recommendations guiding health care professionals in biomedical research involving human participants. Copies of these documents may be obtained from Mr Dirk Booysen should you wish to review them.

Whom do I contact if something goes wrong or I need further information?
Please feel free to contact Mr Dirk Booysen (e-mail: dirk@dirkbooysen.co.za , or telephone 011 954 1000).

Whom do I contact if I wish to make a complaint about the way in which the research is being conducted?
If you have any concerns about the way in which the research has been conducted, you should contact the Secretary of Aston University's School of Life & Health Sciences Research Ethics Committee (AOREC) (e-mail: j.g.walter@aston.ac.uk or telephone 0044 121 204 4665), or the head of the SAMAREC secretariat, Ms M Otto (e-mail: maureeno@samedical.org or telephone +27124812046).

Consent Form.

Title of Project:
Tonometry and Biomechanics of the Cornea in Contact Lens Wear.

Name of Chief Researcher:
Mr Dirk J Booysen

		Initial
1	I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2	I am aware that the results of the study, including personal details regarding my sex, age, date of birth, and diagnosis will be anonymously processed into a research report, but that some of my eye health information may be reasonably disclosed to authorities under certain circumstances	
3	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	
4	I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the above study.	
5	I understand that I shall receive a signed copy of this document	

_____	_____	_____
Name of volunteer	Date	Signature
_____	_____	_____
Researcher	Date	Signature
_____	_____	_____
Name of Person taking Consent (if different from researcher)	Date	Signature

Appendix 5

Indemnity insurance

saoa
South African Optometric Association
Your Custodian of the Profession

561 Nupen Crescent Halfway House Midrand Ext 12
Tel: (011) 805 4517 Fax: (011) 805 3882
E-mail: info@saoa.co.za Web address: www.saoa.co.za

11 February 2013

TO WHOM IT MAY CONCERN

PROOF OF INSURANCE

This letter serves to confirm that as a paid-up member of the South African Optometric Association **DJ Booysen (1114)** has the following cover in place, under our policy in the name of the South African Optometric Association (Policy no.: SPL/SLFG/000002402) :

Insurer:	Etana Insurance Company Limited
Period of Insurance:	1 January 2013 to 31 December 2013
Cover:	Medical Malpractice / Professional Indemnity
Limit of Indemnity:	R2 500 000 in the aggregate, per member, per annum, including costs and expenses
Cover:	General Public Liability including cover for products' liability and defective workmanship
Limit of Indemnity:	R1 000 000 in the aggregate, per member, per annum, including costs and expenses
Territorial Limits:	Worldwide excluding USA and Canada

Subject to all terms and conditions of the policy, we hereby confirm that the cover is in full force and effect.

Yours faithfully

NINA KRIEL
PRESIDENT SAOA

saoa
South African Optometric Association
Your Custodian of the Profession

23 April 2014

TO WHOM IT MAY CONCERN

PROOF OF INSURANCE

This letter serves to confirm that as a paid-up member of the South African Optometric Association **Mr. D Booysen (1114)** has the following cover in place, under our policy in the name of the South African Optometric Association (Policy no.: SPL/SLFG/000002402) :

Insurer:	Etana Insurance Company Limited
Period of Insurance:	1 January 2014 to 31 March 2014
Cover:	Medical Malpractice / Professional Indemnity
Limit of Indemnity:	R2 500 000 in the aggregate, per member, per annum, including costs and expenses
Cover:	General Public Liability including cover for products' liability and defective workmanship
Limit of Indemnity:	R1 000 000 in the aggregate, per member, per annum, including costs and expenses
Territorial Limits:	Worldwide excluding USA and Canada

Subject to all terms and conditions of the policy, we hereby confirm that the cover is in full force and effect.

Yours faithfully

NINA KRIEL
PRESIDENT

Directors: Nina Kriel (SAOA President) | Patrick Mawila | Mark Tonkil | Werner Fourie | Samantha Pillay | Lesego Mokoka | Pax Ramela (CEO)
561 Nupen Crescent, Halfway House, Ext 12 | PO Box 2925, Halfway House, 1685, South Africa
Tel: (011) 805 4517 | **Fax:** 086 634 4367
Reg: 1934/005835/08 - NPC

www.saoa.co.za

Appendix 6

Tests of normality

Tests of normality	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
AGE	0.121	50	0.064	0.965	50	0.145
Refraction	0.154	50	0.004	0.952	50	0.042
ICare IOP	0.173	50	0.001	0.945	50	0.021
Corneal hysteresis	0.066	50	0.200*	0.979	50	0.510
Corneal resistance factor	0.106	50	0.200*	0.954	50	0.049
Corneal corrected IOP	0.121	50	0.066	0.953	50	0.046
Goldmann equivalent IOP	0.122	50	0.060	0.961	50	0.101
CCT without C/L	0.094	50	0.200*	0.958	50	0.077
K-reading Without C/L	0.067	50	0.200*	0.970	50	0.241
ICare with C/L A	0.174	50	0.001	0.908	50	0.001
ICare with C/L B	0.153	50	0.005	0.946	50	0.024
ICare with C/L C	0.097	50	0.200*	0.971	50	0.243
ICare with C/L D	0.177	50	0.000	0.940	50	0.013
CH with C/L A	0.157	50	0.003	0.904	50	0.001
CH with C/L B	0.069	50	0.200*	0.981	50	0.578
CH with C/L C	0.083	50	0.200*	0.973	50	0.294
CH with C/L D	0.103	50	0.200*	0.969	50	0.216
CRF with C/L A	0.163	50	0.002	0.854	50	0.000
CRF with C/L B	0.076	50	0.200*	0.961	50	0.095
CRF with C/L C	0.102	50	0.200*	0.950	50	0.034
CRF with C/L D	0.086	50	0.200*	0.948	50	0.028
IOPcc with C/L A	0.087	50	0.200*	0.983	50	0.664
IOPcc with C/L B	0.103	50	0.200*	0.944	50	0.019
IOPcc with C/L C	0.070	50	0.200*	0.990	50	0.948
IOPcc with C/L D	0.087	50	0.200*	0.975	50	0.373
IOPg with C/L A	0.101	50	0.200*	0.952	50	0.042
IOPg with C/L B	0.083	50	0.200*	0.967	50	0.172
IOPg with C/L C	0.083	50	0.200*	0.985	50	0.762
IOPg with C/L D	0.092	50	0.200*	0.971	50	0.256
CCT with C/L A	0.081	50	0.200*	0.977	50	0.432
CCT with C/L B	0.083	50	0.200*	0.971	50	0.250
CCT with C/L C	0.077	50	0.200*	0.980	50	0.550
CCT with C/L D	0.144	50	0.011	0.944	50	0.020
K-reading with C/L A	0.099	50	0.200*	0.977	50	0.421
K-reading with C/L B	0.084	50	0.200*	0.977	50	0.447
K-reading with C/L C	0.118	50	0.081	0.939	50	0.013
K-reading with C/L D	0.077	50	0.200*	0.982	50	0.631

Table 8.2 Tests of normality.

*** This is a lower bound of the true significance. Although several of the variables have *p* values that indicate significant differences to the normal distribution the Q-Q plots show that these variables data points are close to the normality line. If the data is not normally distributed the value of the statistical tests will still be correct but the significance levels will not be accurate. However, Sawilowsky and Hillman, 1992 found that even with a radically non-normal distribution of the data, significance levels are accurate except when the sample sizes are small and the groups differ in sample size, which is not the case in this study (Sawilowsky and Hillman, 1992)**

Appendix 7

Raw data spread sheet with rebound tonometry measurements averaged

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM
1	REF	GENDER	AGE	Rx	RBT	CH	CRF	IOPcc	IOPg	CCT	K	RBTA	RBTB	RBTC	RBTD	CHA	CHB	CHC	CHD	CRFA	CRFB	CRFC	CRFD	IOPccA	IOPccB	IOPccC	IOPccD	IOPgA	IOPgB	IOPgC	IOPgD	CCTA	CCTB	CCTC	CCTD	KA	KB	KC	KD
2	0	2	45	-1.75	15.75	8.93	8.65	16.2	13.9	522	7.63	20.25	15.75	15.75	16	12.18	8.9	9.33	10.33	11.75	8.78	8.98	9.5	13.53	16.6	15.65	13.65	14.85	14.35	13.8	12.7	545	586	538	567	7.68	7.9	7.84	7.85
3	10176	2	21.00	3.00	24.50	10.38	13.03	23.68	24.40	608.00	7.47	31.00	22.50	18.75	21.00	18.50	12.75	11.85	14.25	20.58	14.93	12.68	16.00	16.55	20.65	17.43	18.43	26.33	23.90	19.00	23.18	604.00	702.00	616.00	694.00	7.46	7.33	7.42	7.20
4	18869	2	33.00	-2.75	11.50	8.85	8.78	16.80	14.50	492.00	8.06	15.50	11.25	10.25	11.00	14.55	10.35	9.68	10.03	12.98	9.08	8.23	8.45	8.80	12.33	12.20	11.73	12.35	11.18	10.23	10.05	532.00	552.00	507.00	535.00	8.12	8.52	8.18	8.45
5	20932	2	41.00	-1.50	13.25	10.25	10.60	17.05	16.53	540.00	7.30	13.50	11.00	11.50	11.50	12.33	9.75	10.43	10.75	11.83	9.85	9.80	10.45	13.35	16.73	14.23	14.90	14.83	15.50	13.50	14.65	551.00	578.00	556.00	607.00	7.43	7.55	7.35	7.52
6	14110	1	51.00	-1.25	13.25	9.65	8.25	12.48	10.48	497.00	7.85	15.25	11.75	12.50	12.25	11.83	9.45	8.95	8.90	10.80	8.38	7.95	8.10	12.15	13.48	14.00	14.65	12.75	11.38	11.35	12.03	518.00	528.00	509.00	545.00	7.94	8.02	8.02	8.04
7	21545	2	54.00	-4.50	23.25	10.85	12.85	21.53	22.48	607.00	7.93	26.50	21.50	20.75	22.50	14.63	11.35	11.58	11.68	15.98	12.50	12.35	13.25	17.15	18.68	17.50	19.70	22.13	19.83	18.70	21.43	648.00	660.00	606.00	647.00	8.79	8.76	8.32	8.59
8	16216	1	30.00	2.25	14.50	8.38	7.68	15.23	12.08	517.00	8.27	16.00	12.25	9.75	11.25	14.35	8.58	8.08	11.63	13.93	7.90	7.43	10.48	12.10	15.18	15.55	11.80	15.98	12.30	12.10	12.23	561.00	610.00	542.00	617.00	8.01	8.17	8.21	7.98
9	20863	2	48.00	1.00	15.00	11.40	10.80	13.55	13.95	539.00	7.50	17.00	15.75	16.25	17.00	14.78	12.05	11.60	13.45	14.20	11.98	11.65	13.23	11.48	14.63	15.45	13.28	15.75	16.03	16.38	16.20	566.00	608.00	563.00	605.00	7.48	7.52	7.54	7.37
10	14938	2	44.00	-3.50	15.50	9.18	8.95	16.20	14.15	504.00	7.47	17.50	12.00	11.25	12.25	12.78	8.90	8.15	9.35	11.88	7.95	7.55	8.35	11.80	14.18	15.58	13.75	13.65	11.53	12.23	11.55	610.00	586.00	543.00	559.00	7.85	7.87	8.34	7.93
11	20709	2	30.00	-3.00	11.75	10.48	9.90	14.28	13.60	553.00	7.61	14.25	10.25	10.75	11.25	13.73	10.75	10.78	11.43	12.38	9.53	9.40	9.73	9.93	12.20	11.83	10.50	12.63	11.55	11.15	10.40	572.00	606.00	585.00	606.00	7.88	7.81	8.11	7.93
12	8835	2	41.00	3.00	12.50	10.08	11.13	13.08	11.70	517.00	7.78	15.25	10.75	9.75	10.75	18.80	11.15	11.43	11.58	17.90	10.13	9.50	10.23	5.73	12.55	13.18	11.33	14.10	12.45	12.33	11.53	617.00	721.00	621.00	657.00	7.06	7.56	6.73	7.00
13	14635	2	49.00	-2.00	11.50	11.10	10.05	12.45	12.28	563.00	7.81	13.25	12.00	11.25	12.25	12.78	9.98	10.73	10.00	12.23	9.60	10.00	9.30	12.85	15.18	13.75	14.30	14.85	13.98	13.30	12.98	584.00	608.00	568.00	605.00	7.85	8.10	8.03	8.05
14	4557	2	42.00	-2.75	17.75	10.05	10.90	18.68	18.23	542.00	8.11	19.50	15.50	16.00	15.75	12.40	10.73	10.23	10.98	12.53	10.95	10.40	10.78	15.05	16.38	16.60	14.95	16.93	16.33	16.03	15.00	571.00	606.00	566.00	606.00	8.34	8.55	8.36	8.56
15	21488	1	23.00	-1.50	10.25	9.03	8.03	13.95	13.95	505.00	7.80	17.00	12.00	9.75	11.00	13.43	9.88	9.95	8.45	11.78	8.83	8.63	7.60	9.33	12.45	12.55	14.83	11.53	10.53	10.93	11.73	525.00	554.00	516.00	541.00	7.69	7.97	7.90	7.90
16	9480	2	41.00	-2.25	12.75	8.38	8.48	17.55	14.78	519.00	7.43	14.25	14.00	8.75	9.00	9.88	10.38	9.08	9.03	9.73	9.28	8.15	8.05	15.85	12.78	14.18	14.08	14.68	11.80	11.73	11.53	546.00	571.00	542.00	569.00	7.59	7.69	7.66	7.70
17	21979	1	38.00	-4.00	12.50	9.83	9.95	16.78	15.68	512.00	7.77	17.50	16.00	14.50	13.25	12.40	10.65	10.20	10.35	11.65	9.23	9.98	9.40	12.48	11.53	15.35	13.23	14.00	10.68	14.50	12.25	534.00	550.00	519.00	559.00	7.98	8.30	8.08	8.16
18	1	2	20.00	2.00	19.00	10.43	12.05	22.68	20.93	535.00	7.73	20.75	17.75	16.25	15.25	15.65	8.60	10.83	11.20	15.50	10.30	10.98	11.60	12.15	22.05	16.08	16.70	17.60	20.20	16.15	17.30	594.00	615.00	594.00	642.00	7.18	7.16	7.34	7.24
19	17488	1	31.00	-2.25	19.75	12.90	13.40	15.80	18.43	613.00	8.29	22.25	20.50	17.00	16.25	15.63	12.85	12.45	14.13	15.58	12.88	12.43	13.55	12.40	14.55	16.65	11.95	17.88	16.90	16.53	15.48	650.00	661.00	630.00	661.00	8.52	8.54	8.51	8.50
20	17797	1	31.00	-6.00	16.25	7.90	8.20	18.15	15.18	473.00	7.73	17.50	14.00	14.00	14.50	10.75	8.18	7.93	8.35	10.30	7.85	7.63	7.83	14.45	16.43	16.63	15.68	14.18	13.18	13.15	12.58	498.00	513.00	496.00	520.00	8.24	8.54	8.22	8.71
21	12069	2	44.00	6.00	16.50	11.08	10.75	14.55	14.73	523.00	7.85	30.50	18.00	17.75	20.75	21.35	10.08	11.25	14.23	22.68	11.50	12.38	15.13	12.65	21.08	18.68	16.03	25.30	21.03	19.68	20.35	554.00	705.00	546.00	653.00	7.46	6.93	7.61	6.84
22	19129	1	45.00	3.00	16.25	7.15	8.33	21.55	17.93	553.00	8.09	20.75	16.25	14.25	16.25	15.73	9.28	7.53	9.80	16.53	9.88	8.53	10.30	14.73	18.35	20.55	17.88	20.70	16.90	17.20	16.95	588.00	667.00	559.00	640.00	7.79	7.75	7.99	7.73
23	20301	2	49.00	2.50	18.75	10.53	12.13	20.58	20.98	539.00	8.04	23.25	17.50	17.25	16.75	19.10	11.33	10.68	12.35	19.90	11.95	11.90	12.15	12.68	17.18	19.48	14.18	22.58	18.03	19.93	15.83	669.00	649.00	561.00	633.00	7.47	7.82	7.43	7.85
24	17892	2	45.00	-3.75	12.75	8.10	8.48	18.45	15.53	483.00	7.54	14.75	13.50	12.00	11.75	12.15	8.68	8.68	8.55	12.08	8.23	7.95	8.28	14.68	15.88	15.10	16.33	16.15	13.18	12.33	13.60	511.00	529.00	498.00	512.00	7.83	8.04	7.79	7.97
25	15674	1	40.00	-1.00	10.50	8.25	7.20	14.45	11.00	494.00	8.00	14.50	10.50	10.25	10.25	12.58	8.48	8.08	8.48	11.30	7.48	7.08	7.10	11.03	13.75	14.50	13.28	12.43	10.35	10.88	9.93	513.00	521.00	507.00	522.00	8.13	8.13	8.12	8.10
26	14970	1	19.00	-0.50	12.75	11.25	10.18	12.33	12.30	553.00	8.03	15.25	13.25	12.25	11.50	14.48	11.45	11.60	11.65	12.80	9.93	10.15	9.95	8.48	10.80	11.15	10.30	11.88	10.83	11.33	10.48	590.00	613.00	566.00	610.00	7.95	8.36	8.08	8.02
27	22359	2	40.00	-2.50	13.25	9.18	8.03	13.50	11.08	520.00	7.44	14.00	10.25	9.75	9.50	13.23	9.15	9.30	9.53	11.93	7.68	8.25	7.70	10.43	12.60	13.70	11.33	12.55	10.00	11.48	8.98	545.00	560.00	529.00	557.00	7.69	7.75	7.67	7.74
28	6347	2	38.00	1.25	18.75	9.53	9.88	17.55	16.23	547.00	7.96	19.50	15.50	16.00	17.00	14.45	9.65	9.55	10.50	14.13	9.73	9.13	9.78	12.30	16.60	15.35	13.85	16.33	15.30	13.68	13.15	568.00	603.00	544.00	627.00	7.95	7.93	7.91	7.62
29	20838	2	46.00	-5.00	17.25	7.30	9.18	23.40	20.25	511.00	7.88	23.50	16.25	16.25	16.25	11.25	7.20	5.98	8.15	12.20	8.65	7.95	8.88	18.15	22.25	20.03	19.58	19.05	8.78	16.25	16.83	537.00	541.00	515.00	546.00	8.30	8.41	8.25	8.58
30	20017	2	25.00	-2.25	9.00	9.85	8.05	11.10	9.15	469.00	7.32	11.75	9.75	10.00	8.50	15.75	9.83	9.98	10.05	13.43	8.03	7.88	7.48	5.88	11.18	10.33	8.78	10.48	9.20	8.35	6.73	493.00	502.00	471.00	497.00	7.35	7.58	7.54	7.60
31	16686	2	37.00	-3.00	9.50	9.63	7.88	11.45	9.23	519.00	7.71	10.75	8.75	9.25	10.25	13.83	10.23	10.13	9.90	11.55	8.33	8.40	8.23	7.23	10.78	11.18	11.43	9.63	9.20	9.58	9.60	539.00	556.00	526.00	562.00	8.00	8.14	7.98	8.12
32	9720	2	43.00	-2.75	16.25	7.28	8.38	21.00	17.45	536.00	7.71	17.25	15.75	17.00	16.00	11.95	7.10	7.90	7.70	12.25	7.78	8.00	8.08	15.88	20.75	17.85	18.88	17.28	16.10	14.55	15.45	588.00	585.00	555.00	565.00	7.76	7.98	7.93	8.00
33	13040	2	38.00	-1.75	13.00	9.23	9.28	16.53	14.80	476.00	7.61	15.50	12.00	13.00	13.00	14.08	8.98	8.60	9.93	13.75	8.30	8.60	9.13	12.83	15.08	17.23	14.10	16.35	12.63	14.63	12.68	500.00	523.00	491.00	530.00	7.81	7.81	7.78	7.80
34	22272	2	39.00	-5.50	13.00	7.45	7.43	17.75	13.88	489.00	7.71	14.00	11.50	8.00	12.25	12.33	8.33	7.88	7.75	11.30	6.90	6.80	6.90	11.68	13.15	14.55	15.20	12.95	9.65	10.68	11.30	506.00	531.00	498.00	521.00	8.14	8.52	8.14	8.39
35	7767	2	40.00	-3.00	17.00	9.68	10.78	19.65	18.83	574.00	7.79	17.75	15.25	13.75	15.00	13.78	10.28	10.65	9.50	13.88	10.45	11.08	9.83	14.10	16.63	17.08	17.30	17.58	16.08	17.05	15.95	593.00	618.00	582.00	604.00	8.05	8.11	8.03	8.16
36	18201	2	30.00	-3.75	12.75	11.88	11.33	13.38	14.33	540.00	7.46	16.00	12.50	12.50	11.75	15.80	11.33	11.50	12.20	14.43	10.25	10.50	10.80	8.43	12.83	12.40	10.95	13.50	12.98	12.70	11.90	567.00	578.00	552.00	579.00	7.66	7.80	7.77	7.76
37	6114	2	44.00	-2.50	17.25	13.38	12.60	11.80	14.35	595.00	7.56	22.25	16.50	14.75	16.25	16.18	12.68	11.38	13.00	15.13	11.70	10.90	12.00	9.38	11.63	13.93	11.43	15.00	13.30	14.33	13.48	609.00	633.00	596.00	635.00	7.73	7.82	7.72	7.82
38	1025	1	46.00	2.75	16.25	7.15	8.30	22.00	18.10	553.00	8.10	20.75	16.25	14.25	16.25	15.80	9.30	7.62	9.90	16.52	10.00	8.62	10.50	14.80	18.50	21.00	18.00	21.00	17.00	17.00	17.00	588.00	667.00	559.00	640.00	7.80	7.75	8.00	7.70
39	21736	2	40.00	-5.00	17.50	10.65	11.75	19.08	19.38	572.00	7.79	23.00	17.25	17.75	17.25	5.78	11.35	11.18	11.45	15.08	11.50	11.03	11.43	10.45	15.65	15.15	15.20	15.78	16.33	15.43	15.90	615.00	646.00	596.00	635.00	7.86	8.30	8.08	8.31
40	17446	2	52.00	5.00	11.50	9.08	8.05	13.88	11.40	526.00	7.89	31.50	16.25	14.00	15.00	24.18	10.68	9.70	12.23	23.45	10.63	9.30	12.80	14.90	15.70	15.20	12.80	19.90	15.48	13.75	14.08	623.00	617.00	538.00	643.00	7.10	7.19	7.71	7.32
41	17650	2	32.00	-2.00	10.75	10.13	9.05	13.05	11.78	508.00	8.33	15.50	11.75	10.50	11.00	12.70	10.65	10.35	10.45	11.63	9.25	8.70	8.98	11.35	11.65	11.20	11.83	13.03	10.83	9.88	10.65	532.00	555.00	522.00	546.00	8.51	8.58	8.53	8.56
42	8827	1	52.00	0.50	13.25	10.15	9.65	14.58	13.58	553.00	8.06	14.50	12.50	10.75	11.25	12.55	10.45	10.03	10.95	12.10	9.83	9.08	10.00	13.23	14.05	13.48	12.83	15.03	13.35	12.13	12.53	585.00	631.00	579.00	610.00	7.93	7.98	8.09	8.02
43	1111	2	38.00	3.75	18.50	10.00	9.68	15.38	14.25	538.00	7.94	33.50	17.50	14.25	16.50	21.50	11.18	10.55	12.13	21.55	10.68	9.88	11.65	9.03	14.03	14.00	13.50	21.30	14.20	13.35	14.78	650.00	690.00	652.00	650.00	6.79	7.30	6.93	7.43
44	2222	1	30.00	4.00	13.50	9.08	7.95	13.58	11.00	520.00	8.26	25.00	12.25	12.00	11.75	21.75	9.88	9.25	11.38	20.78	8.78	8.98	11.10	5.88	13.10	15.95	14.65	17.95	11.48	14.03	15.15	601.00	590.00	543.00	622.00	7.45	7.52	8.08	7.85
45	3333	2	41.00	0.75	15.50	7.83	7.40	16.38	12.73	486.00	8.32	17.25	14.25	13.75	15.00	13.05	9.05	8.08	9.25	12.75	8.75	8.18	9.13	13.40	14.03	17.75	14.35	15.85	13.83	14.63	14.48	515.00	532.00	496.00	531.00	8.29	8.39	8.36	8.26
46	18184	2	55.00	2.50	12.00	11.63	9.85	10.10	10.20	531.00	7.53	24.25	12.00	11.75	11.75	21.78	10.58	10.50	12.80	20.40	9.33	9.43	11.40	4.63	12.23	12.88	10.33	16.58	11.33	12.00	11.95	606.00	662.00	609.00	634.00	6.56	6.82	6.93	7.24
47	16170	1	50.00	-4.00	11.75	11.13	10.20	12.85	12.75	606.00	7.37	19.75	15.25	15.75	18.00	16.53	12.88	11.50	10.18	14.88	11.18	10.88	9.83	7.25	13.03	13.55	15.00	13.08	13.93	14.05	14.13	629.00	669.00	619.00	640.00	7.76	7.90	7.69	7.85
48	22120	1	28.00	-1.50	11.50	10.18	9.30	13.60	12.45	508.00	7.61	13.75	11.00	10.75	12.00	13.93	10.00	9.70	10.40	12.89	9.05	9.13	9.40	10.50	13.40	14.80	13.08	13.55	12.08	13.25	12.13	539.00	572.00	527.00	555.00	7.69	7.83	7.78	7.82
49	9105	2	48.00	1.00	18.00	9.70	10.13	17.50	16.38	559.00	7.66	17.75	17.25	15.25	14.50	13.05	10.13	9.15	10.05	13.60	10.25	9.58	10.70	15.80	16.55	18.00	18.05	18.68	15.80	16.25	17.45	585.00	663.00	586.00	637.00	7.50	7.56	7.70	7.56
50	18713	2	28.00	-3.50	10.25	9.85	8.68	11.75	9.85	512.00	7.70	11.00	10.25	7.75	8.75	12.83	9.53	9.83	9.73	10.65	7.20	7.43	7.35	8.18	9.85	9.38	9.55	9.48	7.23	7.13	7.18	539.00	539.00	518.00	541.00	8.02	8.19	8.08	8.21
51	16216	1	30.00	0.75	10.50	8.53	6.83	12.45	9.00	522.00	8.25	11.50	11.00	8.75	11.00	13.45	9.35	9.05	9.70	11.83	7.20	7.75	7.70	9.25	10.53	13.15	10.73	11.50	7.80	10.48	8.48	554.00	637.00	539.00	527.00	8.15	8.29	8.30	8.26
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Appendix 8

Editors Report

Suzette M. Swart

FULL MEMBER: Professional Editors' Guild

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12 April 2016

TO WHOM IT MAY CONCERN

I, Suzette Marié Swart (ID 5211190101087), confirm that I have edited the noted Doctor of Optometry (by Research) thesis, *Tonometry and Biomechanics of the Cornea in Contact Lens Wear*. The accuracy of the final work is still the student's own responsibility.

STUDENT:

DIRK JOHAN BOOYSEN

TITLE:

TONOMETRY AND BIOMECHANICS OF THE CORNEA IN CONTACT LENS WEAR

Thank you

Suzette M Swart (not signed – sent electronically)

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TO ENSURE THIS STUDY MEETS THE STANDARDS OF ACADEMIC WRITING REQUIRED ON A POSTGRADUATE LEVEL, THE DEGREE OF EDITING INCLUDED:

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