REBOUND TONOMETRY COMPARED WITH GOLDMANN APPLANATION TONOMETRY IN PATIENTS WITH CORNEAL PATHOLOGY – A RELIABILITY STUDY.

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Signed at ***Parktown*** on the ***11th*** day of ***November***, 2016.

To God,

for your unlimited mercy.

To Bertie,

for your example and courage.

To Kayan,

for your faith and support.

ABSTRACT

Purpose: To compare the reliability of rebound tonometry (RT) with that of Goldmann applanation tonometry (GAT) in patients with corneal scars.

Methods: Three measurements were taken with each instrument. Instruments were compared by determining the differences between repeat measurements, by using a non-parametric ANOVA on repeat measurements and by calculating the coefficient of repeatability (CR). A control group with normal corneas were examined to establish baseline correlation, repeatability and observer proficiency.

Results: 61 eyes of 48 patients were included in the group with scarred corneas. The CR of RT was 2.667. The CR of GAT was 4.819. RT was more reliable than GAT in patients with corneal scars. The correlation coefficient of RT with GAT was 0.8959.

Conclusion: RT correlated well with GAT in both scarred and control subjects. RT was more reliable than GAT in patients with corneal scars. GAT was more reliable than RT in control patients.

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LIST OF ABBREVIATIONS

AT – Applanation tonometry

CCT – Central corneal thickness

CR – Repeatability coefficient

GAT – Goldmann applanation tonometry

IOP – Intraocular pressure

JSL – Johann Streicher Lamprecht (Study Observer)

PAT – Perkins applanation tonometry

PKP – Penetrating keratoplasty

POAG – Primary open angle glaucoma

RT – Rebound tonometry

SJEH – St John Eye Hospital

SD – Standard deviation

SPK – Superficial punctate keratopathy

TPXL – Tono-Pen XL

wsSD – Within-subject standard deviation

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1 INTRODUCTION

1.1 Background

Glaucoma is the leading cause of irreversible blindness in not only Africa, but also the world. It is second only to cataract among all visual disorders that lead to blindness.[1,2] Africa has the highest ratio of glaucoma patients to adult population.[2] This is due to a higher prevalence in the elderly compared to other countries, and not due to proportionately more older people, as is the case in certain European and Asian regions.

In Southern Africa, glaucoma has been shown to be a significant health problem in both rural and urban populations, with reports consisting of two major indigenous ethnic groups. Glaucoma has been estimated to be the major aetiologic factor in 20-32% of all blind patients, with primary open angle glaucoma (POAG) and pseudoexfoliative glaucoma being the most common subtypes. It has also been shown that the majority of glaucoma patients in this subgroup are still undiagnosed and untreated.[3,4] Glaucoma in Africans may occur at a younger age, may be associated with higher intraocular pressure (IOP) and more rapid progression, and patients may present with advanced or end-stage disease.[5]

Glaucoma is a heterogenous group of disorders with a multifactorial pathogenesis, including raised intraocular pressure and vascular dysregulation. IOP has been shown to play an important role in retinal ganglion cell apoptosis and changes in extracellular matrix components at the optic nerve head, leading to the characteristic clinical appearance associated with glaucoma.[6] Despite the IOP being normal in some subtypes of glaucoma, IOP continues to be a major risk factor for the development and progression of glaucomatous optic nerve damage.[7,8] IOP is also an important measurable parameter and the main target of current glaucoma treatment modalities. Medical and surgical interventions that lower IOP have been shown to prevent the progression of glaucomatous damage in primary open angle glaucoma (POAG) as well as preventing or delaying the onset of POAG in ocular hypertensive patients.[9,10,11,12] Accurate measurement of IOP therefore remains an important objective in the management of glaucoma patients.

The Goldmann applanation tonometer (GAT) is widely accepted as the gold standard for measuring intraocular pressure. However, the accuracy of applanation tonometry has come into question, with many limitations being proven clinically and through theoretical mathematics. Different corneal pathologies in particular have been shown to cause either overestimation or underestimation of IOP readings.[13,14,15,16,17,18] Corneal pathology is often an exclusion criterion in studies aiming to describe or compare IOP measuring devices.[19,20,21,22,23,24,25,26,27,28,29,30] However, glaucoma itself, as well as pressure lowering procedures, can be associated with or responsible for various corneal abnormalities, especially corneal scars and oedema or bullae. Subsequent infection, thinning, scarring and vascularization may be the result.[14,31,32,33] On the other hand, some diseases and procedures associated with corneal or more widespread anterior segment pathology are also associated with raised intraocular pressures and glaucoma, such as herpetic eye disease, trauma, penetrating keratoplasty (PKP), and the anterior segment dysgeneses.[18,26,34,35,36,37,38,39] Accurate estimations of IOP are therefore an important aspect of adequately managing patients with corneal abnormalities, but are often not possible in these patients due to the inherent limitations of applanation tonometry. (See Table 1.1.)

Rebound tonometry (RT) is an established, albeit relatively new means of measuring IOP. RT measurements have been shown to correlate well with Goldmann applanation tonometry.[18,19,21,27,29,30,40,41,42,43,44] It has been postulated that the small contact surface of the rebound tonometer's probe gives it an advantage over GAT in patients with corneal pathology, and RT has been shown to correlate better with manometric IOP than GAT in eye with severely oedematous corneas.[14,18,42,43,44] It has also been shown that RT is easier to use by less experienced individuals and might therefore be the ideal tool for screening programs.[21,28]

Until recently, the Tono-Pen XL has been an accepted substitute for IOP measurement in patients with corneal pathologies that make GAT difficult or impossible. It is, however, not without limitations and it is not universally accepted as a sufficiently accurate instrument.[26,42,45,46,47] The search is still on for an instrument that is more reliable and user-friendly in this subgroup of patients.

1.2 Literature Review

1.2.1 Goldmann applanation tonometry

A description of the dynamic relationship between the ocular aqueous humour, the ocular wall and the intraocular pressure is beyond the scope of this literature review. The importance of measuring the intraocular pressure (IOP) accurately is explained in the introduction above. Goldmann applanation tonometry (GAT) was described in 1954.[48] It was to serve as another contender in the search for the ideal tonometer.

Applanation tonometry is based on the Imbert-Fick law which states that, the pressure inside a perfect, dry, thin-walled sphere equals the force necessary to flatten an area of its surface divided by the area of flattening,[13]

$P = F/A$ where P = pressure
F = force
A = area

In applanation tonometry, the globe represents a less-than-perfect sphere, flattening occurs at the cornea with its variable thickness and rigidity, and the wall of the sphere is not dry, but covered with a tear film.

In 1957, shortly after the introduction of GAT, Perkins gave an outline of the characteristics of the ideal tonometer, stating that it needed to:
- produce small distortion of the globe
- be light weight
- cause low reading error
- be mechanically stable
- be non-traumatic
- be easy to use, and
- easy to sterilize.[49]

Perkins questioned whether the theory upon which applanation tonometry was based was universally applicable and suggested that "certain other factors were concerned." He

nonetheless referred to Goldmann's design as "ingenious" and suggested that more work needed to be done.[49]

Less than twenty years later, Goldmann applanation tonometry was known as "the most accurate and reproducible measure of intraocular pressure...representing the standard." In fact, it was Perkins himself who eventually developed a portable applanation tonometer based on the same optical principles used by Goldmann – the Perkins applanation tonometer (PAT).[17,50] PAT would later be described to be "of unquestioned excellence", notwithstanding the fact that their use in patients with corneal pathology remained limited.[51]

Since then, however, the effect of not only corneal abnormalities, but also normal corneal parameters, on GAT readings have been studied and reviewed extensively, increasingly bringing into question the accuracy of what has been the gold standard for roughly half a century. [13,14,15,16,17,51] Corneal properties that are known to cause an overestimation of IOP with GAT include steep curvature and against-the-rule astigmatism, mild epithelial oedema, increased stromal thickness, and increased rigidity, which might be normal or due to stromal scarring. Corneal characteristics opposite to these, are likely to cause an underestimation of IOP. Table 1.1 provides a summary of corneal findings and the likely effect on GAT readings taken in these patients.

Despite the known difficulties, Goldmann applanation tonometry is the most widespread tonometer in clinical use, not only in normal, but also abnormal corneas. Although in question, it is still considered by some to be clinically relevant in patients that have previously undergone corneal surgery. In the place of true, manometric IOP measurement, new instruments are clinically correlated with GAT, and there are numerous examples of these correlations being done in patients with corneal pathology.[18,26,34,43,44] In our opinion, one problem with these correlation studies is that their primary endpoints are usually the IOP values and differences thereof between instruments, and this in a setting where it is known that the gold standard is unreliable. Instead, or at least in addition, one should look at the reliability of each instrument in each clinical setting to decide which is most appropriate.

Table 1.1 – Sources of error during Goldmann applanation tonometry.[13,14,15,17,42,51]

Corneal Finding	Effect on GAT IOP estimation
• **Curvature:**	
Steeper	Overestimated
Flatter	Underestimated
Regular astigmatism – with the rule	Underestimated
– against the rule	Overestimated
Irregular astigmatism	Unreproducible, high variability
• **Epithelium:**	
Oedema – mild (<40μm)	Overestimated
– more severe	Underestimated ("Soft" cornea)
Scarring	Difficult endpoint (unreproducible)
• **Stroma:**	
Rigidity (corneoscleral) – higher	Overestimated
Thin (CCT, e.g. Keratoconus)	Underestimated
Thickened (CCT, non-oedematous)	Overestimated (Underestimates effect of rigidity)
Oedema	Underestimated
Scarring	Difficult endpoint (unreproducible)
– May cause increased rigidity	– Overestimated
– Post LASIK	– Underestimated, increased variability
Immune / Crystalline deposits	Unknown
• **Position** – decentred probe	Minimal

There is therefore still need for a tonometer that is less dependent on the corneal properties than the Goldmann applanation tonometer or one that is capable of reliably compensating for these confounding variables. It is also clear that the greatest difficulty in obtaining accurate, repeatable measurements (an "endpoint" with minimal deviation in a given individual at a given time) is caused by irregularities in any one of the above corneal variables, be it curvature, surface, or rigidity and distribution of connective tissue types (scar tissue vs normal). The ideal tonometer would be minimally affected by these irregularities or capable of repeatedly obtaining measurements from corneal areas deemed least abnormal, whilst avoiding contact with areas that would negatively affect the repeatability of readings. In addition, due to the global burden of glaucoma, and due to Africans being disproportionately affected by the disease, the ideal tonometer should be relatively easy and affordable to use and maintain by healthcare professionals working across the spectrum of rural screening clinics to academic institutions.

1.2.2 The Tono-Pen XL

Instruments that involve contact or interaction with only small and, if needed, peripheral areas of the cornea, are considered by some to be more reliable than GAT in patients with scarred, oedematous or irregular corneas.[14,26,42,43,44] The Tono-Pen is a small, hand-held, contact tonometer that works on principles shared by the GAT and MacKay-Marg electronic applanation tonometers. Newer versions, such as the Tono-Pen XL (TPXL), have improved software for faster measurement speeds. The Tono-Pen XL has an applanation area of 2.36mm^2 and is thought to be less affected by CCT and ocular surface abnormalities. It correlates well with GAT and manometric IOP measurements when used on eyes with normal corneas.[47]

It is of important to take multiple measurements with the Tono-Pen XL and use the built in standard deviation (SD) calculator to determine whether measurements are acceptable. For this reason, and due to the fact that frequent recalibrations are needed, it is considered to be slightly less user-friendly than GAT. Casting further doubt on its overall accuracy, the Tono-Pen XL has also been shown to correlate less well with GAT when the IOP is outside the normal range, and as with GAT its measurements might be affected by central corneal thickness, corneal rigidity and corneal deposits.[44,46,47]

The Tono-Pen is, however, used widely in clinical practice for IOP measurements in eyes that have had previous PKP and has also been shown to be more accurate than GAT in severely oedematous corneas.[26,42] It is therefore currently the chosen instrument to use on eyes of which corneal irregularities make GAT impossible.

1.2.3 Rebound Tonometry – The ICare

The rebound tonometer concept was described by Kontiola in 1997.[52] The principle on which it is based was described by Dekking & Coster in 1967.[19] It is a recent addition to the existing arsenal of instruments that estimate intraocular pressure. The system comprises a solenoid, a magnetised probe and analysing electronics. The probe is 25-40mm long, 0.3mm in diameter with a 1.0-1.7mm diameter round, plastic tip, and weighs 26.5g. The probe is placed within the solenoid and the tonometer is held as such that the tip of the probe is 4-8mm from the eye, perpendicular to the corneal surface. The probe is then electromagnetically propelled towards the cornea by the solenoid at a velocity of approximately 0.2 meters per second. As the probe impacts the cornea, it decelerates rapidly before bouncing back from the corneal surface. The inverse of the probe's deceleration time was shown to correlate well with manometric IOP. Built-in analysing software uses this measured rate of deceleration from the time of impact to calculate the intraocular pressure.[29,40] Other key features of RT are that it is small, portable and hand-held, it has a very small contact surface, it does not require the use of topical anaesthetic, and its use causes minimal patient discomfort.[16,30]

The clinical use of RT (ICare Finland, Helsinki, Finland) and its correlation with Goldmann-type applanation tonometry has been well documented. However, most of the studies done, exclude patients with existing corneal pathology.[19,20,21,22,23,24,25,27,28,29,30] The most common finding is a good correlation between rebound tonometry and applanation tonometry.[19,21,23,27,28,30,34,40,41] Mean rebound tonometry values tend to be higher than applanation tonometry, although the difference is often less than 1mmHg and statistically insignificant. There is also very little difference between the standard deviations of each method within each study population. A higher discrepancy between the two instruments have been reported, although even then it is often less than 2mmHg, which is considered a clinically significant cut-off.[22,23,24,25,29,53,54,55] The greatest differences were in a known congenital glaucoma paediatric population and in oedematous grafts following penetrating

keratoplasty. Few reports show rebound tonometry underestimating the IOP compared to applanation tonometry (AT).[21,55]

IOPs outside the normal range are associated with a reduction in the agreement between the two instruments, although, this does not always reach statistical significance. There tends to be a greater overestimation of IOP by RT in patients with IOPs above 21mmHg.[23,25,29,30]

Cannulising the anterior chamber and then correlating instrument measurements with true (manometric) IOP, is the only way to really determine which instrument is most accurate and reliable. However, this is not a practically feasible or ethical in vivo model for use in human subjects.[25,42] In one study on oedematous, thickened corneas (CCT 616-627) mounted on an artificial anterior chamber, the manometric IOP could be used as reference standard.[42] In this study RT was shown to be more reliable across a wide range of IOPs (10-50mmHg) than both GAT and the Tono-Pen XL. GAT measured consistently lower than manometry, except at 10mmHg. RT was consistently within 2mmHg of the manometric value, except at 10mmHg. This shows that agreement with the gold standard (GAT in this case) in terms of values obtained is not the only measure of an instrument's accuracy. The standard deviation for RT was also lower across the entire range of IOPs.

Rebound tonometry is considered easy to use and sufficiently accurate even by health care workers lacking ophthalmic experience.[21,41,43] RT is also reported to be more comfortable in adult patients, even without topical anaesthetic, and reduces the need for general anaesthetic in paediatric populations.[24,27,30,56] Some advantages of RT are listed in table 1.2 below, with the Goldmann-type tonometers (GAT and PAT) shown for comparison.

RT Sources of error: Most authors report a decreasing correlation between RT and GAT as the measured IOP value increases.[23,29] This was, however, not always found to be the case.[27,30,41] Factors that affect corneal rigidity, especially central corneal thickness (CCT), influence not only GAT readings, but also those taken with RT. Increased CCT is associated with increased IOP values with RT. Some authors found this correlation to be similar to the relationship between GAT and CCT, not leading to a reduced agreement between the two instruments,[16,29,41,54] while others found a decreased correlation of RT with GAT as CCT increased.[22,23,24,27] It has also been reported that CCT had minimal effect

Table 1.2 – Advantages of rebound tonometry compared to GAT[16,23,29,30,41,42,56]

Rebound Tonometry:	**GAT / PAT:**
- Portable	- PAT only
- Position independent (ICare Pro only)	- PAT only
- No anaesthetic, more tolerable	- Intolerable without anaesthetic
	- Adults: Topical
	- Paediatric: Topical / GA
- Tear film – no effect	- Significant effect readings
- No fluorescein needed	- More difficult without
- Small contact surface	- Larger contact area required
- Indicates unreliable reading automatically	- User dependant
- Objective digital reading.	- Analogue scale on most GAT / PAT
- Possibly less effect with repeated readings	- Repeats reduce IOP
- Brief contact - Possibly reduced risk	- Longer contact time
- Easy to use, possibly shorted learning curve	- Possibly requires more experience

on IOP readings. It is postulated that RT is affected more by inherent biomechanical properties of the cornea than simply the thickness thereof.[41,55] Taking RT readings directly from an area with corneal pathology, causes increased variability.[44]

Other disadvantages of RT: It is currently advocated that a new probe be used for each patient.[20] This might lead to increased cost of consumables with RT as compared to GAT, the latter in which it is common practice to clean the contact surface with a 70% alcohol swab.[17] In the event that RT probes are re-used, it is the author's experience that the delicate probes are difficult to clean.

Repeatability and RT: Repeatability of measurements is a way of describing variation in repeat measurements made on the same subject under identical conditions, that is, by the same observer (intra-observer), using the same instrument and with minimal time elapsing

between measurements. Variability in measurements made under these conditions (immediate test-retest) is ascribed to errors due to the measurement method itself, and are used to quantify the reliability of measurements made by that particular method.[29,57]

RT shows good baseline repeatability. Intra-observer correlation coefficients of 0.73-0.87 have been reported.[29] Measurements were hardly affected by distance from the cornea (3-5mm) or angle of incidence of the probe onto the cornea. Patients with higher-than-normal pressures were included. Mean CCT was 544.58µm. Corneal pathology was excluded. As described above, corneal pathology is known to reduce repeatability (or increase variability) of multiple measurements done by GAT. It is the purpose of this study to evaluate the repeatability of RT in this specific subgroup of patients and compare it with GAT (or with the Tono-Pen XL in eyes that don't allow GAT). With RT, IOP measurements taken from paracentral areas of the cornea correlated well with central measurements, with slight underestimation of mean values when measuring paracentrally (0.3-1.9mmHg).[20,55] This compares well with the "no large change" reported in the literature for paracentral measurements taken with GAT.[13]

Rebound tonometry has been shown to be less repeatable than GAT when IOPs were measured two weeks apart.[40] It is not clear what the difference in repeatability is between RT and GAT when multiple measurements are taken on patients at a given point in time, i.e. with relatively little time elapsing between measurements. One study also reported good interobserver reproducibility of RT, not comparing it with GAT at the same time.[29]

1.3 Rationale (Introduction Summary)

- Glaucoma is currently an African and global health problem, being the leading cause of irreversible blindness and overall the second most common cause of visual disability.
- Intraocular pressure is a major risk factor in the pathogenesis of glaucoma.
- Corneal pathology and glaucoma are commonly found concurrently in a patient and can be associated with each other in various ways.
- Corneal pathology is a known risk factor for unreliable estimates of intraocular pressure. The negative effect of corneal pathology on the accuracy of the gold standard instrument, Goldmann applanation tonometry, is well documented.

- Corneal pathology is often excluded when instruments for IOP measurement are compared.
- Tonometers with small contact surfaces have been shown to be more reliable in patients with corneal pathology. The rebound tonometer is a new instrument that requires a small contact surface for IOP measurement.
- Rebound tonometry correlates well with Goldmann applanation tonometry.
- Intra-observer test-retest repeatability is an accepted method for assessing the reliability of measurement instruments.

1.4 Purpose, Objectives and Hypothesis of the Study

The purpose of this study was to compare the reliability of the rebound tonometer with the reliability of the gold standard, the Goldmann applanation tonometer, in patients with a specific corneal pathology, namely corneal scars. This was done by determining the repeatability of rebound tonometry (RT) in patients with corneal pathology, and then comparing it with the repeatability of Goldmann applanation tonometry (GAT) in the same group of patients.

Where Goldmann applanation tonometry was not possible due to extreme abnormalities, the rebound tonometer would be compared in the same way to the Tono-Pen XL.

We hypothesized that the repeatability of readings taken with the rebound tonometer would be greater than those taken with GAT in patients with corneal scars, because the small contact surface of the rebound tonometer would allow for measurements to be taken at a clinically pre-selected area of the cornea that was least affected by the scarring. Measurements with the rebound tonometer would therefore be less affected by the corneal scarring and the resulting changes in corneal thickness, rigidity and surface regularity.

The correlation between mean IOP values obtained with each instrument was determined.

RT was also compared to GAT in a control group of patients with normal corneas to assess baseline repeatability and correlation of the instruments in the current setting and to demonstrate observer proficiency with the instruments.

2 METHODS

2.1 Study Design

The overall design was that of a controlled, comparative study. The methods being compared were two different instruments used for measuring intraocular pressure, namely the gold standard Goldmann applanation tonometer (GAT) and the rebound tonometer (RT). The methods were compared on the basis of their repeatability in patients with corneal scars; essentially, two repeatability studies were done on the same population at the same time by the same observer – one with each instrument. The results of the instruments were compared.

Instruments were also correlated in terms of their mean values measured.

The same comparison was done in a control population to determine the baseline repeatability and correlation of the instruments and to show observer proficiency in the current context.

Primary Objective:

- To determine the repeatability of rebound tonometry in a study population of patients with corneal scars.
- To determine the repeatability of Goldmann applanation tonometry in the same study population.
- To compare the repeatability of rebound tonometry with that of Goldmann applanation tonometry in the study population in order to determine which instrument is more reliable in the setting of corneal scarring.

Secondary Objectives:

- To determine the repeatability of rebound tonometry in a control group of patients with normal corneas
- To determine the repeatability of Goldmann applanation tonometry in the same control group.
- To compare the repeatability of rebound tonometry with that of Goldmann applanation

tonometry in the control group in order to determine which instrument is more reliable in patients with normal corneas.

- To determine the correlation between mean IOP values obtained with each instrument in each group.

2.2 Approval

The study protocol was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Reference: M150729) and by the Research Protocol Assessor Group of the University of the Witwatersrand, Department of Neurosciences. The study adheres to the principles set out in the Declaration of Helsinki. The observer has no financial or conflicting interests to declare.

2.3 Site of Data Collection

The study took place at the St John Eye Hospital (SJEH) – Ophthalmology department of the Chris Hani Baragwanath Academic Hospital in Soweto, Johannesburg, South Africa.

2.4 Study population

Patients seen for routine visits at SJEH during the study period and that met the inclusion criteria were examined for the study purposes. Signed, voluntary, informed consent was obtained.

Demographic information was recorded as follows:

- Race – Four groups: African, Caucasian, Asian and Other.
- Gender – Female and Male.
- Age – Three groups: Young Adult (18-39years), Middle Aged (40-59years) and Older Age (60years and older).

Study numbers were assigned. No personal identification information was recorded for study purposes.

Data was collected during September and October 2015.

2.4.1 Inclusion criteria for primary objective (scarred cornea group)

Patients were included if they were 18 years of age or older and had corneal scarring of any extent and cause. Corneal pathologies that were occasionally associated with scarring and were not considered essential, but that were not excluded were vascularization, pigmentation, fibrovascular ingrowth (pannus), elastotic, nodular and other degenerative changes, lipid and other deposits.

Corneal scarring was classified as follows:

- Aetiology – Four subgroups: Trauma, Inflammatory (including Infective), Other, Combined.
- Area/Extent – Three subgroups: Central 4mm, Peripheral, Combined.

2.4.2 Exclusion criteria for primary objective (scarred cornea group)

Patients younger than 18 years.

Refused or unable to give consent.

Absence of corneal scarring.

Active keratitis (infective or sterile), corneal abrasions, severe ectatic thinning, perforation or full thickness laceration, any other corneal pathology without the presence of corneal scarring.

Phthisis bulbi.

Contact lens in situ.

2.4.3 Inclusion criteria for control group

18 years or older.

No corneal pathology.

No contact lens in situ.

2.4.4 Exclusion criteria for control group

Younger than 18 years.

Refused or unable to give consent.

Any corneal abnormality, contact lens in situ, or phthisis bulbi.

2.5 Instruments and measurements

2.5.1 Observer

Counselling, consent, examinations and measurements were done by Dr J S Lamprecht (JSL), with the help of an ophthalmic assistant or registered nurse.

2.5.2 Instruments

Rebound tonometry measurements were taken using the ICare tonometer (ICare Finland, Revenio Group Corporation, Helsinki, Finland). A new probe was used for each measurement session.
Prior to applanation tonometry, the applanation tip was cleaned with a 70% alcohol swab.
Topical anaesthesia was achieved using Novesin Wander 0.4% (oxybuprocaine HCL, Novartis Pharma AG, Adcock Ingram Ltd).
The tear film was stained using Fluorets 1mg (Bausch & Lomb, Chauvin Pharmaceuticals Ltd, UK).
Applanation tonometry was performed using the Goldmann applanation tonometer (CSO, Italy).
In one patient that was obese and wheelchair-bound, applanation tonometry was performed using the Perkins applanation tonometer (Haag-Streit UK).
If applanation tonometry was found to be impossible (three failed attempts), rebound tonometry measurements in that patient would be compared with measurements taken with the Tono-Pen XL (Reichert Inc., NY, USA).

2.5.3 Measurement procedure

Calibration was done according to each instrument's instructions.
After patients had had their routine assessments, they were referred to the observer, JSL for possible inclusion in the study, counselling and consent.
Measurements were taken in the sequence: RT1, RT2, RT3, GAT1, GAT2, GAT3.
Where GAT was not possible, TPXL1 – TPXL3 would be taken.

Step-by-step:

1. GAT applanation surface was routinely cleaned with a70% alcohol swab
   A new RT probe was inserted into the RT solenoid.
2. Anterior segment examination was carried out. The extent of scarring was determined, as well as the part of each cornea that was least affected by the scarring process.
3. Time of RT1 noted.
4. RT1 – RT3 taken. With the ICare, each measurement actually consists of six measurements taken in rapid succession after which the calculated IOP value is digitally displayed on the instrument. Care was taken to hold the instrument upright and to hold it approximately 4-8mm from the cornea when doing measurements. In each case, readings were taken from the area of the cornea that was least affected by the scarring.
5. GAT1 – GAT3 taken. Each patient's head and/or eyes were carefully positioned using the headrest and fixation target to take measurements from the area of the cornea that was least affected by the scarring.
   Each GAT measurement was accepted if all 180˚ of both the mires, including the point of intersection between the prism images (representing the stained tear film meniscus), were visible and the mire thickness was adequate. Where GAT was not possible. TPXL1 – TPXL3 would be taken with a new sleeve.
6. Time of GAT3 (or TPXL3) noted and time from RT1 to GAT3 calculated.

Following all the measurements, complications were excluded and patients were given an opportunity to ask further questions. Follow up appointments were confirmed as per initial routine assessments.

The same procedure was followed on both the corneal scar group and the control subjects.

2.6 Statistical analysis

Data was captured on Excel spreadsheets (Microsoft), and analysis was done using Excel's built-in formulas as well as GraphPad Instat (GraphPad.com).

For the primary aim of the study, the repeatability of the instruments in patients with scarred corneas were determined and compared in the following ways:

First, the differences between measurements (within each set of three) were calculated. We used the first measure as the reference and compared it to the second and third measurements respectively. For each instrument in each group, we looked at the number of times that the second and third measurements respectively differed from the first measurement by 0mmHg, 1mmHgm 2mmHg and 3mmHg or more and determined the range within which the second and third measurements differed from the first. We also determined how many measurements had a difference of 2mmHg or more between any combination of measurement 1 versus measurements 2 and 3 with RT versus GAT. A contingency table was created for each group (one for scarred subjects, one for controls) and Fisher's exact test was used for the significance of the difference between the instruments. These calculations and tables were repeated for a difference of 3mmHg or more.

Secondly, the data was entered into a non-parametric analysis of variance (ANOVA): The Kruskal-Wallis test was used to determine the significance of the difference between measurements in each group.
Finally, the repeatability coefficient (CR) was calculated for each instrument in each group of patients, using the formula:

$(1.96 \times \sqrt{2} \times ws\text{SD})$[57] where wsSD is the within-subject standard deviation.

In other words, two repeatability studies were carried out at the same time, one with RT and one with GAT respectively on the scarred subjects. The CR is an estimate of the absolute difference, or disagreement, between measurements caused by measurement errors only. It is based on the assumption that there is no bias or learning between measurements. The estimate is given in the unit of measurement, in the case of this study, mmHg. Only the first two measurements of each series of three measurements were used (i.e. RT1 and RT2, GAT1 and GAT2). If the differences between two measurements made on a subject are normally distributed, we expect the absolute difference between the two measurements on a subject to differ by no more than the repeatability coefficient on 95% of occasion. By plotting the differences between measurements against their mean values (the Bland-Altman plot), we could also visually assess and compare the disagreements between measurements for each instrument.[57]

As secondary objective, we also compared the repeatability of RT with that of GAT in a control population. Furthermore, we did a comparison between RT and GAT in terms of the correlation of their IOP estimates. Although the latter correlation is described at length in the Literature Review, any difference in terms of repeatability would be of doubtful significance if the instruments were not once again shown to correlate well with each other in this study population.

For each set of three measurements (e.g. RT1 – RT3), the individual mean IOP was calculated. For each instrument, the overall mean IOP (the mean of the means) was calculated. We did a comparison of the individual and overall mean IOPs for RT versus GAT to determine correlation and to see whether RT overestimated or underestimated GAT IOP. We used the correlation coefficient (r) to test the significance of the correlation. We also calculated the number of eyes in which RT overestimated versus underestimated GAT. We used Fisher's exact test on the whole group excluding those that measured the same to determine whether the difference was significant.

Subgroup analyses, for example testing for correlations between repeatability on the one side and extent of scarring, cause of scarring, total measurement time, etc. on the other side, were not done due to sample size. Should this study be extended, these could be considered.

3 RESULTS

Tables 3.1 and 3.2 summarize the population characteristics of the scarred subjects and controls respectively.

In the scarred group, 61 eyes of 48 patients were included. Racial distribution was as follows: African 59 eyes (96.7%), Caucasian 1 eye (1.6%), Asian 0 (0%) and other 1eye (1.6%). There were 33 eyes (54.1%) in female patients and 28 eyes (45.9%) in male patients in the scarred group. Age groups consisted of 28 young adult eyes (45.9%), 18 middle aged eyes (29.5%) and 15 older age eyes (24.6%). The cause of corneal scarring was trauma in 12 eyes (19.7%), inflammatory in 27 eyes (44.3%), other in 14 eyes (22.9%) and combined in 8 eyes (13.1%). The scarring involved only the central 4mm of the cornea in 8 eyes (13.1%), the peripheral cornea in 12 eyes (19.7%), and combined in 41 eyes (67.2%).

Controls were not matched with the scarred group for age, gender or ethnicity. 61 eyes of 31 patients were included. Racial distribution (for eyes, not patients) was 41 African (67.2%), 10 Caucasian (16.4%), 8 Asian (13.1%) and 2 other (3.3%). 48 eyes (78.7%) belonged to female patients and 13 eyes (21.3%) to male patients. Young adult eyes numbered 24 (39.3%), middle aged 22 (33.1%) and older age 15 (24.6%).

Figures 3.1 and 3.2 represent the differences between measurements in the scarred and control groups respectively. In each patient, RT1 was compared to RT2 and RT3 respectively and GAT1 was compared to GAT2 and GAT3 respectively.

In the scarred corneas, for RT1 vs RT2, there was no difference in 17 eyes, 1mmHg difference in 19 eyes, 2mmHg difference in 16 eyes and 3mmHg or more difference in 9 eyes. For RT1 vs RT3, there was no difference in 20 eyes, 1mmHg difference in 18 eyes, 2mmHg difference in 8 eyes and 3mmHg or more difference in 15 eyes.
In the scarred corneas, for GAT1 vs GAT2, there was no difference in 6 eyes, 1mmHg difference in 13 eyes, 2mmHg difference in 21 eyes and 3mmHg or more difference in 21 eyes. For GAT1 vs GAT3, there was no difference in 14 eyes, 1mmHg difference in 19 eyes, 2mmHg difference in 12 eyes and 3mmHg or more difference in 16 eyes.

Table 3.1 – Study population: Scarred corneas

Scarred Subjects	**n = 61**	**(%)**
Race:		
- African	59	(96.7%)
- Caucasian 1	1	(1.6%)
- Asian	0	
- Other	1	(1.6%)
Gender:		
- Female	33	(54.1%)
- Male	28	(45.9%)
Age:		
- Young Adults	28	(45.9%)
- Middle Aged	18	(29.5%)
- Older Age	15	(24.6%)
Aetiology:		
- Trauma	12	(19.7%)
- Inflammatory	27	(44.3%)
- Other	14	(22.9%)
- Combined	8	(13.1%)
Area Involved:		
- Central	8	(13.1%)
- Peripheral	12	(19.7%)
- Central and Peripheral	41	(67.2%)

Table 3.2 – Study population: Controls

Controls	**n = 61**	
Race:		
- African	41	(67.2%)
- Caucasian	10	(16.4%)
- Asian	8	(13.1%)
- Other	2	(3.3%)
Gender:		
- Female	48	(78.7%)
- Male	13	(21.3%)
Age:		
- Young Adults	24	(39.3%)
- Middle Aged	22	(33.1%)
- Older Age	15	(24.6%)

In the control corneas, for RT1 vs RT2, there was no difference in 23 eyes, 1mmHg difference in 28 eyes, 2mmHg difference in 8 eyes and 3mmHg or more difference in 2 eyes. For RT1 vs RT3, there was no difference in 17 eyes, 1mmHg difference in 22 eyes, 2mmHg difference in 14 eyes and 3mmHg or more difference in 8 eyes.
In the control corneas, for GAT1 vs GAT2, there was no difference in 34 eyes, 1mmHg difference in 21 eyes, 2mmHg difference in 5 eyes and 3mmHg or more difference in 1 eye. For GAT1 vs GAT3, there was no difference in 26 eyes, 1mmHg difference in 25 eyes, 2mmHg difference in 10 eyes and 3mmHg or more difference in no eyes.

Table 3.3 shows the number of eyes in which repeat measurements differed by 2mmHg and more, and by 3mmHg and more, as well as the range of the differences.

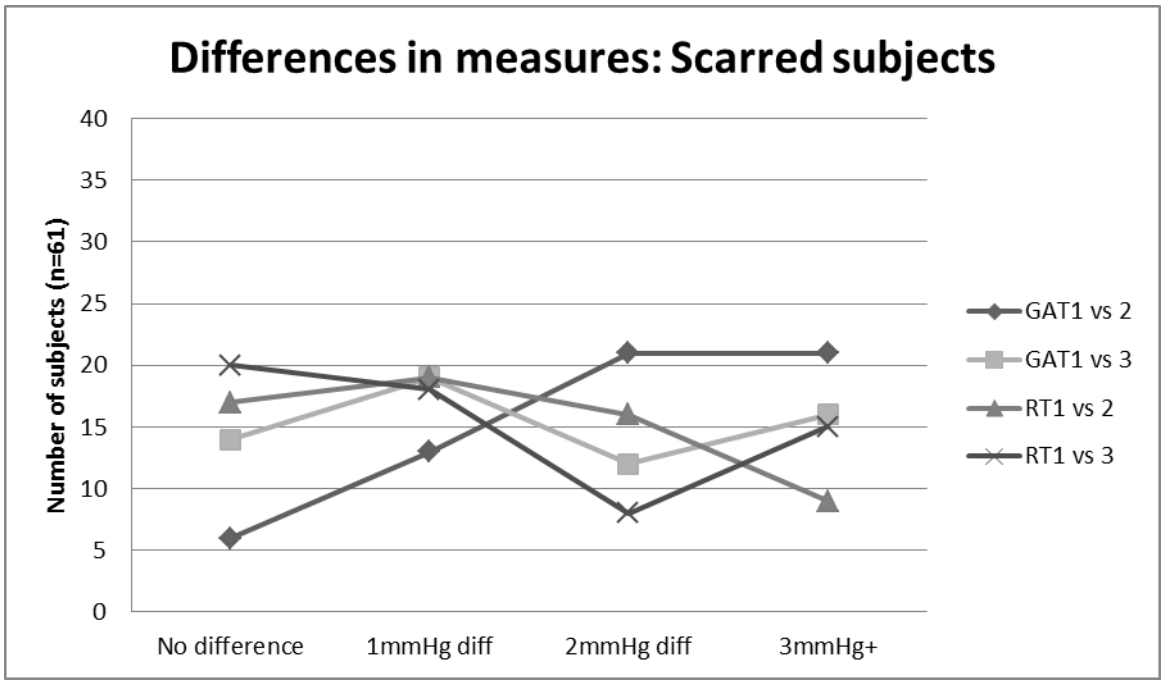

Figure 3.1 – Differences in measures: Scarred subjects

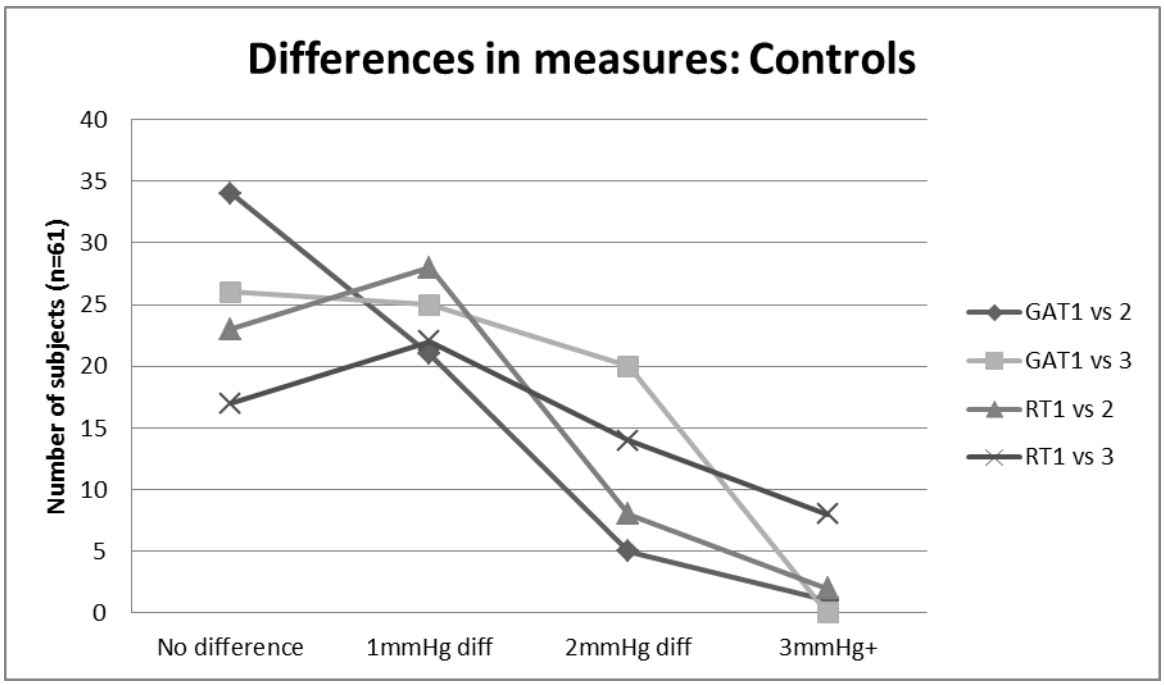

Figure 3.2 – Differences in measures: Controls

Table 3.3 – Difference in measures: 2mmHg or more, 3mmHg or more, and range

Scars		n Difference of 2mmHg or more	n Difference of 3mmHg or more	Range
RT1 vs	RT2	25	9	-5 to +5
	RT3	23	15	-5 to +5
GAT1 vs	Gat2	42	21	-9 to +13
	Gat3	28	16	-5 to +19
Controls				
RT1 vs	RT2	10	2	-2 to +3
	RT3	22	8	-4 to +5
GAT1 vs	Gat2	6	1	-2 to +3
	Gat3	10	0	-2 to +2

The data for differences of 2mmHg or more between either combination of measurements (1st vs 2nd and 1st vs 3rd) and for RT vs GAT, shows that RT was significantly more reliable than GAT in the group with scarred corneas (Fisher's exact test: $p = 0.0218$). 32 combinations with RT and 45 combinations with GAT had differences of 2mmHg or more. 16 patients for RT and 24 patients for GAT had both 2nd and 3rd measures 2mmHg or more different from measure 1.

In the control group, GAT was significantly more reliable than RT (Fisher's exact test: $p = 0.0014$). 27 combinations with RT and 10 combinations with GAT had differences of 2mmHg or more. 5 patients for RT and 6 patients for GAT had both 2nd and 3rd measures 2mmHg or more different from measure 1.

Repeating these calculations for differences between measurements of 3mmHg or more, showed that RT was no longer significantly more reliable than GAT in the scarred group (Fisher's exact: $p = 0.4416$) and that GAT was still significantly better than RT in the control group (Fisher's exact: 0.0166).

Kruskal-Wallis test on the differences between repeat measurements showed that there was one set of measurements in the scarred group where the differences were significantly different, namely between either combination with RT and the first repeat of GAT ($p < 0.01$). Differences between GAT 1 and 3 and either combination of RT did not reach statistical significance. Overall, the difference between differences were significant in the scarred group ($p = 0.0006$), but not in the control group ($p = 0.6738$).
Analysis of the raw data showed that, overall, neither of the instruments obtained significantly different values with repeat measurements in either population. The significance of the differences were as follows (Kruskal-Wallis):

Scarred Corneas:	RT	$p = 0.9259$
	GAT	$p = 0.4902$
Controls:	RT	$p = 0.9536$
	GAT	$p = 0.9910$

The results of the repeatability coefficient studies are presented in table 3.4. In the scarred group, repeatability was better with RT than with GAT, with estimated measurements errors of 2.667mmHg and 4.819mmHg respectively. In the control group, GAT was better than RT, both with estimated measurement errors of less than 2mmHg and that of GAT being only 1.092mmHg.

Table 3.4 – Repeatability coefficients of RT and GAT in scarred corneas and controls

Group:	**Instrument:**	**Repeatability coefficient (CR)**
Scarred corneas	RT	2.667mmHg
	GAT	4.819mmHg
Controls	RT	1.607mmHg
	GAT	1.092mmHg

Bland-Altman plots of the differences between repeat measurements for each instrument in each subgroup are seen in figures 3.3, 3.4, 3.5 and 3.6. Plotted values represent the size of measurement errors (vertical axis) at a range of mean IOPs (horizontal axis). Data points that are in general grouped more closely around the horizontal line through the vertical midpoint (the zero difference line) indicate greater repeatability, and vice versa.

In figures 3.3 and 3.4 it can be seen that data points representing RT measurement error are less widely distributed around the zero difference line than those for GAT, indicating greater repeatability of RT in patients with scarred corneas. Figures 3.5 and 3.6 represent the measurement errors of RT and GAT respectively in the control population. Both instruments show good repeatability in this subgroup of patients with data point lying close to the zero difference line.

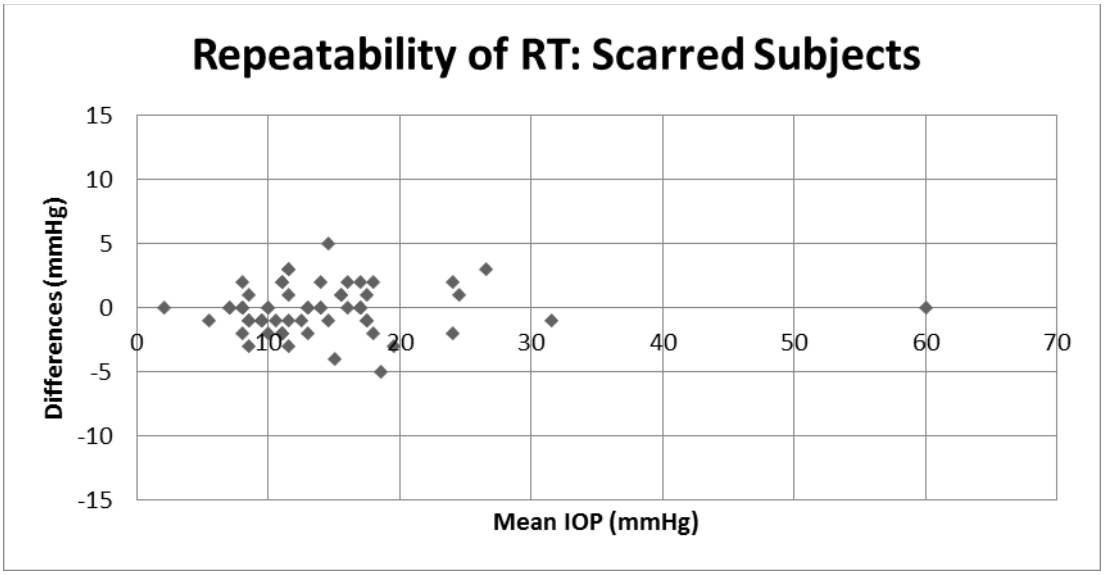

Figure 3.3 – RT repeatability at different IOPs in scarred corneas (Bland-Altman plot)

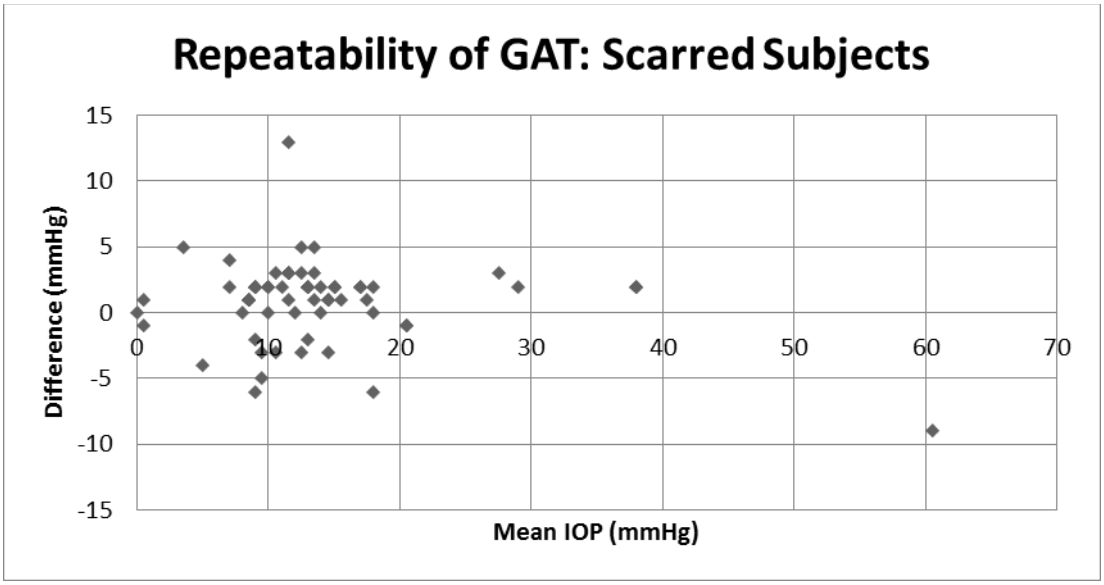

Figure 3.4 – GAT repeatability at different IOPs in scarred corneas (Bland-Altman plot)

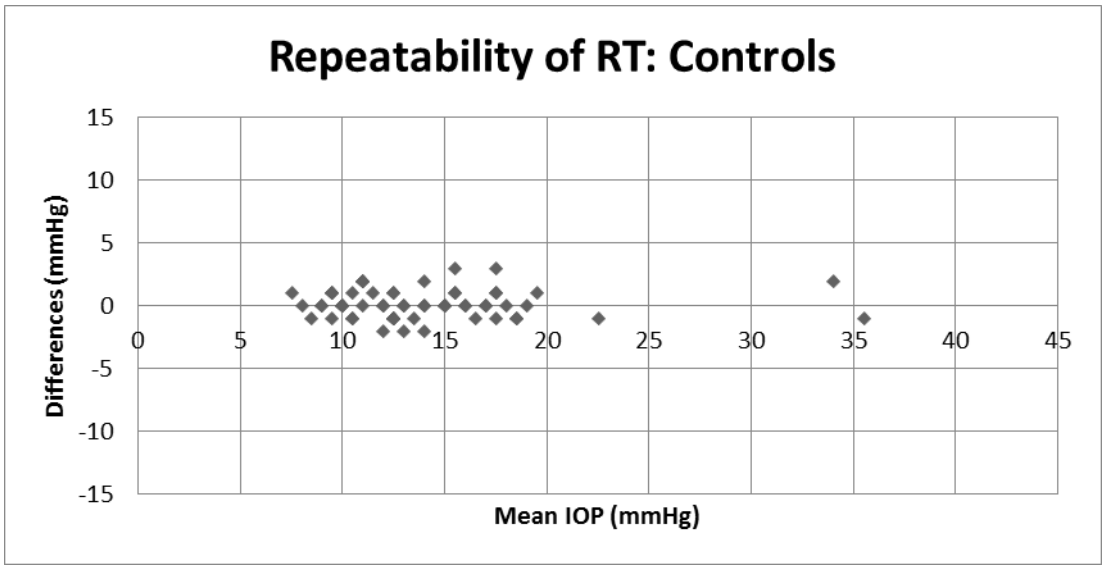

Figure 3.5 – RT repeatability at different IOPs in normal corneas (Bland-Altman plot)

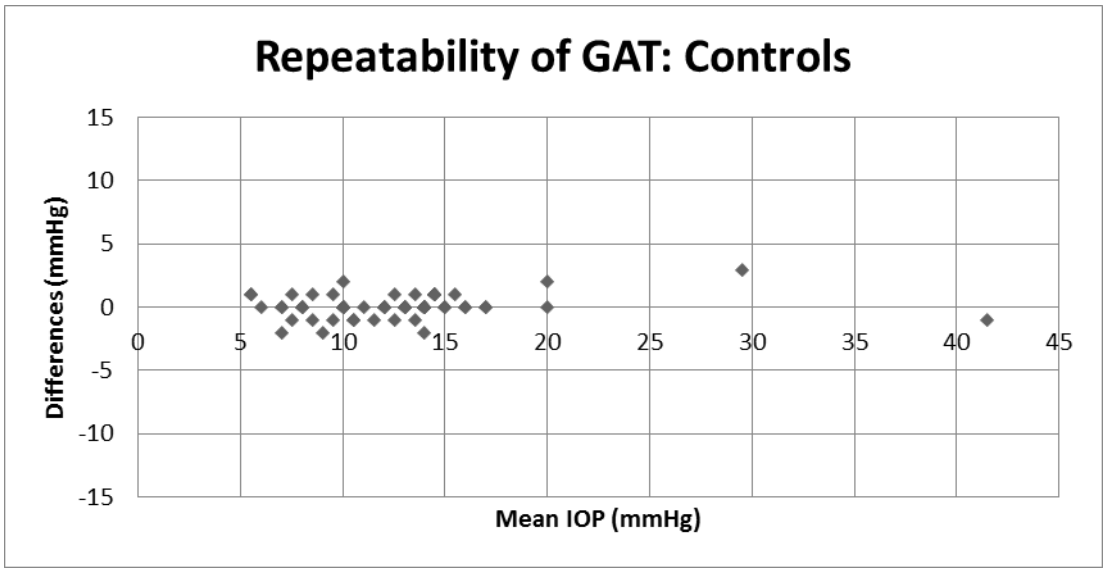

Figure 3.6 – GAT repeatability at different IOPs in normal corneas (Bland-Altman plot)

Our method comparison study showed good correlation between RT and GAT in both study subgroups. The individual means of RT and GAT are plotted against each other in figure 3.7 for patients with corneal scars and figure 3.8 for the controls. The difference between the individual mean IOPs of RT vs GAT are plotted against the mean IOP in figure 3.9 for the scarred subjects and figure 3.10 for the controls.

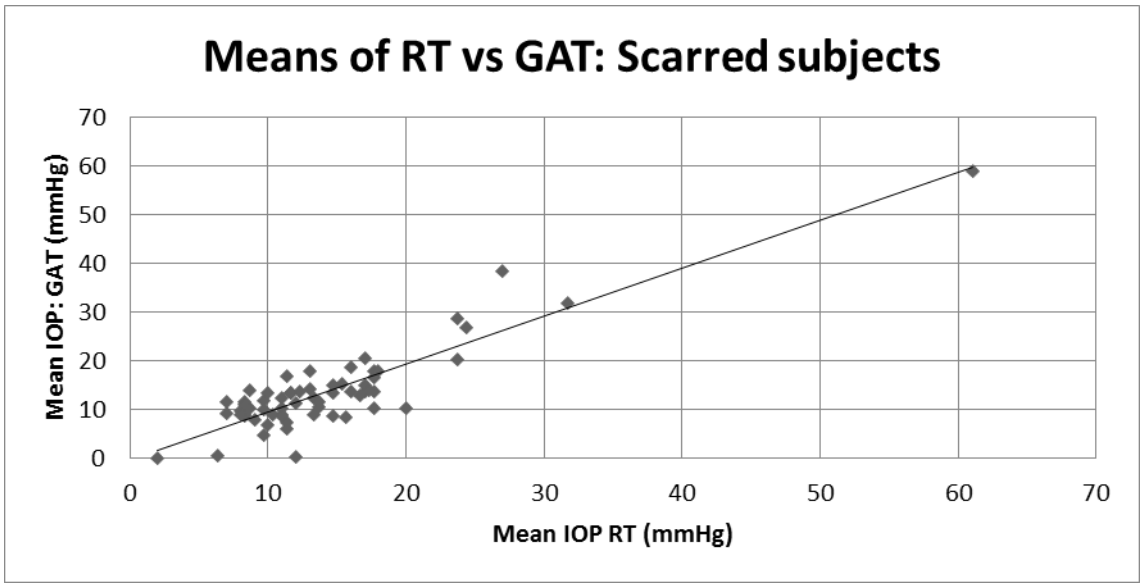

Figure 3.7 – Correlation of RT vs GAT – Individual means: Scarred subjects

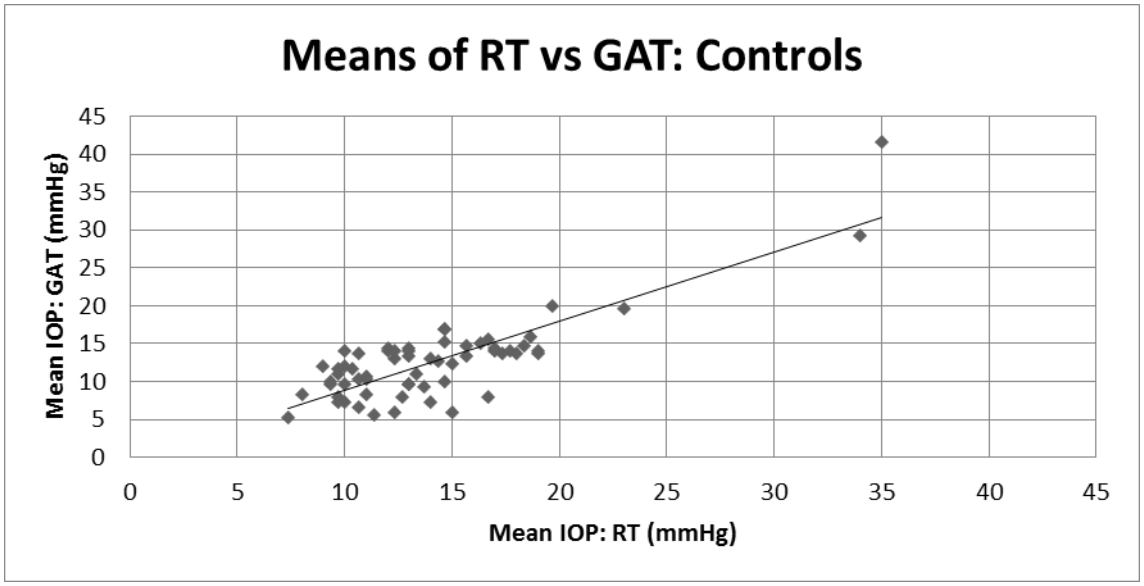

Figure 3.8 – Correlation of RT vs GAT – Individual means: Controls

The correlation coefficient for individual means of RT vs GAT in the two study subgroups were as follows:

Scarred Corneas: $r = 0.8959$; $p < 0.0001$

Controls: $r = 0.8298$; $p < 0.0001$

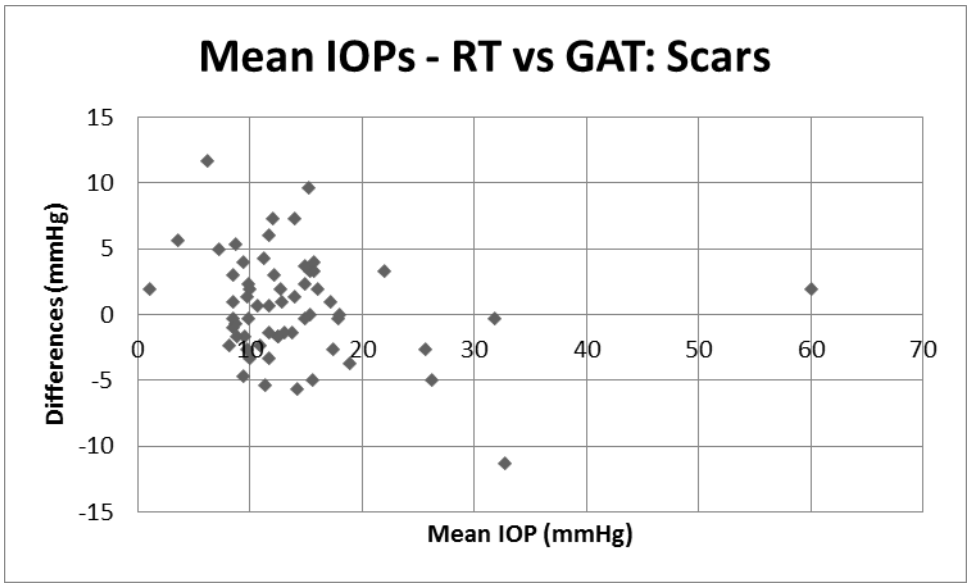

Figure 3.9 – Differences between RT and GAT – Individual means: Scars

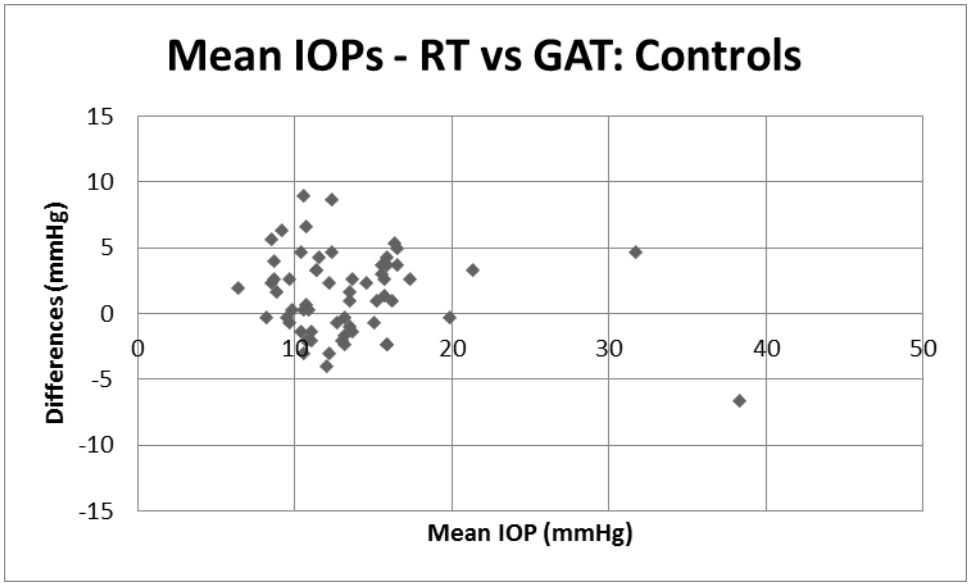

Figure 3.10 – Differences between RT and GAT – Individual means: Controls

In the scarred group, the overall mean IOP with RT was 14.2mmHg (with an overall mean standard deviation of 0.8) and the overall mean IOP with GAT was 13.6mmHg (overall mean SD of 1.4). RT therefore produced a mean IOP estimation in the scarred subjects that was 0.6mmHg higher than that of GAT.

In the controls, the overall mean IOP with RT was 14.1mmHg (with an overall mean standard deviation of 0.7) and the overall mean IOP with GAT was 12.6mmHg (overall mean SD of 0.4). RT therefore produced a mean IOP estimation in the controls that was 1.5mmHg higher than that of GAT.

In both figures 3.9 and 3.10 the distribution of data points are skewed towards the positive side. These plots represent the values of RT minus GAT (and not GAT minus RT) and therefore also indicate higher IOPs obtained with RT than with GAT. In the scarred group, RT obtained individual mean IOPs that were higher than GAT in 31 eyes, lower than GAT in 28 eyes, and the same in 2 eyes. In the control group, RT obtained individual mean IOPs that were higher than GAT in 37 eyes and lower than GAT in 24 eyes. Fisher's exact test on the whole group excluding those that measured the same gave a p-value of 0.4614, showing again that the difference between the instruments were not significant.

Time elapsed between RT1 and GAT3 in the scarred population was a mean of 12minutes and 44seconds.
Time elapsed between RT1 and GAT3 in the control population was a mean of 37minutes and 13seconds.

There was no need for the Tono-Pen XL to be used in this study. By carefully selecting the area of the cornea from which measurements were to be taken, and by positioning the patient's head and eyes with the help of the headrest and fixation target, we managed to get acceptable GAT measurements in all patients.

No complications were caused by the study procedure during the entire course of the study.

4 DISCUSSION

In this study we set out to directly compare the reliability of rebound tonometry (RT) with the reliability of Goldmann applanation tonometry (GAT) in patients with corneal pathology. In our study we specified the type of corneal pathology, namely corneal scars. With corneal pathology being known to cause unreliable GAT measurements,[13,14,15,16,17,18] our main was not to test the correlation of RT with GAT in terms of their IOP measurements, but rather to determine the repeatability or inversely, test-retest variability with both instruments in the same population at the same time.

RT has been shown to have good intraobserver and interobserver correlation coefficients in normal eyes, ranging between 0.46 and 0.96 (intraobserver) and between 0.62 and 0.92 (interobserver).[29] The repeatability coefficient was not used in this particular series and no direct comparison was made with the correlation coefficients of GAT in the same patients. In another study, the test-retest repeatability was assessed using values taken two weeks apart.[40] RT was directly compared with GAT in the same population. Bland-Altman plots were also used to show differences between measurements and the repeatability was expressed in terms of 95% limits of agreement. The limits of agreement between repeated measurements were ±5.11mmHg for RT and ±3.15mmHg for GAT. One could argue against the relevance of this comparison due to the dynamic, fluctuating nature of IOP and therefore the likely difference between measurements taken two weeks apart, but considering that GAT is the proven gold standard and that this study was done on normal eyes, one would accept that the results reflect a true comparison between the repeatability of the two instruments.

In our study, repeat measurements were taken seconds to minutes after one another and followed within minutes by the repeat GAT measurements to try and achieve a relevant comparison. We also did multiple different analyses of the difference between measurements to determine whether findings were statistically consistent and significant. The first measurement was used as the reference and compared to the second and third measurements respectively. In clinical practice, one would preferably do only one measurement. The repeatability of the first measurement is therefore the most important. A difference between measurements of 2mmHg or more was used as a clinically significant cut-off, but we also looked at smaller and larger differences. All analyses showed RT to

have less test-retest variability and therefore greater reliability than GAT in patients with corneal scars, with most tests reaching statistical significance.

Basic analysis of the difference between repeat measurements showed that RT had the highest number of "no difference" between measurements and the lowest number of "2mmHg or more" and "3mmHg or more" difference between measurements in patients with corneal scars. The range of difference between repeat measurements was also lower with RT than with GAT in the scarred population (Table 3.3). Using Fisher's Exact test on the measurement series that had differences of 2mmHg or more showed that RT was significantly more reliable than GAT in patients with corneal scars. Interestingly, when using the same test for differences of 3mmHg or more, RT was still more reliable, but not statistically significantly so. This finding can be interpreted in different ways, one being that, although RT performed better than GAT when using a difference of 2mmHg as cut-off, GAT was not far behind in terms of reliability in these patients.

Analysis of variance (ANOVA) is a way of testing differences between more than two groups. The Kruskal-Wallis test is an ANOVA used on non-parametric data. In our study we had three groups of IOP values for each instrument in each patient, as well as two groups of differences between measurements for each instrument in each patient. Kruskal-Wallis test on the raw data showed that difference between measurements were not statistically significant. This supports previous findings that GAT is still clinically relevant for measuring IOP in patients with corneal pathology despite its known limitations.[26,43] However, the difference between differences were highly significant for either combination or RT compared the difference between GAT1 and GAT2. Interestingly, the difference between GAT1 and GAT3 compared to the difference between either combination of RT did not reach statistical significance, and we cannot explain why this is the case.

The third way in which we compared the reliability of the instruments was by calculating the repeatability coefficient (CR) of each instrument in each subgroup. The usefulness of this measure is that it represents an estimation of the absolute measurement error in the unit of the original measurement.[57] For example, in our study and in the scarred subgroup, RT had a CR of 2.667. This means that one would expect the absolute difference between repeat measurements with RT on subjects with corneal scars to differ by no more than

2.667mmHg on 95% of occasions.[57] The CR of GAT in the scarred patients was 4.819. RT therefore once again showed greater repeatability than GAT in patients with corneal scars. As mentioned in the Results section, the Bland-Altman plots in figure 3.3 and figure 3.4 give a visual representation of the differences between the repeatability of the instruments.

We also tested the correlation of mean IOP with RT versus GAT in our study population. If RT was found to greatly over- or underestimate GAT IOP, or not correlate with GAT at all, any advantage in terms of repeatability would be of little clinical relevance.
Most studies report excellent correlation and good agreement of RT with GAT, with a mean difference between IOP estimates of 1mmHg or less.[19,21,23,27,28,30,34,40,41] In all but one of these studies RT overestimated GAT IOP.[21] A reduced agreement between the two instruments have also been reported, the worst being a mean overestimation of 6.5mmHg in patients with oedematous corneal grafts. In most instances, the patient population in these studies had some form anterior segment abnormality, either structural or in the form of raised IOP.[22,23,24,25,29,54,55] Again, in all but one study RT overestimated GAT IOP.[54]
Our study revealed excellent correlation of RT with GAT ($r = 0.8959$; $p < 0.0001$) and excellent agreement, with RT overestimating GAT IOP by a mean of 0.6mmHg. This finding was more in keeping with previous correlation studies done with normal corneas, despite the fact that our study population had abnormal corneas. We did not specifically select patients with a wide range of IOPs to test the correlation across this range.

In our control subjects (absence of corneal pathology), GAT performed better than RT in terms of repeatability and reliability. In figure 3.2 it can be seen that GAT had the highest number of "no difference" between repeat measurements and the lowest number of "3mmHg or more" difference between measurements. The range of differences between measurements was also lower with GAT than with RT. ANOVA showed excellent repeatability with both instruments, but when looking at the measurement series with differences of 2mmHg or more, GAT was significantly more reliable in the control population ($p = 0.0014$). The repeatability coefficient of GAT was also better than RT's. The correlation of RT with GAT in the control population was excellent ($r = 0.8298$; $p < 0.0001$) and agreement was similar to that found in previous reports, with RT overestimating GAT IOP by a mean of 1.5mmHg. Our findings in the control population support the continued use of Goldmann applanation tonometry as the gold standard for IOP measurement in patients with normal corneas.

The time elapsed between RT1 and GAT3 was different for the scarred group versus the controls. This time represented mainly the time between RT3 and GAT1, and was different for the two groups due to the different days on which patients were recruited. Scarred subjects were recruited throughout the week whereas controls were mainly recruited on two consecutive Fridays. The dynamics of the out-patient department with its different subspecialty clinics on different days of the week inherently influenced the types and numbers of corneal pathologies seen on each day as well as the availability of a slit lamp for examining the study subjects and controls. Despite the longer waiting period between RT and GAT in the control group, there was only a slight reduction in correlation and agreement between the two instruments which was not statistically significant.
One also needs to consider the possibility of learning, that is, bias caused by taking repeat measurements in too rapid succession. However, we considered the relatively short interval between repeat measurements to be the best way to estimate the true repeatability. The bias caused by learning is reduced by instruments such as RT and Tono-Pen XL that give an objective, digital reading, as opposed to instruments which have an analogue scale that needs to be fine-tuned by the observer, as is the case with most Goldmann applanation tonometers.

A more useful measure of time would have been comparing the time taken from RT1 to RT3 with that of GAT1 to GAT3. Although not formally tested, it is the author's experience that RT was faster and easier to use than GAT.

It is important to note that we did not match the controls with the scarred subjects in terms of race, gender or age. Another way of stating the purpose of the study is that we determined the effect of corneal scarring on the repeatability of measurements with two different instruments. The main purpose of the control group was therefore not to compare results in scarred versus normal corneas, but to demonstrate observer proficiency at both measurement techniques so as to strengthen the significance of any findings in the scarred group. Baseline repeatability, correlation and agreement were expected to be good and comparable with previous reports in this particular population and setting, and this was found to be the case. Basic demographic data were recorded as part of routine study procedure and for the purpose of possible future study extensions or comparisons, but subgroup analyses were not done due to sample size and time restrictions. We do not

expect these variables to have a major effect on the outcomes of our study; however, this cannot be concluded without being formally tested.

The Tono-Pen XL was tested before measurement sessions, and as reported in the literature[47] multiple recalibrations had to be done, sometimes consecutively, before the instrument was ready for use. In one study directly comparing GAT, RT and Tono-Pen with each other, RT was shown to correlate better with GAT than Tono-Pen.[19] In another report, RT and Tono-Pen was shown to be more accurate than GAT over a wide range of IOPs in oedematously thickened corneas.[42] There was no need to use the Tono-Pen XL in our study. By carefully selecting the area of the cornea from which measurements were to be taken, and by positioning each patient's head and eyes with the help of the headrest and fixation target, we managed to achieve GAT measurements in all patients. GAT measurements were considered acceptable if all 180˚ of both the mires, including the point of intersection between the prism images, were visible and the mire thickness was appropriate. ANOVA of differences between GAT1, 2 and 3 showed that differences were not statistically significant (Kruskal-Wallis, $p = 0.4902$). This is in keeping with previous findings that GAT is still clinically relevant for measuring IOP in patients with corneal pathology despite its known limitations.[26,43] On the other hand, the CR of GAT in the scarred population was 4.819, which means that one can expect the absolute difference between repeat measurements with GAT in patients with corneal scars to be no more than 4.819mmHg on 95% of occasions.[57] This would be considered too high a measurement error by many and supports the opinion that GAT is not clinically relevant in patients with corneal pathology. [13,14,15,16,17,18,51] We acknowledge that there are circumstances in which GAT would not be possible at all, but this was not the case in the consecutive patients seen during our study. Correlations with extent and cause of corneal scarring were not done due to sample size. Greater extent of scarring and certain other causes of severe ocular surface irregularity, such as diffuse bullous keratopathy and chronic cicatrizing conjunctivitis might render GAT useless, in which case the clinical relevance of RT might be even greater and it would need to be compared to other instruments such as the Tono-Pen XL. Including more patients and a wider range of corneal pathologies could give a better indication of the clinical usefulness of each instrument in specific situations.

Finally, although repeatability is an important measure of an instrument's reliability, the only way of truly knowing which tonometer is more accurate would be to compare it to

manometric (true) IOP. RT and Tono-Pen XL have been shown to be more accurate than GAT in oedematously thickened corneas when compared to manometric pressures.[42]

4.1 Conclusion

In patients with corneal scars, rebound tonometry (RT) was found to be more reliable than Goldmann applanation tonometry (GAT) on the basis of its greater repeatability. This, along with the good correlation found between RT and GAT, makes RT the ideal measurement tool for IOP in these patients. Our findings support the continued use of GAT as the gold standard for IOP measurement in patients with normal corneas. However, RT correlated well with GAT and showed good reliability in patients with normal corneas, which, together with its ease of use, make it a viable option to use as screening tool and in patients in whom GAT might not be possible for reasons other than corneal pathology.

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