

Intraocular pressure

- clinical aspects and new measurement
methods

Gauti Jóhannesson



**Department of Clinical Sciences, Ophthalmology
Department of Radiation Sciences, Biomedical
Engineering and Informatics
Umeå University
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*Vits er þörf
þeim er víða ratar.
Dælt er heima hvað.
Að augabraði verður
sá er ekki kann
og með snotrum situr.
-Hávamál*

*Vett behöver,
den som vida färdas;
lätt är hemma vadhelst.
Mång ögonkast får,
den som intet förstår
och sitter med kloka tillsammans.
-Den Höges sång (Eddan)*

*Wit needs the wanderer
in foreign lands.
At home all is easy.
Boast not your deeds
among those who are wise.
-Lay of Odin (The Edda)*

Til Therese, Elsu Maríu og Eyju Rúnar

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Abstract

Intraocular pressure (IOP) measurement is a routine procedure and a fundament in glaucoma care. Elevated IOP is the main risk factor for glaucoma, and to date, reduction of IOP is the only possible treatment.

In a retrospective clinical material, the prevalence of open angle glaucoma was estimated on the west coast of Iceland. IOP measurement and optic nerve head examination were used to capture glaucoma suspects, within the compulsory ophthalmological examination for the prescription of eye glasses. The results were mainly in agreement with a recent prospective study in the same region. This indicated that retrospective data, under certain conditions, may contribute with useful information on the prevalence of glaucoma. However, normal tension glaucoma is underestimated if perimetry and/or fundus photography are not included in the examination.

Three studies focused on the measurement of IOP. Goldmann applanation tonometry (GAT) is the standard method. GAT is affected by corneal properties, e.g. central corneal thickness (CCT) and corneal curvature (CC). Refractive surgery changes these properties. This has put focus on how corneal biomechanics translate into tonometric errors and stimulated the development of new methods. As a result, Pascal® Dynamic Contour Tonometry (PDCT) and Icare® rebound tonometry have been introduced. A method under development by our research group is Applanation Resonance Tonometry (ART). It is based on resonance technology and estimates IOP from continuous measurement of force and contact area.

Comparison of PDCT, Icare and GAT in a prospective study showed that the concordance to GAT was close to the limits set by the International Standard Organization (ISO) for PDCT, while Icare was outside the limits.

To investigate if laser-assisted subepithelial keratectomy (LASEK) affects tonometry, a study was performed where measurements with GAT, PDCT and ART were obtained before, three and six months after LASEK. The hypothesis was that PDCT and ART would be less affected by LASEK than GAT. The results showed a statistically significant reduction of measured IOP three and six months after LASEK for all tonometry methods. Change in visual acuity and IOP between three and six months suggested a prolonged postoperative process.

A servo-controlled prototype (ART_{servo}) was developed. A study was undertaken to assess the agreement of ART_{servo} and a further developed

manual prototype (ART_{manual}) with GAT. The study design was in accordance with the requirements of the ISO standard for tonometers. ART_{manual} fulfilled the precision requirements of the ISO standard. ART_{servo} did not meet all the requirements of the standard at the highest pressure levels.

Four tonometry methods, GAT, PDCT, Icare and ART, were investigated. None of them was independent of both CCT and CC. The inconsistencies in the results emphasize the importance of study design. A meta-analysis comprising healthy eyes (IOP \leq 21 mmHg) in the three papers, revealed age as an important confounder.

In summary, glaucoma prevalence in Iceland was investigated and the results indicated that a retrospective approach can contribute with meaningful information. ART and PDCT had a similar agreement to GAT. ART_{manual} fulfilled the precision requirements set by the ISO-standard, ART_{servo} and PDCT were close, while Icare was distinctly outside the limits. All tonometry methods were affected by LASEK and no method was completely independent of corneal properties.

Svensk sammanfattning

Mätning av ögontryck är en rutinmetod inom ögonsjukvården. Ögontryck är viktigt för behandling och uppföljning av glaukom men ingår inte längre i diagnosdefinitionen. Förhöjt ögontryck är den största riskfaktorn för att insjukna eller försämrans i sjukdomen. Sänkning av ögontrycket är idag den enda kända behandlingsmetoden.

Ögontrycksmätning är således intimt förknippat med glaukom och används ofta tillsammans med undersökning av synnerven och/eller synfältet som en typ av screeningmetod för att avslöja glaukom. De regler som tidigare gällde på Island vid glasögonförskrivning samt befolkningsstatistikuppgifter i kombination med en systematisk retrospektiv journalgenomgång möjliggjorde att prevalensen av öppenvinkelglaukom på Islands västkust kunde skattas. Mätning av ögontryck och undersökning av synnervshuvudet användes för att identifiera misstänkt glaukom. Resultaten av denna undersökning liknade i många avseenden en prospektiv studie från samma region, men antalet normaltrycksglaukom var betydligt färre. Vi drar därför slutsatsen att retrospektiva undersökningar, under speciella förhållanden, kan bidra med information om glaukomprevalens.

Alla metoder för ögontrycksmätning som används kliniskt är indirekta, dvs mäter utanpå ögat. Goldmanns applanationstonometri (GAT) är standardmetod. Mätningar med GAT, liksom med andra instrument som utnyttjar applanationsprincipen, påverkas av hornhinnans egenskaper, t.ex. av hornhinnans tjocklek och kurvatur. Refraktiva kirurgins förändring av dessa egenskaper har medfört ett ökat intresse för hur biomekaniska egenskaper påverkar ögontrycksmätningen och också drivit utvecklingen av nya metoder för att mäta ögontryck. Pascal® Dynamic Contour Tonometry (PDCT) och Icare® rebound tonometry är metoder som nyligen introducerats. Applanationsresonanstonometri (ART) är en ny metod som utvecklats av vår forskargrupp. Den baseras på resonansteknik som beräknar ögontrycket utifrån kontinuerlig mätning av både kraft och kontaktyta (frekvensskifte).

En jämförelse av PDCT, Icare och GAT i en prospektiv studie visade att PDCT var nära att uppfylla kraven för ögontrycksmätare enligt svensk och internationell standard (ISO standard) när den jämfördes med referensmetoden, GAT. Icare hade sämre överensstämmelse och klarade inte ISO standarden.

I nästa studie undersöktes hur refraktiv kirurgi med LASEK-metoden (laser-assisted subepithelial keratectomy) påverkade ögontryckmätningar. Ögontrycket mättes med GAT, PDCT och ART före LASEK-operationen, samt tre och sex månader efter operation. Med alla metoder uppmättes ett lägre tryck efter operationen. Hypotesen att ögontryck mätt med PDCT- och ART-metoderna skulle påverkas mindre än GAT kunde därmed inte bekräftas ($p = 0.11$). Förändring av synskärpa och tryck mellan tre och sex månader tyder på en förlängd postoperativ läkningsprocess.

ART metoden har vidareutvecklats och en servokontrollerad prototyp (ART_{servo}) har tagits fram. I en prospektiv studie undersöktes överensstämmelsen mellan ART_{servo} respektive en vidareutvecklad manuell prototyp (ART_{manual}) och GAT. Studien genomfördes i enlighet med ISO standarden. ART_{manual} uppfyllde ISO standardens precisionskrav. ART_{servo} klarade inte kraven i den högsta tryckgruppen.

Fyra mätmeter, har studerats i denna avhandling. Ingen var oberoende av både hornhinnetjocklek och hornhinnekurvatur. Ålder kan vara en bidragande orsak till beroendet vilket visar att studiedesign är viktig.

Sammanfattningsvis undersöktes glaukomprevalens på Island och resultaten visade att en retrospektiv studie under vissa förhållanden kan bidra med värdefull information. Ögontrycksmätarna ART och PDCT uppvisade liknande överensstämmelse med GAT. ART_{manual} uppfyllde internationellt ställda krav på ögontrycksmätare, ART_{servo} och PDCT var nära, medan Icare var tydligt utanför kraven. Alla tryckmätningssmetoder påverkades av LASEK behandlingen och ingen av metoderna var helt oberoende av hornhinnans egenskaper.

Almenn samantekt

Mæling augnþrýstings er fastur hluti augnskoðunar. Hækkaður augnþrýstingur er ekki lengur hluti glákuskilgreiningar en er engu að síður mikilvægur þáttur við greiningu gláku og sérstaklega fyrir meðferð og eftirlit sjúkdómsins. Hingað til hefur lækkun augnþrýstings verið eina mögulega meðferðin.

Augnþrýstingsmæling er þar af leiðandi nátengd gláku og er oft notuð ásamt smásjárskoðun sjóntaugaróss og/eða sjónsviðsmælingu sem eins konar skimunaraðferð til að finna gláku. Sú staðreynd að augnlæknar höfðu einir rétt til sjónmælinga á Íslandi þar til fyrir fáeinum árum gerði það að verkum að hægt var að áætla tíðni gláku á Vesturlandi með afturvirkri skoðun á sjúkraskrá og hliðsjón af upplýsingum frá Hagstofu Íslands. Augnþrýstingsmæling og skoðun sjóntaugaróss voru notaðar sem skimunaraðferðir til að finna einstaklinga með gláku. Niðurstöður rannsóknarinnar voru að mörgu leyti svipaðar niðurstöðum nýlegrar framvirkrar rannsóknar á svipuðu svæði en fjöldi einstaklinga með normótensíva gláku var lægri. Við ályktum því að afturvirk rannsókn geti undir vissum kringumstæðum gefið gagnlegar upplýsingar um tíðni gláku en að sérstaklega verði að taka tillit til skekkjuvalda.

Allar aðferðir til að mæla augnþrýsting sem notaðar eru klínískt eru óbeinar, þ.e.a.s. mæla þrýstinginn utan á auganu. „Goldmann Applanation Tonometry“ (GAT) er algengasta augnþrýstingsmæliaðferðin í dag og við hana miðast nýir augnþrýstingsmælar. Mælingar með GAT eru háðar hornhimmueiginleikum svo sem hornhinnuþykkt og –sveigju. Sjónlagsaðgerðir breyta þessum eiginleikum. Þessi staðreynd hefur beint athygli að því hvernig hornhimmueiginleikar hafa áhrif á augnþrýstingsmælingar og þar af leiðandi örvað þróun á nýjum aðferðum til að mæla augnþrýsting. „Pascal® Dynamic Contour Tonometry“ (PDCT) og „Icare® rebound tonometry“ eru mæliaðferðir sem hafa nýlega verið kynntar til sögunnar. Rannsóknarhópur okkar hefur hannað og þróað nýja aðferð til að mæla augnþrýsting sem nefnist „Applanation Resonance Tonometry“ (ART). Aðferðin byggist á eins konar ómunartækni sem mælir augnþrýsting út frá samfelldum mælingum á bæði krafti og snertiflatarmáli.

Samanburður á PDCT, Icare og GAT í framvirkri rannsókn sýndi að PDCT í samanburði við GAT uppfyllti næstum því kröfur alþjóðlegra staðla fyrir augnþrýstingsmæla (ISO) en Icare var klárlega utan staðlanna.

Til að rannsaka hvort ein tegund sjónlagsaðgerða, „laser-assisted subepithelial keratectomy“ (LASEK), hefði áhrif á augnþrýstingsmælingar, framkvæmdum við rannsókn þar sem mældur var augnþrýstingur með GAT, PDCT og ART fyrir LASEK sem og þremur og sex mánuðum eftir aðgerð. Niðurstöður sýndu fram á tölfræðilega marktæka lækun á mældum augnþrýstingi þremur og sex mánuðum eftir LASEK með öllum mæliaðferðum. Vinnutilgátan að augnþrýstingur mældur með PDCT og ART yrði fyrir minni áhrifum af LASEK en GAT var því ekki staðfest ($p = 0.11$). Breytingar á sjónskerpu og þrýstingi á milli þriggja og sex mánaða gáfu í skyn áframhaldandi breytingar í hornhimnu eftir þrjá mánuði.

ART aðferðin var þróuð áfram og sjálfstýrður mælir (ART_{servo}) kynntur. Framvirk rannsókn var framkvæmd til að meta 95% samræmismörk milli ART_{servo} og nýrrar tegundar af handstýrðum ART (ART_{manual}) annars vegar og GAT hins vegar. Rannsóknin var framkvæmd samkvæmt kröfum ISO staðla fyrir augnþrýstingsmæla. ART_{manual} uppfyllti allar nákvæmniskröfur staðlanna. ART_{servo} uppfyllti ekki kröfur í hæsta þrýstingshópi.

Í samantekt var glákutiðni á Íslandi rannsökuð og niðurstöðurnar gáfu til kynna að afturvirk nálgun við sérstakar aðstæður gæti gefið gagnlegar upplýsingar. ART og PDCT höfðu svipað samræmi við GAT. ART_{manual} uppfyllti nákvæmniskröfur ISO, ART_{servo} og PDCT voru nálægt því að uppfylla staðlana en Icare var klárlega utan þeirra. Allar mæliaðferðir urðu fyrir áhrifum af LASEK og enginn þeirra augnþrýstingsmæla sem rannsakaðir voru reyndist algjörlega óháður eiginleikum hornhimnunnar.

Abbreviations

ANOVA	=	Analysis of variance
ART	=	Applanation Resonance Tonometer/ry
ART _{manual}	=	Manual ART
ART _{servo}	=	Servo-controlled ART
ART _{dyn}	=	ART with dynamic analysis
ART _{stat}	=	ART with static analysis
ART _{25mm}	=	ART with sensor element of 25 mm
ART _{30mm}	=	ART with sensor element of 30 mm
CC	=	Corneal curvature
CCT	=	Central corneal thickness
CCT _{Orbscan}	=	CCT measured with Orbscan
CCT _{Pachymeter}	=	CCT measured with Handy Pachymeter
CCT _{Pentacam}	=	CCT measured with Pentacam
CI	=	Confidence interval
EGS	=	European Glaucoma Society
GAT	=	Goldmann Applanation Tonometer/ry
IOP	=	Intraocular pressure
ISO	=	International Standard Organization
LASIK	=	Laser in-situ keratectomy
LASEK	=	Laser subepithelial keratectomy
LoA	=	Limits of agreement
logMAR	=	Logarithm of minimal angle of resolution
OAG	=	Open angle glaucoma
ORA	=	Ocular Response Analyzer
NCT	=	Noncontact tonometry
NTG	=	Normal tension glaucoma
PDCT	=	Pascal Dynamic Contour Tonometer/ry
PEX	=	Pseudoexfoliation
SBU	=	Swedish Council on Health Technology Assessment (Statens beredning för medicinsk utvärdering)
SD	=	Standard deviation

Original papers

This thesis is based on the following publications which are referred to by their Roman numerals.

- I. Jóhannesson G, Guðmundsdóttir GJ, Lindén C. Can the prevalence of open-angle glaucoma be estimated from a retrospective clinical material? A study on the west coast of Iceland. *Acta Ophthalmologica Scandinavica*. 2005; 83: 549-553.
- II. Jóhannesson G, Hallberg P, Eklund A, Lindén C. Pascal, Icare and Goldmann – a comparative study. *Acta Ophthalmologica Scandinavica*. 2008; 86: 614-621.
- III. Jóhannesson G, Hallberg P, Eklund A, Koskela T, Lindén C. Change in intraocular pressure measurement after myopic LASEK - a study comparing Goldmann, Pascal and Applanation resonance tonometry. *Journal of Glaucoma*. 2011. *In press*.
- IV. Jóhannesson G, Hallberg P, Eklund A, Lindén C. Introduction and clinical evaluation of servo-controlled Applanation resonance tonometry. *Acta Ophthalmologica Scandinavica*. 2011. *In press*. E-pub ahead of print (doi: 10.1111/j.1755-3768.2011.02111.x).

1 Introduction

1.1 Glaucoma

Background

Glaucoma is a group of diseases that all have degeneration of the optic nerve in common. It is the second leading cause of blindness worldwide (Quigley & Broman 2006). The largest group of glaucoma is open angle glaucoma (OAG). The aetiology of OAG is still not completely understood (SBU 2008).

Glaucoma was once believed to be a disease synonymous with increased intraocular pressure (IOP) and for many years elevated IOP was part of the definition. In recent years the definition has changed and does not include IOP anymore. Today OAG is defined as a chronic, progressive optic neuropathy associated with characteristic visual field defects and/or morphological damage of the optic nerve head (EGS 2008; SBU 2008).

Epidemiology

Prevalence studies regarding glaucoma usually include people 40 years of age and older because glaucoma is uncommon below 40. With growing and older populations, the number of people with glaucoma worldwide has been estimated to become approximately 60 million by 2020 (Quigley & Broman 2006). At least half of the population diagnosed with OAG are not aware of the disease (Grørdum et al. 2002; Leske 2007). There are substantial variations in prevalence throughout the world due to genuine differences in populations but also due to methodological differences, such as differences in diagnostic criteria and sampling methods. The average prevalence of OAG in European populations > 40 or > 70 years of age is estimated to 2% (Quigley & Broman 2006) and 6% (Rudnicka et al. 2006), respectively.

There are indications of regional differences regarding prevalence in the Nordic countries. OAG seems to be more frequent in the northern parts of the region including Iceland, Norway, Finland and northern Sweden (Ringvold et al. 1991; Hirvela & Laatikainen 1995; Ekström 1996; Jonasson et al. 2003; Aström & Linden 2007; Aström et al. 2007) compared to southern Sweden (Bengtsson 1981) and Denmark (Goldschmidt et al. 1989). However, comparison is difficult because of methodological differences. A recent large population study, the Malmö Eye Survey, comprising approximately 33 000 subjects, showed a prevalence of > 5% in people 75 years of age (SBU 2008).

In the Nordic countries pseudoexfoliation (PEX) glaucoma is usually regarded as a subgroup of OAG, although in many countries it is classified as secondary glaucoma. PEX glaucoma is prevalent in the Nordic countries (Ringvold et al. 1991; Hirvela & Laatikainen 1995; Ekström 1996; Jonasson et al. 2003; Aström & Linden 2007), and it may contribute to the high prevalence of OAG in the area. In many cases, PEX glaucoma has a more difficult and severe course with faster progress of visual field defects compared to other subgroups of OAG (Heijl et al. 2009).

Risk factors

The most important risk factor for the development (Kass et al. 2002) and the progress (Heijl et al. 2002; Bengtsson et al. 2007) of OAG is elevated IOP. Elevated IOP is still the only risk factor that is modifiable (Leske 2007; Sena et al. 2010). Other ocular risk factors include thin corneas (Gordon et al. 2002) and PEX in combination with elevated IOP (Grødum et al. 2005), which increase the risk for both OAG development and progression of the disease.

The prevalence increases with increased age (Rudnicka et al. 2006). Being of African ancestry implies a higher risk for development of OAG (Leske et al. 1994). Having a close relative with OAG also increases the risk (Leske et al. 2008).

1.2 Physiology of IOP

IOP is a result of a fluid system in the human eye where balance between in- and outflow determines the level of IOP. It is maintained by the production of aqueous humor in the ciliary body in the posterior chamber and the outflow through the trabecular meshwork or the uveoscleral pathway originating in the anterior chamber (Figure 1) (Goel et al. 2010). The flow of aqueous humor against resistance in a healthy eye creates an IOP of approximately 16 mmHg (Leydhecker et al. 1958; Shiose 1990). An imbalance of this system, by increased production or increased outflow resistance, results in an increase of IOP. Aqueous humor is produced at a flow rate of 2.75 $\mu\text{l}/\text{min}$ (Brubaker 1991) and the uveoscleral outflow is approximately 1.1 – 1.5 $\mu\text{l}/\text{min}$ (Toris et al. 1999) .

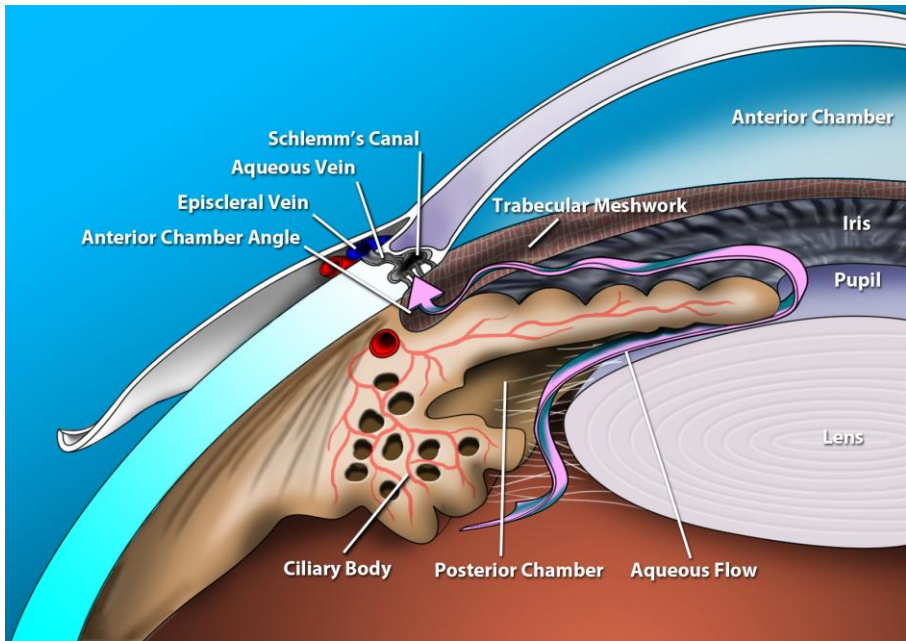


Figure 1. A cross section of the anterior segment of the eye. The flow of the aqueous humor is shown with arrow.
Illustration by G. Andersson.

1.3 Intraocular pressure

IOP plays a central role throughout ophthalmology. It is part of routine ophthalmologic examinations and important in the management and follow-up of glaucoma patients.

The association between glaucoma and elevated IOP was established in the first half of the 19th century (Mackenzie 1830). The first instruments to measure IOP, tonometers, were introduced in the latter half of the same century (Donders 1863; Draeger 1961). Since then, numerous techniques to measure IOP have been introduced, each with its advantages and disadvantages. Hitherto, no method is regarded to be totally independent of corneal properties and no method measures the true IOP.

Glaucoma can develop irrespective of IOP level, and glaucoma with “normal” IOP has in large population studies been shown to account for a considerable portion of OAG (Dielemans et al. 1994; Grødum et al. 2002; Jonasson et al. 2003). Statistically, 21 mmHg can be argued to be a correct level for normal pressure. Based on large screening studies, the mean IOP for healthy individuals is approximately 16 mmHg with a standard deviation of 2.5 mmHg (Leydhecker et al. 1958; Shiose 1990).

1.4 Tonometry methods

Direct measurement of IOP requires invasive methods during surgery and is not used in clinical practice. Thus, all current clinical tonometry methods measure IOP indirectly, i.e. it is an estimation of the true IOP.

Tonometry methods can be divided into four different categories according to their principles of measurement: applanation, indentation, contour matching and rebound tonometry (Kniestedt et al. 2008).

Applanation tonometry

The gold standard for tonometry methods is the Goldmann Applanation Tonometer (GAT) (Figure 2). Goldmann and Schmidt based their novel tonometer on the law of Imbert-Fick (Eq.1) which states that the IOP is proportional to the force (F) needed to applanate a pre-defined area (A) (Goldmann 1957).

$$IOP = \frac{F}{A}$$

Eq. 1. Imbert-Fick's law

However, Eq. 1 is only applicable to an infinitely thin membrane with perfect elasticity and a dry surface (Goldmann 1957). Since the cornea meets none of these conditions, Goldmann and Schmidt compensated for potential errors by presuming that the corneal thickness would be approximately 500 μm in most healthy eyes. Furthermore, they recognized that the influence of the tear fluid and the rigidity of the cornea would cancel out each other at a contact area with a diameter of approximately 3.0 mm (Figure 3). The pre-defined area of the tonometer probe was chosen to be 7.35 mm^2 (diameter 3.06 mm) because of practical reasons; then 1 g of force is interpreted as 10 mmHg (Goldmann 1957). GAT has been shown, in numerous studies, to be dependent on corneal properties such as central corneal thickness (CCT) and corneal curvature (CC). Additional sources of error include high astigmatism, inter- and intra-variability, etc (Thorburn 1978; Whitacre & Stein 1993; Doughty & Zaman 2000; Kniestedt et al. 2008).

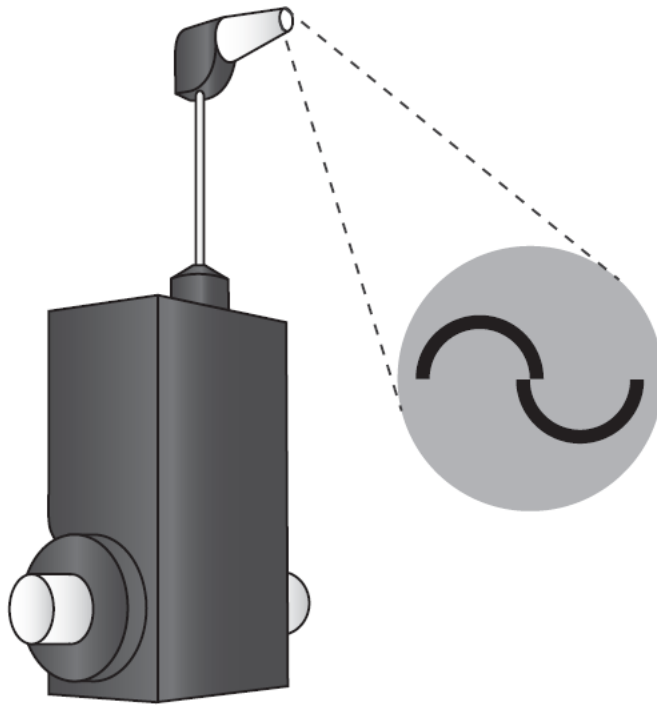


Figure 2. The Goldman Applanation Tonometer.
Illustration by A.Wählin.

In order to measure IOP with GAT, a drop of anaesthetic and fluorescein is instilled in the eye. Through an optical prism, the examiner sees two semicircles and adjusts the force until the inner edges of the semicircles connect. GAT is mounted on a biomicroscope and thus requires the patient to be in a sitting position. Perkins and Draeger are handheld versions of GAT.

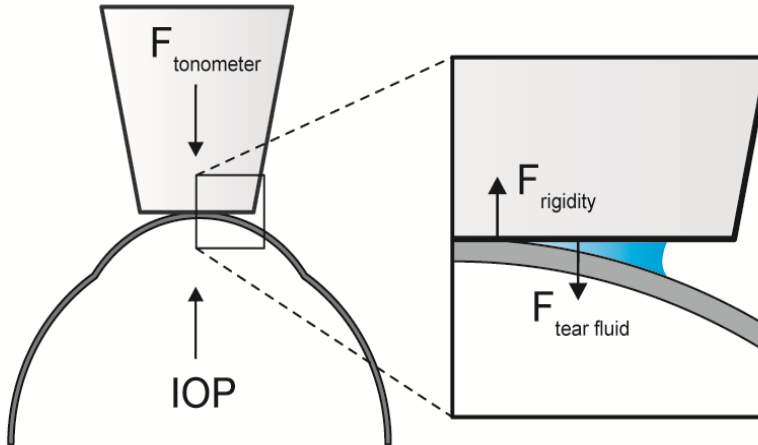


Figure 3. A schematic illustration of forces affecting the appplanation force in GAT. F_{rigidity} acts as a repelling force while $F_{\text{tear fluid}}$ acts as an adhesive force on GAT. Goldmann presumed that in normal corneas, F_{rigidity} and $F_{\text{tear fluid}}$ would cancel each other out.

Illustration by A. Wählin.

The appplanation principle is also used by the Tono-Pen[®]. After applanating the cornea with this handheld tonometer, it presents an average IOP of several measurements (Hessemer et al. 1989). The Tono-Pen is especially useful in irregular corneas and in patients who cannot sit at the biomicroscope (Kniestedt et al. 2008).

Noncontact tonometry (NCT) works with the appplanation principle. An air pulse applanates a predefined area of the cornea. An optical sensor registers when the appplanation is complete and IOP is calculated depending on the force needed to applanate the cornea (Forbes et al. 1974). The NCT technology has been further developed into the Ocular Response Analyzer[®] (ORA) that has the advantage of being able to measure a parameter believed to describe the visco-elastic dampening of the cornea, corneal hysteresis (Luce 2005).

Appplanation Resonance Tonometry (ART) is a tonometry method under development by our research group (Eklund et al. 2003a; Eklund et al. 2003b; Hallberg et al. 2004; Hallberg et al. 2006a; Hallberg et al. 2006b; Hallberg et al. 2007). It is based on the same principle as GAT, i.e. Imbert-Fick's law, but instead of a single reading of contact force and area, as with GAT, it samples information continuously. An early prototype of ART has been shown to fulfil the requirements of the International Standard

Organisation (ISO) for tonometry methods (Hallberg et al. 2007). The method is described in more detail in the method section.

Indentation tonometry

The Schiøtz tonometer was widely used before GAT was presented. It is still used in many regions in the world. The technique is based on assessing how much indentation of the cornea that is caused by a particular weight (Schiøtz 1905).

Rebound tonometry

Icare is a recently launched tonometry method based on a rebound technique. Icare is a hand-held apparatus that consists of two coils coaxial with the probe shaft. A solenoid coil propels a probe to the cornea and a sensing coil monitors the movement. IOP is calculated by the deceleration in the probe's velocity. One measurement consists of six corneal readings. An average IOP is presented after the highest and lowest readings have been eliminated in order to minimize the standard deviation. Icare has a quality indicator that indicates how reliable the measurement is (Kontiola 1997). Icare requires no anaesthetics and is user-friendly, thus the field of application includes children and disabled people.

Contour tonometry

The PDCT is also recently launched (Kaufmann et al. 2003; Kanngiesser et al. 2005). The method is based on direct trans-corneal IOP measurements. Many studies have shown PDCT to be less dependent or even independent of corneal biomechanics (Kaufmann et al. 2004; Pache et al. 2005; Barleon et al. 2006; Ku et al. 2006; Schneider & Grehn 2006), although conflicting results exist (Francis et al. 2007; Salvetat et al. 2007; Muller & Kohnen 2009). The device has a concave sensor tip which enables the cornea to take the contour of the tip at contact. The IOP is then measured through a piezoresistive pressure sensor in the centre of the probe. Similar to GAT, it is mounted on a biomicroscope and requires anaesthetics. A quality control indicates how reliable each measurement is. Apart from measuring IOP, PDCT is able to measure the ocular pulse amplitude (Kanngiesser et al. 2005; SMT Swiss Microtechnology AG 2005).

Standard for new tonometry methods

As early as 1929, a commission was appointed at the International Congress in Amsterdam to try to standardize tonometers (Friedenwald 1937). In recent years, the ISO has established a standard for tonometry methods to warrant the accuracy of new methods. In order to fulfil the ISO standard (ISO 2001), the new method has to meet certain requirements that are regarded as minimum for tonometers used in clinical practice. These include measurements from at least 150 eyes with IOP divided into three subgroups with ≥ 40 eyes in each group. Furthermore, the 95% limits of agreement compared to the reference method (GAT) have to be smaller than ± 5 mmHg for ± 1.96 SD (ISO 2001). Studies II and IV were designed in accordance with the requirement of this ISO standard for tonometers. In 2009, a new standard was published. The requirements of the new standard are similar to the ISO 2001 with certain important exceptions. These include a reduced minimum amount of eyes to 120 and additional exclusion criteria regarding CCT (ISO 2009).

1.5 Corneal properties

Corneal properties measured in these studies comprise CCT and CC. The normal CCT is estimated to be 534 μm according to a meta-analysis of 300 data sets identified from nearly 700 publications (Doughty & Zaman 2000). Goldmann and Schmidt assumed that CCT did not differ much from 500 μm when they invented their tonometer in the 1950s (Goldmann 1957). It is now recognised that the variation in the normal population is approximately 470 to 600 μm (Doughty & Zaman 2000). A significant relationship between CCT and IOP measured with GAT is established; a thick cornea may give a false too high IOP reading and vice versa for a thin cornea (Whitacre & Stein 1993). However, there is an ongoing debate on how much of the IOP measurement variance can be explained by CCT alone (Kotecha 2007).

Normal CC is often in the range of 7.7 – 7.9 mm (Jonsson et al. 2006; Kim et al. 2010). True IOP may be overestimated when measured with applanation tonometry on steep corneas and underestimated in eyes with flat corneas. As for CCT, only a small portion of IOP measurement variance can be explained by variations of CC (Kotecha 2007).

Geometrical properties such as CCT and CC together with elastic properties of the cornea will have potential to affect IOP measurement due to corneal rigidity. Capillary forces due to tear fluid will also act on the applanation probe (Figure 3). These properties influence the tonometry in opposite directions. When a tonometer comes into contact with the eye, the tear fluid

acts as an adhesive and can therefore theoretically facilitate the appplanation. Corneal rigidity, on the contrary, offers resistance to the tonometer and thereby potentially affects the IOP measurement toward a falsely high IOP (Goldmann 1957).

Mechanics can be applied to the analysis of dynamic systems and when applied to biology it is termed biomechanics (Fung 1993). CCT and CC are examples of structural attributes that give rise to biomechanical properties of the cornea. Biomechanical properties have been difficult to measure routinely. Recently, a new biomechanical parameter of the cornea, corneal hysteresis, has been introduced. It is a parameter that is believed to describe the viscoelastic properties or dampening effects of the cornea. Hitherto, only one apparatus is available on the market that is able to measure corneal hysteresis, the ORA (Luce 2005; Kotecha 2007).

1.6 Refractive surgery

Improvements in terms of increased safety and predictable results have been made in the field of refractive surgery during the last two decades. Refractive surgery has become increasingly popular in recent years. The structural modification of corneal properties, e.g. CCT and CC, by refractive surgery, has augmented the risk for measurement error of IOP and consequently brought attention to the IOP measurement. Generally, preoperative examinations include a thorough ocular examination, refraction, pupillometry, tonometry and measurements of corneal properties. Based on these variables and individual needs, the surgical technique is chosen. The techniques can mainly be classified into lamellar (e.g. laser in-situ keratectomy (LASIK)) and surface (e.g. laser assisted subepithelial keratectomy (LASEK)) ablation (Figure 4) (Sakimoto et al. 2006). LASEK is a subgroup in which the effect on IOP measurement has been sparsely investigated.

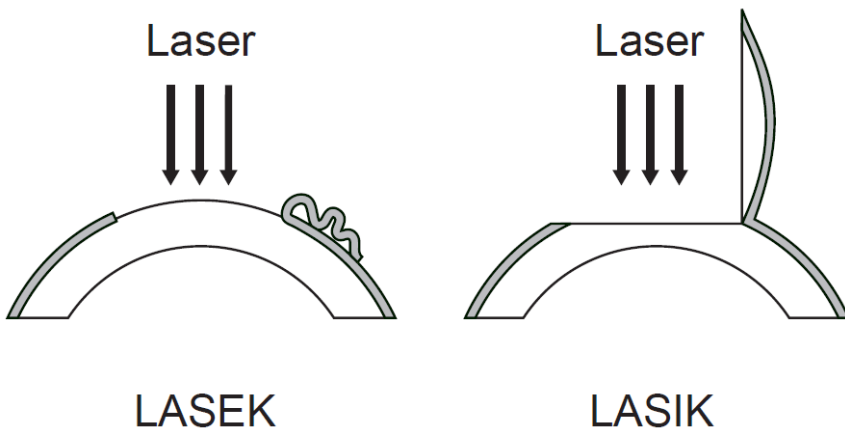


Figure 4. A schematic picture comparing LASEK and LASIK procedures. The grey layer represents the corneal epithelium and the white layer the corneal stroma.

Illustration by A.Wählin.

The fundamental difference between lamellar and surface ablation is the site of laser treatment in the corneal stroma and the indications for surgery. In lamellar ablation, a flap is created in the corneal stroma with a keratome and ablation carried out deep in the stroma. The patient experiences a rapid increase in visual acuity and few discomforting symptoms. During surface ablation only the epithelium is loosened and moved aside followed by external treatment of the stroma. The postoperative discomfort is greater and visual acuity improvement slower than with lamellar surgery. A general advantage with lamellar ablation is that patients with larger myopia/hyperopia and/or astigmatism can be treated compared to surface ablation (Sakimoto et al. 2006).

2 Aims

The general objective of this thesis was to evaluate new tonometry methods. An additional aim was to investigate if the prevalence of open-angle glaucoma could be estimated from a retrospective clinical material, where IOP and optic nerve head examinations were used as screening tools.

The specific aims of the thesis were

- to investigate if a retrospective design in a defined population could be used to estimate the prevalence of OAG and to compare the estimate with a recent prospective Icelandic study,
- to compare two newly introduced tonometry methods, PDCT and Icare, to the reference method GAT,
- to evaluate three tonometry methods – the gold standard, GAT, a new method, PDCT, and a method under development, ART – with respect to IOP before and three and six months after LASEK,
- to assess if a further developed manual ART and a new motorized prototype of ART fulfil the ISO standard by comparison to GAT,
- to investigate the influence of corneal properties on IOP measurement with GAT, PDCT, Icare and ART.

3 Material and methods

3.1 Subjects

Population (Paper I)

The clinical data used in Paper I was collected through records from the sole ophthalmologist serving the west coast of Iceland. Only records of patients aged 50 years or more that were alive on December 1, 2001 were reviewed. Patients with glaucoma were recognized and information about their disease acquired from the records. After re-evaluation, glaucoma patients were included in the study if the inclusion criteria were met and if they had visited the eye clinic between December 1, 1996 and December 1, 2001. The study was divided into two subcategories: one for the main clinic in the town of Akranes and the other for the whole of the west coast region (Figure 5).

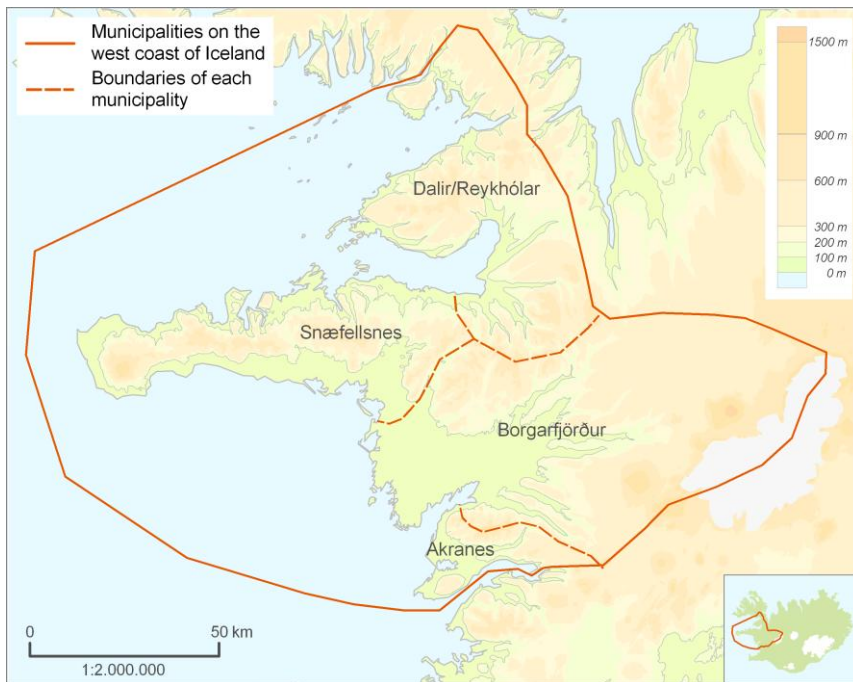


Figure 5. A map of the west coast of Iceland.

The main study was carried out in Akranes where prevalence was investigated.

Minimum prevalence was calculated from the whole west coast (solid line).

Illustration by G. Guðmundsson.

Patients (Papers II-IV)

Glaucoma patients with and without elevated IOP from the Department of Ophthalmology, Umeå University Hospital, Umeå, participated in studies II and IV. Healthy patients scheduled for LASEK at a private practice in Umeå, Koskela Eye Clinic, participated in study III.

Healthy volunteers (Papers II & IV)

Healthy volunteers participated in the studies presented in Papers II and IV.

More detailed information on all subjects is given in Papers I-IV. An overview of demographic data in the studies is presented in Table 1.

Table 1. An overview of demographic data in Papers I-IV.

Study	No. subjects/eyes	Sex (F/M)	Design	Subjects	Age mean (range)
Ia	1443*/-	757/686	R	Population	≥ 50
Ib	3782*/-	1867/1915	R	Population	≥ 50
II	76/150	42/34	P	Patients/volunteers	58 (18-83)
III	53/53	28/25	P	Patients	29 (19-52)
IV	77/152	37/40	P	Patients/volunteers	61 (43-88)

*Inhabitants ≥ 50 years of age in Akranes (Ia) and on the west coast of Iceland (Ib).

R: retrospective; P: prospective.

3.2 Methods for measuring IOP

Applanation Resonance Tonometry

Applanation Resonance Tonometry (ART) is a tonometry method under development by our research group. ART is based on simultaneous and continuous sampling of both contact force and contact area. The device consists of a sensor with a piezoelectric ceramic element composed of lead, zirconate and titanate and a force transducer. Alternating voltage is applied through the element resulting in oscillation in its resonance frequency. When the sensor comes into contact with the cornea, the oscillation changes and results in a frequency shift. This frequency shift is proportional to the contact area. Thus, knowing the contact area (A) and contact force (F), the IOP can be calculated according to Imbert-Fick's law (Eq. 1). The ART technique is able to analyse data in two ways. Firstly, focus is on the dynamic phase of the measurement, i.e. the indentation of the cornea, and secondly, focus is on a more static phase when the cornea is fully applanated (Figure

6). Two different prototypes were used, a manual version (Papers III-IV) and a servo-controlled version (Paper IV). In both cases the ART sensor was mounted on a biomicroscope in a manner similar to GAT.

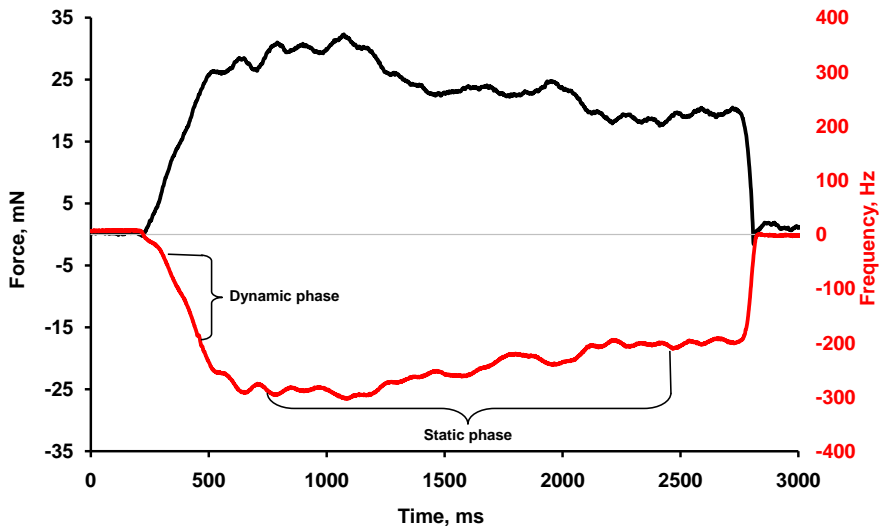


Figure 6. The relationship between force (black line) and frequency shift (red line) over time with the ART technique. Two analyses were used, one based on the initial dynamic phase, and one based on the static phase.

Manual ART

The manual ART instrument was moved by the operator towards the cornea until a sound signalled for an acceptable application against the cornea. A different sound indicated that the probe could be brought back from the cornea. During the work of this thesis the development of the manual ART has progressed and different further developed prototypes have been used in the different studies. Initially, ART was planned to be included in Paper II. Shortly before the start of the study, ART was modified and due to technical problems, the prototype was out of order and measurement results were incorrect.

Two manual ART prototypes were used in Paper III, the difference being the length of the sensor element; one was 25 mm and the other 30 mm.

Servo-controlled ART

The servo-controlled ART (ART_{servo}) utilized the same technique for IOP measurement as the original manual version. Instead of pushing the sensor towards the cornea manually, the ART was brought approximately one centimetre in front of the cornea and then a remote control was activated, starting an automated applanation of the cornea. A miniature motor, controlled by feedback information from the continuously measured area and force, generated the sensor movement (Figure 7). In Paper IV, one instrument containing both a servo-controlled and manual function was used.

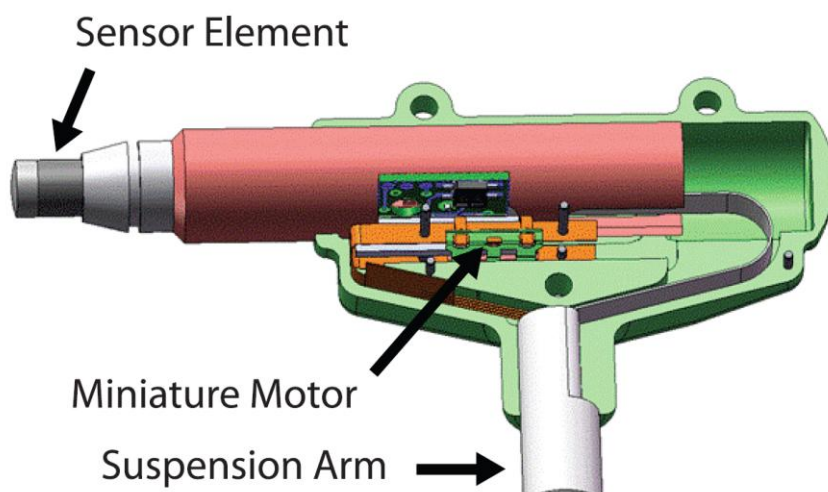


Figure 7. Conceptual illustration of the ART_{servo} prototype (Paper IV).

The sensor is moved forward by a miniature motor. A force transducer connected to the suspension arm measures the force and the sensor element measures the contact area. The information from these measurements controls the movement of the sensor.

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Other tonometry methods

Three other tonometry methods were investigated in this thesis: GAT (Papers I-IV), PDCT (Papers II-III) and Icare (Paper II). They have all been described in the Introduction.

3.3 Methods for assessment of corneal properties

Several methods were used for documentation of the anterior segment. Orbscan II® (CCT_{Orbscan}) is a scanning slit (light)-based optical reflectance method that requires no anaesthesia (Papers II & III). This procedure enables the apparatus to topographically map the cornea (Doughty & Jonuscheit 2010). The CCT was measured within a central sector with a diameter of 3.06 mm.

The Handy Pachymeter SP-100® is an ultrasound instrument that measures CCT (CCT_{Pachymeter}) through a contact probe placed perpendicular to the central cornea. A mean of eight measurements was registered according to the instrument manual (Paper III). In a recent review article, Doughty & Jonuscheit conclude that Orbscan and pachymetry should be contemplated as measuring different characteristics of the cornea instead of adjusting CCT values of Orbscan to pachymetry (Doughty & Jonuscheit 2010).

In Paper IV, the anterior segment was photographed using a Pentacam®. It is a Scheimpflug camera that rotates while it photographs and captures detailed information of the anterior segment including CC and CCT_{Pentacam} (Optikgeräte 2003).

3.4 Surgery

LASEK, one of the refractive surgery procedures, was performed at the Koskela Eye Clinic (Paper III). During this procedure the epithelium was loosened using alcohol and moved to the side. A laser ablation was then performed with Schwind ORK-CAM aspherical profile and Schwind ESIRIS flyingspot excimer-laser in order to correct refractive errors. Lastly, the epithelium was repositioned on the stroma. Postoperative treatment consisted of antibiotics, topical steroids and tear drops.

3.5 Ethics

All studies followed the tenets of the Declaration of Helsinki and were approved by the Ethics Committee of the Medical Faculty of Umeå University or the Regional Ethical Review Board in Umeå. Study I was also approved by the Data Protection Authority of Iceland and the National Bioethics Committee of Iceland. In studies II-IV, all subjects signed an informed consent.

3.6 Statistical methods

SPSS 16.0 statistical software was used for analysis in Paper II and SPSS 17.0 in Papers III-IV.

In all statistical analyses where independent observations were assumed, only one eye per individual was used in order to fulfil statistical requirements of independency (Altman & Bland 1997). In general, values were presented as mean \pm standard deviation (SD) (Papers II - IV). In Paper I, prevalence was measured as the ratio between living patients with OAG and people examined during the study period. Confidence intervals were calculated and presented. Bivariate correlations (Pearson correlation coefficients) were performed to analyse linear relationships between different parameters (Papers II - IV). A paired-sample *t*-test was used in order to analyse differences between methods (Papers II - III). One-way ANOVA was used for analysis of differences between tonometer methods (Papers III - IV). Bland and Altman analysis evaluated pressure dependency of the difference between methods (Paper II). The 95% limits of agreement (LoA) of a tonometry method was defined as $\pm 1.96 \times$ SD of the difference between the reference method, i.e. GAT, and ART (Paper IV). ART was calibrated against GAT through a procedure described in detail by Eklund et al. (Eklund et al. 2003a). This calibration procedure eradicated systematic variations between the tonometers. Since ART was calibrated against preoperative GAT measurements in Paper III, it did not affect the comparison between the different methods postoperatively. However, the calibration procedure in Paper IV limited the scope of the study to the assessment of the precision of ART.

A $p < 0.05$ was considered statistically significant.

4 Results

4.1 Prevalence of glaucoma on the west coast of Iceland

Akranes

A total of 1141 inhabitants (79% of the total population) aged 50 years or more of the town Akranes had visited the eye clinic during the study period (Paper I). The participation rate increased with increasing age as can be seen in Table 2. A total of 55 patients fulfilled the inclusion criteria for OAG. Thus, the overall prevalence was 4.8% (95% CI 3.6 - 6.1) in the investigated population. Division of age-specific prevalence is shown in Table 3. Of all glaucoma cases, simplex glaucoma made up about 47%, PEX glaucoma made up about 47%, and normal tension glaucoma (NTG) made up 5.5%.

Table 2. The cumulative participation rate in Akranes.

Age (years)	Examined (n)	Inhabitants (n)	Participation rate (%)
≥ 50	1141	1443	79.1
≥ 60	706	871	81.1
≥ 70	416	485	85.0
≥ 80	147	166	88.6

n: number

Table 3. The prevalence of OAG in Akranes and the minimum prevalence of OAG on the west coast of Iceland.

Age (years)	Akranes (prevalence)			West coast (minimum prevalence)		
	(n)	(%)	(95% CI)	(n)	(%)	(95% CI)
50-59	1	0.2	0.0 - 0.7	2	0.1	0.0 - 0.3
60-69	5	1.7	0.2 - 3.3	21	2.0	1.1 - 2.9
70-79	20	7.4	4.2 - 10.6	45	5.7	4.1 - 7.4
≥ 80	29	19.7	13.2 - 26.3	76	17.3	13.7 - 20.9
Total	55	4.8	3.6 - 6.1	144	3.8	3.2 - 4.4

n: number; CI: confidence interval

West coast

On the whole west coast, including Akranes, a total of 144 patients were identified as having OAG (Table 3). The minimum prevalence in this age group was 3.8% (95% CI 3.2 - 4.4). The largest subcategory of OAG was

simplex glaucoma (48.6%) followed by PEX glaucoma (45.8%) and NTG (5.6%).

4.2 Concordance between tonometry methods

An overview of measured variables in Papers II-IV can be seen in Table 4.

ART (Papers III & IV), Icare (Paper II) and PDCT (Papers II & III) correlated significantly with GAT (Table 5). There was also a significant correlation between Icare and PDCT ($n = 149$, $r = 0.84$ (II)).

Table 4. An overview of measured variables in studies II-IV.

Parameter	Units	II (\pm SD)	III (\pm SD)			IV (\pm SD)
			Pre	3 months	6 months	
CCT _{Orbiscan}	μm	560 (\pm 41)	536 (\pm 29)	485 (\pm 41)	492 (\pm 38)	-
CCT _{Pentacam}	μm	-	-	-	-	552 (\pm 37)
CCT _{Pachymeter}	μm	-	556 (\pm 31)	513 (\pm 35)	512 (\pm 37)	-
CC	mm	7.87 (\pm 0.24)	7.92 (\pm 0.24)	8.08 (\pm 0.24)	8.07 (\pm 0.25)	-
Visual acuity	logMAR	-	-	- 0.12 (\pm 0.09)	- 0.15 (\pm 0.08)	-
GAT	mmHg	19.4 (\pm 6.7)	14.3 (\pm 2.5)	13.0 (\pm 2.8)	12.6 (\pm 2.5)	19.1 (\pm 5.7)
PDCT	mmHg	20.5 (\pm 5.5)	14.5 (\pm 2.2)	14.1 (\pm 2.1)	13.5 (\pm 2.1)	-
Icare	mmHg	21.4 (\pm 6.8)	-	-	-	-
Manual ART _{dyn}	mmHg	-	14.1 (\pm 2.1)	13.4 (\pm 1.7)	13.1 (\pm 1.7)	19.1 (\pm 5.3)
Manual ART _{stat}	mmHg	-	14.0 (\pm 2.1)	13.0 (\pm 1.7)	12.9 (\pm 1.7)	19.1 (\pm 5.3)
Servo ART _{dyn}	mmHg	-	-	-	-	19.1 (\pm 5.3)
Servo ART _{stat}	mmHg	-	-	-	-	19.1 (\pm 5.3)

CCT: Central corneal thickness; CC: Corneal curvature; IOP: Intraocular pressure; GAT: Goldmann Applanation Tonometry; PDCT: Pascal Dynamic Contour Tonometry; ART: Applanation Resonance Tonometry; dyn: dynamic analysis; stat: static analysis.

Three tonometry methods were compared in Paper II. The relationship between their IOP readings can be characterized by a linear regression (mean IOP by each method from each eye):

$$IOP_{GAT} = 1.12 IOP_{PDCT} - 3.7$$

$$IOP_{GAT} = 0.91 IOP_{Icare} + 0.17$$

$$IOP_{PDCT} = 0.70 IOP_{Icare} + 5.57$$

The 95% limit of agreement (LoA) between IOP_{GAT} and IOP_{Icare} was - 7.9 to 3.9 mmHg (n = 897), and between IOP_{GAT} and IOP_{PDCT} it was - 6.0 to 3.6 mmHg (n = 881).

In order to evaluate the newly developed ART_{servo} and a further developed ART_{manual} , a study was designed according to the ISO standard for tonometers. GAT was used as the reference method (Paper IV). The 95% LoA of ART_{manual} was ± 4.5 mmHg with dynamic and static modes (Figure 8). An improvement of the 95% LoA to ± 4.3 mmHg for ART_{manual} was observed when both analysis modes were merged. The 95% LoA of ART_{servo} was ± 5.7 mmHg using the dynamic mode and ± 4.9 mmHg with the static mode (Figure 9). When 95% LoA for ART_{manual} was calculated from only the first three measurements, approximately the same LoA was reached as with all six measurements. The number of eyes with differences between the ART prototypes and GAT that exceed ± 5 mmHg are shown in Table 6.

Table 5. The correlations between tonometers in Papers II-IV. All correlations are compared with GAT.

	II r (n)	III (Pre-LASEK) r (n)	IV r (n)
Icare	0.89* (897)	-	-
PDCT	0.91* (881)	0.86* (53)	-
Manual ART_{dyn}	-	0.84* (53)	0.91* (152)
Manual ART_{stat}	-	0.86* (53)	0.92* (152)
Servo ART_{dyn}	-	-	0.86* (152)
Servo ART_{stat}	-	-	0.90* (152)

GAT: Goldmann Applanation Tonometry; PDCT: Pascal Dynamic Contour Tonometry; ART: Applanation Resonance Tonometry; servo: servo-controlled ART; dyn: dynamic analysis; stat: static analysis; r: correlations coefficient; n: number of eyes. *Correlation was significant at 0.05 level.

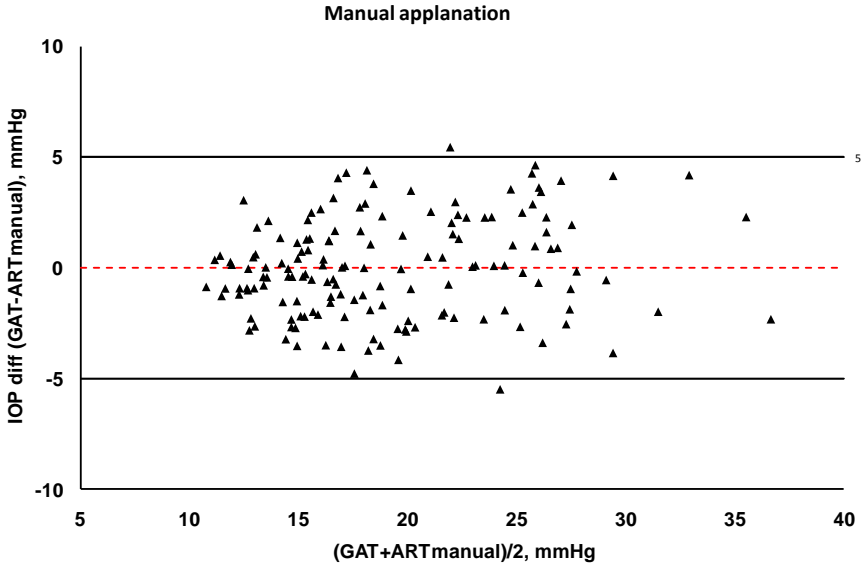


Figure 8. Bland-Altman plot showing the difference between GAT and ART_{manual} static analysis (IOP_{diff}) as a function of their mean IOP (n = 152 eyes (Paper IV)).
 Solid lines show ± 5 mmHg.

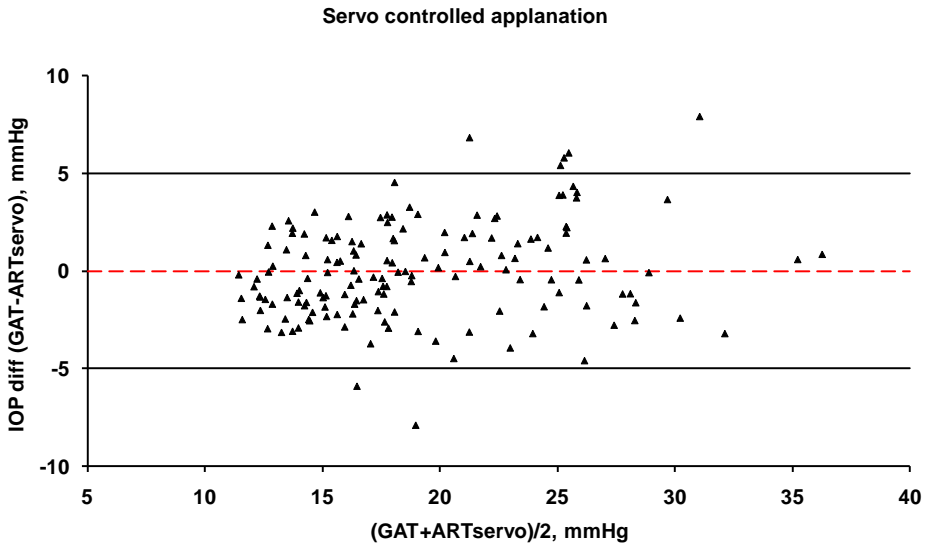


Figure 9. The difference between GAT and ART_{servo} static analysis (IOP_{diff}) as a function of their mean IOP (n = 152 eyes (Paper IV)).
 Solid lines show ± 5 mmHg.

Table 6. The difference between manual and servo-controlled ART as compared to GAT that exceed ± 5 mmHg expressed in percentages. The ISO standard states that only 5% of the differences may be greater than ± 5 mmHg.

IOP range (mmHg)	No of eyes	Manual ART static (% (n))	Manual ART dynamic (% (n))	Servo ART static (% (n))	Servo ART dynamic (% (n))
7-16	63	0	1.5 (1)	3.0 (2)	3.0 (2)
>16 to <23	45	2.0 (1)	4.5 (2)	0	11.0 (5)
≥ 23	44	2.0 (1)	4.5 (2)	11.5 (5)	20.5 (9)
Total	152	1.5 (2)	3.5 (5)	4.6 (7)	10.5 (16)

GAT: Goldmann Applanation Tonometry; ART: Applanation Resonance Tonometry; Servo ART: servo-controlled ART; IOP: intraocular pressure; n: number of eyes; SD: standard deviation.

4.3 Corneal properties and IOP measurement

The results from Paper II showed that CCT_{Orbscan} correlated significantly with both GAT and Icare (Table 7). In contrast, no significant correlation was found between CCT_{Orbscan} and PDCT. There was a significant correlation between CCT_{Orbscan} and age as well as with IOP and age indicating age as a confounder. This brought about a selection of more homogenous data, i.e. individuals > 50 years of age, in order to avert age as a confounding factor. In this subgroup, neither GAT nor PDCT showed a correlation to CCT_{Orbscan} as Icare still did.

After randomization of eyes in study IV, 77 eyes from 77 subjects were analyzed with regards to CCT_{Pentacam}. There was a significant correlation between IOP and CCT_{Pentacam} for all tonometry methods (Table 7). However, the correlation between IOP and CCT_{Pentacam} was not significant ($p = 0.1-0.3$) when the group with the fellow eyes was analyzed.

None of GAT, PDCT or ART tested in Paper III showed a significant correlation with CCT_{Pachymeter} or CCT_{Orbscan} before LASEK surgery (Table 7).

Regarding CC measured in Paper II, both GAT ($r = - 0.26$) and PDCT ($r = - 0.27$) showed a significant correlation with CC whereas Icare ($r = - 0.06$, $p = 0.6$) did not. In Paper III, none of the tested tonometers showed a significant correlation with CC before LASEK; GAT $p = 0.13$, PDCT $p = 0.69$, ART_{dyn} $p = 0.67$ and ART_{stat} $p = 0.85$.

Table 7. The correlation between tonometry methods and CCT in Papers II-IV.

	II ^ψ		III (pre-LASEK)		IV ^λ
	All	> 50 years	All ^ψ	All ^φ	
	r (n = 76)	r (n = 58)	r (n = 47-52)	r (n = 47-52)	r (n = 76)
GAT	0.23*	0.04	- 0.11	0.22	0.29*
Icare	0.43*	0.33*	-	-	-
PDCT	0.12	- 0.09	- 0.27	- 0.02	-
Manual ART _{dyn}	-	-	- 0.11	0.21	0.32*
Manual ART _{stat}	-	-	- 0.22	0.12	0.34*
Servo ART _{dyn}	-	-	-	-	0.30*
Servo ART _{stat}	-	-	-	-	0.34*

CCT: central corneal thickness; ψ : CCT measured with Orbscan II; ϕ : CCT measured with Pachymeter; λ : CCT measured with Pentacam; GAT: Goldmann Applanation Tonometer; PDCT: Pascal Dynamic Contour Tonometer; ART: Applanation Resonance Tonometer; Servo ART: servo-controlled ART; r: correlation coefficient. *Correlation is significant at 0.05 level.

Meta-analysis of Papers II-IV

Because of contradictory results regarding the relationship between corneal properties and measured IOP with the various tonometers, we randomized one eye per subject and merged all data from Papers II-IV in a meta-analysis. In the meta-analysis we excluded IOP >21 mmHg, glaucomatous eyes and eyes treated with topical treatment, i.e. only eyes considered healthy were included. Correlations between the different tonometry methods and corneal properties are shown in Table 8. CCT measurements with Orbscan were used from Papers II and III while CCT from Paper IV was measured by Pentacam.

Table 8. The correlations between corneal properties and tonometry methods in a meta-analysis of Papers II-IV. The meta-analysis was based on one healthy eye/subject after exclusion of IOP > 21 mmHg (no glaucoma, no topical treatment). However, there was still a significant correlation between age and CCT ($r = 0.31$) and between age and IOP measured with GAT ($r = 0.47$).

	CCT r (n)	CC r (n)	Mean IOP (\pm SD)
GAT	0.34* (123)	-0.14 (84)	14.7 (\pm 2.9)
PDCT	0.30* (78)	-0.01 (78)	15.6 (\pm 3.1)
Icare	0.58* (32)	0.17 (32)	17.7 (\pm 4.8)
ART _{dyn}	0.15 (90)	-0.05 (51)	14.8 (\pm 2.5)
ART _{stat}	0.15 (90)	0.05 (51)	14.8 (\pm 2.5)

CCT: central corneal thickness; CC: corneal curvature; IOP: intraocular pressure; SD: standard deviation; GAT: Goldmann Applanation Tonometry; PDCT: Pascal Dynamic Contour Tonometry; ART: Applanation Resonance Tonometry; dyn: dynamic analysis; stat: static analysis. *Correlation significant at 0.05 level.

There was a significant dependency between age and CCT ($r = 0.31$) and age and IOP ($r = 0.35 - 0.70$). In order to find homogenous data where age was not significantly correlated with CCT, different age groups were analysed (Table 9). Based on this analysis, the cut-off age of 60 years was chosen and the meta-analysis repeated in subjects younger than 60 years of age (Table 10). An independent *t*-test between older (≥ 60) and younger (< 60) subjects showed a statistically significant difference between the CCT in the two groups.

Table 9. The correlations between CCT and age in a meta-analysis of Papers II-IV, after dividing into groups of young and old with different age cut-off. The meta-analysis was based on one healthy eye/subject after exclusion of IOP > 21 mmHg (no glaucoma, no topical treatment).

Age group divider (years)	Younger (<) r (n)	Older (\geq) r (n)
40	-0.06 (59)	0.40* (64)
50	-0.06 (75)	0.47* (48)
60	0.11 (105)	0.34 (18)
70	0.27* (120)	-0.92 (3)

r: correlation coefficient; n: number of eyes

Table 10. The correlations between corneal properties and tonometry methods in a meta-analysis of Papers II-IV in subjects younger than 60 years of age. The meta-analysis was based on one healthy eye/subject after exclusion of IOP > 21 mmHg (no glaucoma, no topical treatment).

	CCT	CC	Mean IOP
	r (n)	r (n)	(± SD)
GAT	0.19 (105)	-0.12 (77)	14.4 (± 2.7)
PDCT	0.07 (71)	0.04 (71)	15.0 (± 2.5)
Icare	0.51* (25)	0.28 (25)	16.7 (± 4.8)
ART _{dyn}	0.08 (79)	-0.05 (51)	14.7 (± 2.5)
ART _{stat}	0.07 (79)	0.05 (51)	14.7 (± 2.5)

CCT: central corneal thickness; CC: corneal curvature; IOP: intraocular pressure; SD: standard deviation; GAT: Goldmann Applanation Tonometry; PDCT: Pascal Dynamic Contour Tonometry; ART: Applanation Resonance Tonometry; dyn: dynamic analysis; stat: static analysis. *Correlation significant at 0.05 level.

4.4 Effect of LASEK on IOP measurement

The third study in the thesis (Paper III) aimed to elucidate how measured IOP is affected by LASEK using three tonometry methods: the gold standard GAT, a new method, PDCT, and our method under development, ART. A total of 53 myopic eyes with a spherical equivalent of - 3.1 diopters from 53 individuals were included in the study.

Measured IOP decreased significantly at both three and six months postoperatively, irrespective of method used. PDCT showed the least change in IOP at three months and ART_{dyn} showed the least change at six months. GAT underestimated IOP the most compared to baseline at both occasions (Table 4 & Figure 10). Nevertheless, no significant difference was found between any of the methods at three months (ANOVA $p = 0.10$) or at six months (ANOVA $p = 0.11$). A significant decrease in measured IOP between three and six months occurred with PDCT but not with GAT ($p = 0.10$), ART_{dyn} ($p = 0.14$) or ART_{stat} ($p = 0.39$).

Uncorrected visual acuity was also found to improve significantly from 1.32 (SD = 0.28) at three months to 1.43 (SD = 0.32) at six months on a decimal score. The same tendency was seen with CCT_{Orbscan} that significantly increased from three to six months. The results of CCT_{Pachymeter} and CC were quite the reverse with no significant change between the two occasions as shown in Table 4.

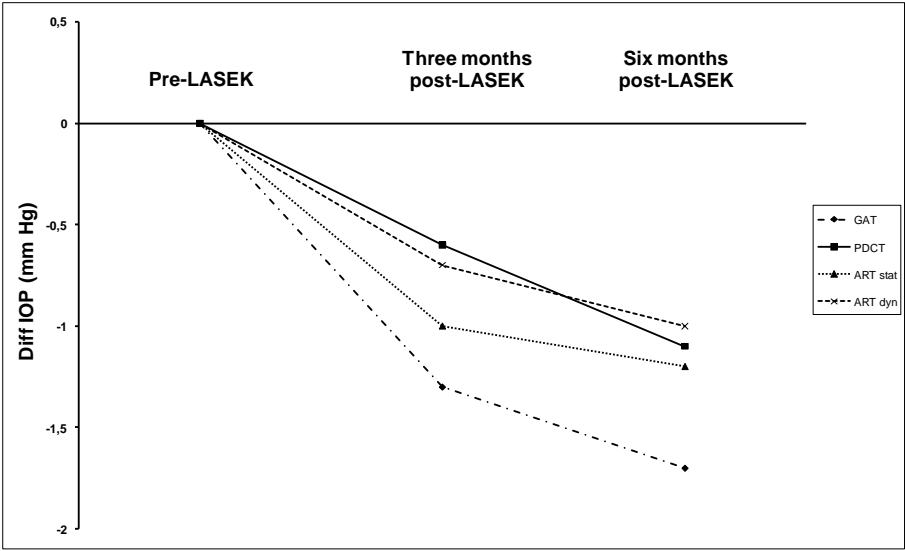


Figure 10. The change in measured IOP after LASEK surgery.
 IOP: intraocular pressure; LASEK: laser subepithelial keratectomy; GAT: Goldmann Applanation Tonometry; PDCT: Pascal Dynamic Contour Tonometry; ART: Applanation Resonance Tonometry

5 Discussion

5.1 Can a retrospective material be used to estimate prevalence of glaucoma?

In the first part of the thesis, a retrospective material was used to estimate the prevalence of OAG (Paper I). Although prospective studies have higher scientific value, retrospective studies can be of importance as they might contribute to the evidence base. Furthermore, the significance of retrospective studies can be increased if sources of error can be detected as was attempted in this study.

A few previous studies have reported results on the frequency of glaucoma in Iceland (Bjornsson 1967; Bjornsson 1980; Viggoosson et al. 1986; Jonasson & Thordarson 1987). A recent prevalence study, the Reykjavik Eye Study, is a prospective study with contemporary diagnostic criteria (Jonasson et al. 2003) and thus served as a reference to assess the relevance of the current study. The overall prevalence of OAG in people aged 50 years or more in the Reykjavik Eye Study was 4.0% (Jonasson et al. 2003), while it was 4.8% and 3.8% in the same age group in Akranes and on the west coast respectively. The latter was a minimum prevalence. The results are similar in many respects. This indicates that data from private practice clinics, under special circumstances, may be used for gathering epidemiological information.

However, there are important differences between the results of the two studies and various factors can be discussed. Firstly, it appears that this study underestimated the proportion of NTG considerably as compared to the Reykjavik Eye Study. As pointed out in a large epidemiological screening study in Sweden, NTG patients are often under-diagnosed in clinical data (Grødum et al. 2002). A possible explanation is that perimetry and/or fundus photography are not part of routine examinations on all patients that visit ophthalmologists. Therefore, NTG patients are at particular risk of being under-diagnosed in retrospective data.

Secondly, patient selection is a major source of error in epidemiological studies. To minimize the risk of bias, prospective studies use randomly sampled participants. Although patient selection in general is a weakness for the retrospective procedure, it may be conceivable to obtain a representative group retrospectively. At the time of the study period, national health regulations stated that prescription of eyeglasses could only be done by an ophthalmologist. Thus, healthy individuals were automatically screened almost as frequently as patients with other ophthalmological complaints

than presbyopia. As a consequence, Iceland offered a unique opportunity to calculate prevalence from retrospective data.

Furthermore, a low participation rate is an important source of error. In the present study the term “participation rate” was used for comparison purposes although “proportion of examined” would perhaps be a more accurate term of choice since no person was indeed invited to participate in the study. Nevertheless, the participation rate was similar to that in the Reykjavík Eye Study, 79% and 76%, respectively (Jonasson et al. 2003). This is in accordance with large population studies (Klein et al. 1992; Leske et al. 1994; Mitchell et al. 1996). Non-attendants still constitute a potential bias, and one reason for not participating might be high age. In the Reykjavík Eye Study there was a large dropout in the oldest age group, whereas in this study the oldest age group had the highest participation rate. This might strengthen the results of the present study as glaucoma prevalence increases with age.

In conclusion, the study showed that retrospective data, under certain conditions, may contribute with useful information on the prevalence of glaucoma. However, the risk for underestimating the prevalence of NTG is high when perimetry and/or fundus photography are not part of routine examinations.

5.2 Concordance between different tonometry methods

Comparing GAT, Icare and PDCT in the same study (Paper II), we found the concordance between GAT and PDCT to be close to the limits of the ISO standard. Icare was clearly outside the limits. Icare measured IOP significantly higher than GAT which may partly be caused by the measurement order since Icare was always the first method tested. It is known as the Bechrakis’ effect, i.e. reduction of IOP after repeated measurements (Bechrakis 1966). Further, Hallberg et al. have previously suggested that a relaxed patient may contribute to a lower IOP measurement (Hallberg et al. 2007). However, our results are in accordance with most previous studies showing an overestimation of the IOP by Icare as compared to GAT (Fernandes et al. 2005; Martinez-de-la-Casa et al. 2005; Iliev et al. 2006; Nakamura et al. 2006; Munkwitz et al. 2008). A few studies have not shown significant difference between measured IOP by the two methods (Brusini et al. 2006; Davies et al. 2006; Vandewalle et al. 2009).

With equilibrium at 27 mmHg (Paper II), PDCT measured higher IOP at low pressure levels compared with GAT and vice versa at higher pressures. The same tendency has been shown in earlier studies, yet with different

directions (Salvetat et al. 2007) or different equilibria (Barleon et al. 2006; Ku et al. 2006). In earlier studies the mean difference between PDCT and GAT measurements has been in the range of 1.0 to 3.2 mmHg (Pache et al. 2005; Ku et al. 2006; Schneider & Grehn 2006; Salvetat et al. 2007; Kotecha et al. 2010). This is in agreement with the results of the present study (+1.2 mmHg).

As an attempt to show a possible calibration of Icare and PDCT against GAT, linear regression analysis was used to illustrate the relationship between the tonometers. It is important to keep in mind that this calibration only regards a single apparatus per method. Therefore, the results should be interpreted with caution in terms of generalisation since there can be individual variations between different apparatuses of each method.

The correlation between GAT and PDCT preoperatively in Paper III was slightly lower than in Paper II (Table 5) and even lower at postoperative controls. Both ART_{stat} and ART_{dyn} also had a decrease in correlation after LASEK when compared to GAT. However, considering the fact that the subjects in Paper III were healthy individuals with normal IOP and a small range, the correlation was expected to be lower due to the study design. A possible explanation for the lower correlation seen at postoperative controls may be that the LASEK-inflicted changes in the cornea affected the tonometers differently.

It is common that the correlation coefficient (r) is used to measure the agreement between two clinical methods. In a Paper with >17000 citations, Bland & Altman explain the disadvantages of using correlation to measure agreement (Bland & Altman 1986). For instance, correlation is dependent on the range of the quantity in the sample, resulting in better correlation when the range is wide than if it is narrow. Thus, study design is of importance. The authors recommend the use of 95% limits of agreement (LoA) when agreement between two methods is sought. 95% LoA describes the variance between methods and is less influenced by, e.g. study design (Bland & Altman 1986).

5.3 Corneal properties and IOP measurement

Corneal curvature has been shown to be significantly correlated to IOP measured with GAT (Mark 1973; Harada et al. 2008). However, it is not clear if this relationship can give rise to clinically relevant IOP errors. (Damji et al. 2003). In a theoretical model, Liu and Roberts showed that a 10% change in CC gave an equivalent IOP difference as the same change in CCT would have given. Furthermore, they demonstrated that steeper

curvature has more impact on IOP accuracy than flatter curvature (Liu & Roberts 2005).

In Paper II including both healthy volunteers and glaucoma patients, both IOP measured with GAT ($r = -0.26$) and PDCT ($r = -0.27$) showed a significant correlation with CC whereas IOP measured with Icare ($r = -0.06$, $p = 0.6$) did not. This dependency between PDCT and CC is supported by two studies (Francis et al. 2007; Yalcinbayir et al. 2010). However, most previous findings have not shown this (Kaufmann et al. 2004; Siganos et al. 2004; Kanngiesser et al. 2005; Schneider & Grehn 2006) and the findings were not supported in Paper III where no significant correlation was found between any tonometry method and CC in healthy subjects.

Differences in CCT can affect IOP measurements. Ehlers et al. showed this in the 1970s (Ehlers et al. 1975a; Ehlers et al. 1975b), and several studies have verified it since (Doughty & Zaman 2000). This has resulted in various nomograms that attempt to correct the measured IOP depending on CCT deviation from the expected norm under the assumption that the relationship between CCT change and IOP is linear. However, Liu and Roberts have recently shown that the relationship between CCT and IOP is non-linear. Thus, the nomograms cannot fully correct measured IOP depending on a single measurement of CCT (Liu & Roberts 2005).

Measurements by GAT (Whitacre et al. 1993) and Icare (Brusini et al. 2006; Iliev et al. 2006; Nakamura et al. 2006) can be significantly influenced by CCT. The findings regarding PDCT in Papers II and III in this thesis are supported by most earlier studies which have shown PDCT to be independent of CCT (Kaufmann et al. 2004; Pache et al. 2005; Barleon et al. 2006; Ku et al. 2006; Schneider & Grehn 2006), but conflicting results have also been reported (Francis et al. 2007; Salvetat et al. 2007). Neither GAT nor PDCT were significantly dependant on CCT in a more homogenous age group (Paper II). The inconsistency in measured IOP between GAT and PDCT, i.e. PDCT measuring higher/lower than GAT at different IOP levels, is therefore difficult to explain by the CCT dependency of GAT as Ku et al. have previously proposed (Ku et al. 2006).

Contradictory results regarding the relationship between CCT and IOP measured by GAT and ART are reported in this thesis. In Paper III, with healthy subjects, there is no significant correlation between CCT and the IOP as measured with the two tonometers preoperatively. This is in contrast to the findings in Paper IV, which includes both glaucoma patients and healthy subjects, where there is a significant correlation between CCT and both tonometers after randomisation. However, when the group of the fellow eyes

that were randomized out of Paper IV was analysed, no correlation was found.

The conflicting results from the different studies of this thesis concerning correlations between corneal properties and tonometry methods raise questions about how this inconsistency can be explained. The study design and subjects of the studies differ considerably. There are differences in, e.g. age distribution, IOP variances, health of the subjects, medications, etc. If the main goal would be to assess the effect CCT and CC on IOP measurement, then investigators would need a larger sample size with as homogeneous subjects as possible apart from variations in CCT and CC.

In an attempt to investigate the relationship between corneal properties and measured IOP on more homogenous and larger data set, a meta-analysis of Papers II-IV was performed. To minimize variations in IOP, only healthy subjects with $IOP \leq 21$ mmHg were included. In this larger data, there was no CC dependency of any tonometry method. There was a significant CCT dependency for both GAT and PDCT but not for ART ($p = 0.15$). We observed that there was a significant relationship between age and CCT in the meta-analysis, and we know that IOP increases with age. In order to eliminate age as a confounder we analysed the data to find 60 years as an eligible cut-off in age where CCT and age were not significantly correlated (Table 9). In this homogenous data with $IOP \leq 21$ mmHg and one randomized eye/healthy subject, there was no CCT dependency for GAT, PDCT or ART while Icare still showed a significant correlation (Table 10).

Although these results might give a more accurate picture of the relationship between the tonometry methods and corneal properties, the results should be interpreted carefully. This is because the data was not sampled in a single study, CCT was measured with two different methods and finally, the measurement order was standardized differently in the different studies.

From the above stated, it is evident that the study design is of uttermost importance when a study is planned and aims are formulated. Neither Paper II, III nor IV had the primary aim to assess the effect of uncorrected CCT or CC on IOP measurement; those were secondary aims. As a consequence, none of the studies was perfectly designed to answer this secondary aim.

5.4 Effect of LASEK on IOP measurement

Refractive surgery enhances visual acuity by altering the structure of the cornea including CCT and CC. For a long time, these corneal properties have been known to bias the accuracy of IOP measurements (Whitacre et al. 1993; Doughty & Zaman 2000). This has led to an increased interest in factors that influence IOP measurements and promoted innovation in the field of tonometry aimed at minimizing the effect of these factors.

The success of refractive surgery may paradoxically become a problem for individuals that have gone through surgery and develop glaucoma later in life. There is a risk that IOP will be underestimated due to changes in corneal properties of the cornea. Thus, glaucoma diagnosis may be delayed if the accuracy of IOP measurement is low.

The influence of LASIK on IOP measurement is well-known (Duch et al. 2001; Rashad & Bahnassy 2001; Kaufmann et al. 2003; Duba & Wirthlin 2004; Siganos et al. 2004; Cheng et al. 2005; Chihara et al. 2005; Jarade et al. 2005; Svedberg et al. 2005; Shemesh et al. 2007; Kirwan & O'Keefe 2008; Muller & Kohnen 2009), but only a few small studies with 15-20 patients in their respective LASEK groups, have shown results regarding LASEK and effects on IOP measurements (Svedberg et al. 2005; Kirwan & O'Keefe 2008; Qazi et al. 2009; Shah et al. 2009). In the present Paper III, the measured IOP of GAT decreased by 1.7 mmHg at six months. Most studies have shown a more pronounced underestimation of IOP measured by GAT after LASIK (Siganos et al. 2004; Cheng et al. 2005; Kirwan & O'Keefe 2008; Muller & Kohnen 2009), while others support our results (Pepose et al. 2007; Shemesh et al. 2007).

The results show no significant differences between the tonometry methods. However, there is an indication that both prototypes of ART and PDCT might be less influenced by LASEK than GAT. In contrast to our findings, most previous studies of LASIK report no significant change in measured IOP with PDCT after LASIK (Kaufmann et al. 2003; Siganos et al. 2004; Pepose et al. 2007). However, a recently published study found PDCT to measure significantly lower IOP at three months after LASIK than before treatment (Muller & Kohnen 2009).

The continuing change of measured IOP and further increased visual acuity indicate an ongoing healing process between three and six months. Yet CCT_{Pachymeter} and CC did not change during the same period. Most studies of refractive surgery and IOP have followed patients for three months or less (Duch et al. 2001; Duba & Wirthlin 2004; Siganos et al. 2004; Pepose et al.

2007; Shemesh et al. 2007; Kirwan & O'Keefe 2008; Muller & Kohlen 2009), while there are a few exceptions with contradictory results (Rashad & Bahnassy 2001; Hjortdal et al. 2005; Sanchez-Naves et al. 2008). One hypothesis might be the formation of subepithelial fibrosis at three months that causes a microscopic haze, which affects both CCT_{Orbscan} and VA negatively. As the haze decreases, both parameters would increase. The possible fibrosis would probably stiffen the cornea, and as it disperses over time, a decrease in measured IOP would be expected. In order to investigate whether changes in VA and measured IOP continue after six months, further studies with longer follow-up are needed.

A mean IOP change <2 mmHg was in the same order as the measurement variation to be expected when measuring with GAT (Thorburn 1978). If the change in IOP is absolute, i.e. the reduction in mmHg is the same regardless of the IOP, it might be clinically irrelevant. On the other hand, if the change is relative, i.e. the decrease in IOP is a percentage of the measured IOP, it might be more relevant. Furthermore, the range of IOP change was from - 6 to + 4 mmHg, showing that for a specific patient the measurement error will become clinically relevant and highly important. From a biomedical engineering point of view, systematic errors in a measurement system that repeatedly appear in a number of studies cannot be accepted. Further investigation of the biomechanical background along with development of the new tonometry techniques should be pursued.

5.5 ART – a feasible method?

Our research group has developed the ART method during the last decade. As previously described, ART uses continuous sampling of both contact force and area in order to calculate IOP. This multipoint approach of measuring IOP gives the ART potential advantages compared to standard tonometry methods that rely on one or a few readings of the same parameters (Eklund et al. 2003a).

In theory, ART is possibly less affected by corneal properties than standard tonometry methods. As discussed earlier, this hypothesis was not confirmed significantly although a trend ($p = 0.11$) was seen that supported the hypothesis (Paper III).

The ART has two possible analysis modes, a dynamic one that calculates IOP from data collected during the indentation phase, and a static one that uses data sampled after full applanation has been reached. Earlier prototypes have only included the dynamic mode. The first time an evaluation of ART

tonometer capable of measuring with both analysis modes was reported was in Paper III. Thus, the two modes differ methodologically. The dynamic mode takes shorter time and should be less dependent of constant capillary forces that affect static applanation methods (Goldmann 1957). However, possible advantages of the static mode are less influence of ocular pulsations and viscoelastic properties of the eye on the IOP measurement. The use of information from both analysis modes when calculating IOP might improve the LoA of ART (Paper IV).

Both dynamic and static modes of the further developed manual ART were shown to meet the requirements of the ISO standard for tonometers (Paper IV).

In most ART studies, six measurements have been undertaken for statistical purposes. In clinical practice, time is often limited. In this sense it would be preferable if the number of measurements could be reduced without worsening the measurement quality. An analysis of the SD for different numbers of measurements revealed a similar SD for three measurements compared to six measurements (Paper IV). Thus, three measurements with ART should be sufficient in the future.

Two different prototypes of ART_{manual} were used in Paper III. The main difference was the length of the sensor element, 25 mm (ART_{25mm}) vs. 30 mm (ART_{30mm}). Earlier prototypes were equipped with ART_{25mm}. The resonance frequency of ART_{25mm} produces a wave length similar to the length of the eye bulb and suspicion arose that it could disturb the IOP measurement. ART was therefore further developed into ART_{30mm}. A preliminary analysis showed ART_{30mm} to be better than ART_{25mm}. Only results of ART_{30mm} were reported since a thorough technical comparison of the pros and cons of the two prototypes would shift focus from the principal aim of the study. A separate article is planned to report these results more from an engineering point of view.

The first evaluation of a servo-controlled ART (ART_{servo}) is presented in this thesis. The development of ART_{servo} was an important step towards improving usability of the method and shortening the learning process for new operators. ART_{servo} did not meet all the requirements of the ISO standard. Although the static mode showed a 95% LoA within ± 5 mmHg in total, it failed to meet the requirements in the highest IOP range. The dynamic mode of ART_{servo} needs further development. In comparison with ART_{manual}, the precision was lower with both analysis modes.

Two problems were identified as explanations for the lower precision of ART_{servo}. Firstly, acceleration forces formed an oscillating force signal in the beginning of the applanation. This occurred when movement was initiated, and it resulted in reduced precision of the dynamic mode. Secondly, variable applanation velocities were identified due to instability in the motor. This could have affected the precision of both the dynamic and static modes. In the future, these problems could be solved by a more stable motor with reduced acceleration and improved velocity control.

To conclude, the results show that ART has developed into a feasible method for IOP measurement. It meets the requirements of the ISO standard regardless of analysis mode. Improvements in usability have been reached with ART_{servo} although further development is needed in order to improve the 95% LoA.

6 Conclusions

- Retrospective data may under special circumstances provide meaningful information regarding glaucoma prevalence. However, NTG will be underestimated if perimetry and/or fundus photography are not included in the regular examination.
- The concordance to GAT was close to the limits set by the ISO standard for PDCT while Icare was clearly outside the limits.
- GAT, PDCT and ART showed a low but significant reduction of measured IOP three and six months after LASEK. However, the trend towards less reduction with PDCT and ART should be further investigated. Furthermore, changes in visual acuity and IOP measurement between three and six months after LASEK indicate a still ongoing postoperative process after three months.
- Both dynamic and static analysis modes of the manual ART fulfil the requirements of the ISO standard. The servo-controlled ART was close to fulfilling the ISO standard.
- No tonometry method investigated in this thesis, i.e. GAT, PDCT, Icare and ART, was independent of both CCT and CC. The inconsistencies of the results emphasize the importance of the study design.

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