



Universitat de Girona

Facultat de Medicina

FINAL DEGREE PROJECT

**THE INFLUENCE OF A CERTAIN VOLUME OF
FLUID IN THE LOWER TEAR MENISCUS ON
INTRAOCULAR PRESSURE MEASUREMENTS
USING THE NON-CONTACT TONOMETER**

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Gràcies al Dr. Joan Tarrús de Vehí per haver fet possible aquest treball

Admiració per la gran implicació en la seva feina i les hores dedicades

Girona, 2014

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ABSTRACT

Background: Intraocular pressure (IOP) is the pressure inside the eye that helps to maintain the integrity and the suitable form of the ocular globe. Precise and accurate measures of IOP are needed for the diagnosis as well as follow-up of glaucoma. In daily clinical practice, Goldmann applanation tonometer (GAT) and Non-contact tonometer (NCT) are the most common devices for measuring IOP.

A close agreement between these methods has been showed, particularly in normotensive patients and a poor agreement, especially when IOP levels are above the normal range. Ophthalmologists have noticed a poor agreement between NCT and GAT, observing that by using NCT and after comparing with GAT, there is an overestimation of IOP readings, and particularly it occurs when the eyes are tearful. Previous studies investigate the effect of tears in Non-contact tonometer readings by the instillation of artificial tears, concluding in one of the studies that the variation was less than 1mmHg and not clinically significant, in contrast with another study which the increases were statistically significant.

Tear menisci are a thin strip of tear fluid located between the bulbar conjunctiva and the eyelid margins. We think that the overestimation of IOP readings using NCT could be due to the presence of a higher volume of tear in the lower tear meniscus which might cause an optical interference in the optoelectronic applanation monitoring system of this device.

Objectives: To research the influence of a certain volume of fluid in the lower tear meniscus on IOP measurements using the NCT in healthy eyes. Moreover, to investigate the agreement between IOP readings obtained by NCT and GAT in the presence and absence of this volume of fluid.

Methods: The study design will be transversal for diagnostic tests of repeated measures. We will study patients with no ocular pathology and IOP<21mmHg. It will consist in the measurement of IOP using NCT before and after the instillation of COLIRCUSÍ FLUOTEST, used as a volume of fluid in the lower tear meniscus, to observe if there will be differences using the paired t-test. Moreover, we will take IOP measures by GAT in order to know the agreement between these methods after and before the application of these eyedrops, using the ICC (intraclass correlation coefficient) and the Bland-Altman method.

Keywords: intraocular pressure, non-contact tonometer, goldmann applanation tonometer, lower tear meniscus, agreement.

1. INTRODUCTION

1.1 INTRAOCULAR PRESSURE (IOP)

1.1.1 Concept

Intraocular pressure (IOP) is the pressure inside the eye that helps to maintain the integrity and the suitable form of the ocular globe. Aqueous humor is the responsible for maintaining IOP. "It is continuously secreted by the ciliary processes to the posterior chamber and goes through the pupil to the anterior chamber (inflow). It then leaves the anterior chamber through the trabecular meshwork to the venous system (outflow)". Therefore, IOP is determined by the equilibrium between aqueous humor formation and outflow, and by episcleral venous pressure. (1–3)

1.1.2 Distribution of IOP in the general population

It is difficult to define "normal" IOP, however R. Rand Allingham and co-authors define it as "that pressure which does not lead to glaucomatous damage of the optic nerve head, and it cannot be expressed in precise numerical terms". (4)

Theoretically, as Leydhecker and associates showed, the distribution of IOP in general population is Gaussian, but is skewed to the right. It means that skews toward the higher pressures, especially in population over 40 years. They interpreted that there were two populations which are nonglaucoma (N) and glaucoma (G) populations (**Image 1, Annex I**). In general, other subsequent screening studies have agreed with them. However, precise limits of both groups are not known and there are many factors that affect IOP. (4) Furthermore, eyes have a different response at the same pressure levels, so "it is difficult to know *a priori* what level will be harmful to a given patient". (5)

As an approximation, if we take into account the first curve, the mean IOP is 16mmHg (millimeters of mercury) +/- 2SD (standard deviation), so "normal" IOP is distributed in the range of 11 and 21 mmHg (**Image 2, Annex I**). As stated above, there is not an absolute pathological point, but 21 mmHg is considered the upper limit of normal. (6)

IOP is similar in both eyes of normal individuals. Differences between the eyes are common in patients with glaucoma. However, in less than 4% of normal individuals there are differences of ≥ 4 mmHg. (5)

1.1.3 Fluctuation

IOP is a dynamic variable. It fluctuates over days (temporal or seasonal variation) and over 24 hours (diurnal variation). (1) The most common pattern of the daily cycle in normal subjects is having IOP peak in the morning and IOP decreases after midday and evening. (6)

To accept that a single pressure taken at a certain time is representative of the average pressure which the patient has over time could be an error. For this reason, sometimes obtaining an “office diurnal curve” may be easy and useful, it means checking IOP every 1 or 2 hours from about 8 a.m. to 6 p.m. (5) Doing this, we can determine at what time of the day IOP is highest, and it is interesting for future pressure checks. (4)

1.1.4 Factors affecting IOP

It is important to take into account that there are different factors that can affect the formation or drainage of aqueous humor, and consequently it can cause changes in IOP. (2)

There are many different factors that can influence IOP, some of the most important are explained in **Table 1 (Annex I)**.

1.1.5 Implications

“Glaucoma is a large group of disorders that are characterized by widely diverse clinical and histopathologic manifestations. It consists in an optic neuropathy which derives from various risk factors, including increased IOP. It is associated with a progressive loss of the visual field, which can lead to total, irreversible blindness if the condition is not diagnosed and treated properly”. (4) It is considered the second leading cause of blindness worldwide. (2)

Nowadays, the diagnosis of glaucoma is made by structural and functional alterations in the retinal nerve fiber layer and visual field, so the importance of IOP measures in the diagnosis has been diminished. (1,5,7) We should take into account the existence of normal tension glaucoma (NTG) where there is glaucomatous lesion with normal IOP and ocular hypertension (OH) where there is increased IOP without a detectable glaucomatous lesion. (1,6) However, increased IOP is considered the most important risk factor for the development and progression of glaucoma. (7,8) Moreover, it is considered the only risk factor that can be controlled to prevent its development and progression. (2)

Therefore, the best and only evidence-based treatment option to decrease the disease progression is the reduction of IOP. (1,3,7) For this reason, "IOP is the single most important and only modifiable factor to assess the effectiveness of treatment"(5)because all treatments of glaucoma have as an objective the reduction of IOP. For every 1mmHg of IOP reduction, there is a 10% of decrease in the rate of progression as well as visual field damage.(2,5) Nevertheless, it has been considered that there are other factors which can be important in the pathogenesis of glaucoma, because despite targeted levels of IOP the progression of glaucoma may continue. (1,3)

For all these reasons, precise and accurate measures of IOP are needed for the diagnosis as well as follow-up of glaucoma. (2,7,9)

1.2 INSTRUMENTS FOR MEASURING IOP

1.2.1 Direct methods

- ❖ Manometric technique: It consists in the insertion of a needle into the anterior chamber through a corneal puncture which is connected to a manometer. Despite this method is probably the most accurate in the IOP measurements, clinical application is difficult because it is an invasive method. (5) It is the only direct method. (10)

1.2.2 Indirect methods: we can see the eye's response by applying a force. (5)

- ❖ Palpation: It consists in the application of digital pressure to the ocular globe which can reveal a fluctuation sensation and its consistency, if the eye is soft or stiff to the touch. It is an inaccurate technique, but can guide to the examiner only in major changes of IOP. (5)
- ❖ Tonometry: tonometers are devices which “measure IOP by relating a deformation of the globe to the force responsible for the deformation”. There are two types of tonometers, applanation and indentation instruments (**Table 2, Annex II**). The difference between both is the shape of the deformation (**Image 3, Annex II**) and the way they do it. (4)

1.3 GOLDMANN APPLANATION TONOMETER

1.3.1 Concept

Goldmann applanation tonometer (GAT) is the international gold standard for IOP measurement and the most used in daily practice. (2,5)

The physical principle is based on the modification of the Imbert-Fick law:

Imbert-Fick law: "an external force (W) against a sphere equals the pressure in the sphere (P_t) times the area flattened by the external force (A); $W = P_t \times A$. The validity of the law requires that the sphere be perfectly spherical, dry, perfectly flexible and infinitely thin". (4) This law accepts that the wall of the sphere has not have any effect on the force. However, the physical properties of the globe wall such as thickness, elasticity and compressibility can influence on this force needed to flatten the wall. (10)

Imbert-Fick law modified by Goldmann: the cornea does not meet any of the previous conditions because it is aspherical and wet, and neither perfectly flexible nor infinitely thin. Goldmann add to this formula other important features of the cornea, which are: a tear surface tension (S), the lack of flexibility requires a force to bend the cornea (B), an external (A) and internal (A_1) area of flattening; $W + S = P_t A_1 + B$. (4)

GAT determines IOP by the force needed to flatten a constant internal area of the cornea, which is 7.35mm^2 with a diameter of external area, which is 3.06mm. At this fixed area, the two opposite forces -force of tear surface tension (S) and the corneal elasticity (B)- are almost equal, therefore they cancel out one another and the result is $W = P_t$ (**Image 4, Annex II**). Moreover, the coiled spring of the tonometer produce a force in grams, and when it is multiplied by 10 agrees with the IOP in millimeters of mercury. (5,10)

1.3.2 Description of instrument

The tonometer is mounted on a slit-lamp or biomicroscope (**Image 5, Annex II**). It is composed of a plastic biprism, a rod, a housing and a adjustment knob (**Image 6, Annex II**). The plastic biprism is placed on the tonometer tip and is connected by a rod to a housing. Inside the housing there are a coil spring and levers, these are attached to an adjustment knob which allows to control the force of the biprism against the cornea. (4)

1.3.3 Technique

1. For 2 hours before measuring the IOP, the patient must not drink alcohol or large amounts of fluid (500ml or more). (5)
2. Patient is seated on an adjustable stool or examining chair in front of the slit lamp and placed in an upright position. It is important to adjust the heights of the chair and the slit lamp in order to place the patient in a proper position. Furthermore, the chin and forehead are supported by the chin rest and the forehead bar, respectively. The clinician sits in front of the patient and looks through the biomicroscope, the direction of the observer view is directed through the center of the plastic biprism. (5,10)
3. It is important to inform the patient the aim of the test and it will be painless. They should be calm, maintain the position and leave the eyes widely open. The patient gaze should be no more than 15° above the horizontal. Furthermore, the patient should breath normally and avoid Valsalva's maneuver during the measurement. (5)
4. For Goldmann tonometry, it is necessary the instillation of a combination of fluorescein and anesthesia in the conjunctival sac in order to differentiate the cornea and the tear film. The patient should blink the eyes once or twice to distribute the fluorescein-stained tear film over the cornea. Then, the eye surface is illuminated with a cobalt blue light from the slit-lamp and the tear layer is transformed to a bright yellow-green color. Ambient lighting must be reduced. (5)
5. The tonometer dial should be set at 1g before each IOP measure. It shows force applied to appanate the cornea and the examiner can change it by rotating this tension knob. (5)
6. When the split prism is in contact with the apex of the cornea (**Image 7, Annex II**), forms a meniscus at the perimeter of the flattened cornea (10) and allows the clinician to view a central blue circle at the flattened corneal surface. Then,

the circle is divided into an upper and lower yellow-green semicircles with respect to the horizontal line thanks to the doubling prism. (5,6)

7. The rings experiment a rhythmic movement due to the cardiac cycle. The tension knob is rotated until the inner margins touch each other at the midpoint of their pulsations, aligned in an S, which means the correct applanation degree (**Image 8, Annex II**). Therefore, at this moment is when IOP measurement is proper. (5) The reading is an average IOP between diastolic and systolic (10) and comes from a scale on the tonometer housing. (4)
8. Firstly, IOP is measured in the right eye until three consecutive readings are within 1mmHg. The procedure may take 3 minutes, including the administration of anesthesia and fluorescein. (2) Then, the operation is repeated in the left eye. (5)

1.3.4 Calibration

The calibration of GAT should be at least once a month. The tonometer should be repaired if it is not within 0.1g (+1mmHg) of the proper calibration. Nevertheless, calibration errors of up to +2.5mmHg can be tolerated clinically. (5)

1.3.5 Disadvantages

- ❖ Transmitting infections with the tonometer head is possible, such as epidemic keratoconjunctivitis (EKC), herpes simplex virus type 1, hepatitis B, Jacob-Kreutzfeld and, supposedly, acquired immunodeficiency syndrome (AIDS). For this reason, it is proper to wash with alcohol and dry the biprism immediately after use. Moreover, to soak the biprism in a solution such as diluted bleach or 3% hydrogen peroxide for 10 or more minutes, between uses is necessary. Take into consideration that some sterilizing solutions may be toxic to the corneal epithelium, for that thoroughly remove the disinfectant from the contact surface is very important. (4,5) Nevertheless, the best way to disinfect the tips remains unknown. There are disposable tips, but they are not as accurate as the original design tip. (10)

- ❖ GAT is needed to be attached to a slitlamp, so it is not portable and patient must be in an upright position. Therefore, it is not possible to be used in young children and people with physical disability. (11) However, there are tonometers which have Goldmann tips and are battery powered, portable and the measures may be taken in an upright or supine position (Perkins' tonometer). (10)
- The readings are operator dependent with an interobserver variability of 0-3mmHg and intraobserver variability up to 2mmHg. (1,5)
- Sources of error by using GAT:

GAT is reliable, accurate and reproducible. (5) However, there are a number of factors that can influence the IOP measurements and cause errors (**Table 3, Annex II**).

Taking into account the thickness of the cornea GAT would be inaccurate with thin and thick corneas. (12,13) It occurs because GAT is based on an alleged average central corneal thickness (CCT) which is 520 μ m. (6) There is not an agreement about the use of correction factors to adjust the readings in corneas whose thickness deviates from the mean. (4) Nevertheless, the errors are not linear and there is not yet an exact formula which considers the range of corneal thickness and IOP. Therefore, it is important to know the pachymetry which is the measurement of corneal thickness, for any given cornea (10) and "it is probably best to use the corneal thickness as a rough guide to the direction and magnitude of the error". (5)

1.4 NON CONTACT TONOMETER

1.4.1 Concept

As Robert L Stamper and coauthors say “the NCT (Non-Contact Tonometer) applanates the cornea by a standardized jet of air, therefore there is no direct contact between the device and the surface of the eye” (**Image 10, Annex II**). (5) To define the exact nature of the corneal appplanation is difficult, however it is suggested that the central cornea is deformed at the same time the pressure measure is made. (4)

1.4.2 Description of instrument

NCT is placed on a table and consists of three subsystems: (**Image 11,12, Annex II**)

- 1) Alignment or optical system: it allows the clinician to optically organize the cornea in three dimensions (axial, vertical, and lateral). (4)
- 2) Optoelectronic appplanation monitoring system: it consists in a transmitter, and a receiver and detector. The transmitter projects a collimated beam of light at the corneal vertex. The corneal surface acts like a plane mirror (3) because the light is reflected from the central cornea and then received by a receiver and detector, which accepts only parallel, coaxial rays. (4,5)

“Corneal appplanation is measured by collecting light reflected from the central cornea”. (3)

- 3) Pneumatic system: it produces a puff of air which goes straight to the cornea.

The force of the air puff has a fast and gradually increase with time. (5) By deforming the cornea, there is an increase of the number of light rays received and detected (4) In order to avoid an excessive air pressure, after the first jet of air subsequent pulses of air are adjusted to the IOP of the patient and reduced. (14)

The moment of maximum light detection presumably corresponds to the force of air which is required to flatten a corneal area of 3.06 mm in diameter, and the instrument

shows the IOP which corresponds to this force. (3–5) The time needed for these rays to be detected is converted into IOP. (14) This conversion is based on calibrations with GAT and displayed on a digital screen. (4)

There is a strong reduction in light rays received as a result of a constant jet of air, that causes a momentary concavity of the cornea. However, when cornea returns to undisturbed state and is again flattened, it causes another light peak. (4)

1.4.3 Technique

1. The patient gazes at an internal target while the operator uses the optical system. The alignment of the cornea is done by superimposing a reflection of the target from the cornea on an immobile ring. (4)
2. Once the cornea is aligned, the operator pushes the trigger button which emits a puff of air against the cornea and IOP is measured. (4)

1.4.4 Calibration

NCT has an internal calibration system. (5)

1.4.5 Advantages:

- In contrast with GAT, NCT can be used by non-medical and unlicensed personnel without the direct supervision of an ophthalmologist, and topical anesthesia or fluorescein are not necessary. (2,3,5) Therefore, it is especially useful for screening programs and possibly in studies of topical antiglaucoma drugs. (4)
- In contrast with GAT and other contact tonometers, some risks are avoided such as abrasion of the cornea and reactions to topical anesthetics. (4)
- There is not contamination risk (2) and it seems not necessary to disinfect the NCT. However, there is a recent study which says that the air puff produces a tear film aerosol where could be potentially infectious material and theoretically it can produce a virus transmission by an airborne route. (3,5) In

addition, the front surface of the device may be contaminated with tear film and it is necessary to clean it after use. (4)

- NCT operates faster, the time interval for an average measurement is 1 to 3ms. (4) It is recommended at least three readings within 3mmHg, but it is much better four in each eye. (4,5)
- The readings are largely examiner independent. (3,7)
- Repeated IOP measures do not cause an IOP reduction as happens with GAT. (15,16)

1.4.6 Disadvantages:

- The air puff can be alarming for patients due to the force sensation and the noise, so the clinician should warn them about that. (3,5)
- NCT is limited to table top, needs electricity and it is difficult to take it everywhere. However, Pulsair-Keeler tonometer is portable and handled. (10)
- Measuring IOP in small children and infants is not possible. (2) However, as GAT portable devices allow taking IOP measures in children and people with physical disability. (2,11)
- It seems that NCT measurements are more influenced by CCT than GAT measurements, especially thin corneas. (12,13)

1.5 THE LACHRYMAL FUNCTIONAL UNIT

The lachrymal functional unit (LFU) is composed of the tear film, corneal and conjunctival epithelium, Meibomian glands, the main and accessory lachrymal glands, the eyelids and the neural pathways which connect these structures. (17)

1.5.1 Lachrymal secretion and lachrymal drainage system

The lachrymal secretion comes from the main glands which produces a 95% of the aqueous component, Krause and Wolfring accessory lachrymal glands; Meibomian and conjunctival caliciform cells which produce the lipid and mucous component, respectively. (6) In basal conditions, the lachrymal production is $1.2\mu\text{l}/\text{minute}$. (18)

The lachrymal drainage system is composed of lachrymal punctums, the lachrymal canaliculis, the lachrymal sac and the nasolachrymal duct (**Image 13, Annex III**). Moreover, the tears elimination is mainly through this system and a small quantity is eliminated through evaporation. (18)

1.5.2 Tear film

❖ Concept

The tear film is the first refractive surface forming an interface between the air and the corneal epithelium. (18) It comprises a total volume of $6-9\mu\text{l}$ and its thickness is $6.0\mu\text{m} \pm 2.4\mu\text{m}$ in normal subjects. (17,18)

❖ Structure and functions

Tear film is composed of three layers that provide different functions, which are: an internal mucosal layer, an intermediate aqueous layer and an external lipid layer. In addition, the thickness is $0.2\mu\text{m}$, $7.0\mu\text{m}$ and $0.1\mu\text{m}$, respectively (**Image 14, Annex III**). (6)

The internal mucosal layer has an adherent function, providing a barrier against the bacterial invasion, and a humidification and lubrication function. The intermediate aqueous layer supplies proteins, electrolytes, oxygen, glucose and growth factors to

the corneal epithelium; contents antimicrobial components; eliminates waste and noxious stimulus and provides an optical smooth refracting surface. Finally, the external lipid layer allows to the uniform distribution of the tear film thanks to the low surface tension function; avoids the aqueous layer evaporation and the overflow maintaining the tear film thickness and a stable tear meniscus in contact with the lid margins of the eyelid. (6,17,18)

In summary, tear film contributes to the ocular surface comfort, protection, maintaining corneal health and provides a smooth and powerful refracting surface in order to maintain a clear vision. (17)

❖ Distribution of the tear film

The uniform spread of the tear film over the ocular surface depends on blinking. The replacement of the tear film comes from the lower tear meniscus by this mechanism. Moreover, three factors are needed for a properly recovery of the tear film, which are: physiological blink reflex, contact between the external ocular surface and the eyelids and a normal corneal epithelium. (6,17)

1.5.3 Tear meniscus

❖ Concept

The upper and lower tear menisci are a thin strip of tear fluid located between the bulbar conjunctiva and the eyelid margins (**Image 15, Annex III**). (19) They retain approximately 75% to 90% of the total tear volume of the ocular surface. (20)

The adhesion forces between oculopalpebral epithelium molecules and tear molecules, and the cohesion forces between tear molecules contribute to the formation of the tear meniscus. The positive and negative action of the gravity forms the upper and lower tear meniscus, respectively. Moreover, their shape is like a triangular prism with a concave curvature. The posterior face is supported by anterior bulbar surface; the superior and inferior faces are supported by the eyelid margins and the anterior face is in contact with the air. Between the tear film and the tear meniscus

there is a transition zone formed by a thin liquid layer, known as the McDonald and Brubacker line or the Black Line. (19)

The tear meniscus is a simple measure of the aqueous volume in tear film. Tear meniscus height (TMH) in a healthy eye is usually $\geq 1\text{mm}$, and in the dry eye is thinner or absent. (6) Its volume is situated between 2 and 3 microliters (Holly, 1981). (19)

When there is an increase in the tear volume, the lower tear meniscus overflows and becomes convex. The Meibomian, Zeiss and Moll glands provide different hydrophobic barriers that not allow spillage of the tears though the anterior face of the inferior eyelid. (19)

❖ Evaluation of the tear meniscus

There are different methods which have been proposed to evaluate the tear meniscus quantitatively and qualitatively, such as by a slitlamp examination using a calibrated variable slit beam height, a micrometer or an incorporated camera which allows taking photographs; video recording, reflective meniscometry, tear interference imaging, and strip meniscometry. In most of them the use of fluorescein is needed which may interfere in the tear volume. (19,21)

Anterior Segment Optical Coherence Tomography (OCT) is a practicable and noninvasive method that allows a precise and quantitative evaluation of the tear meniscus and does not require the use of fluorescein. The Spectral OCT, also known as Fourier-domain (FD) OCT provides three dimensional imaging; so the meniscus is well defined and its height, area, depth and volume can be precisely measured (**Image 16, Annex III**). Moreover, the procedure is very fast and it is performed asking the patient to look straight at a fixation light and within a stable ambient room light. During the procedure, the patient may blink spontaneously and OCT images are captured immediately after blinking. (20)

OCT shows higher repeatability and reproducibility, and high sensitivity and specificity in diagnosis of dry eye syndrome. (20,21)

2. JUSTIFICATION

Precise and accurate measures of IOP are needed for the diagnosis as well as follow-up of glaucoma. (2,7,9) In daily clinical practice, GAT and NCT are the most common tonometers for determining IOP. (3) As previously mentioned, GAT is the gold standard test for IOP measurement. Despite of this, NCT is often more adequate, comfortable, faster and easier to use in daily practice. (3,22) NCT can be carried out by a non-medical and unlicensed personnel and the readings are largely examiner independent, the use of topical anesthesia or fluorescein are not needed and in general, there is no risk of contamination because it is a non-invasive tool. (2,3,5,7)

Some studies have been showed that there is a good agreement between the IOP readings obtained with NCT and those taken by GAT, particularly in normotensive patients. (2,14,23,24)

Nevertheless, there are studies which showed that NCT comparing with GAT overestimates the readings, especially when IOP levels are higher, above the normal range, (3,7,9,11) concluding that there was a poor agreement at high IOP levels. However, in their first study J. Jorge and co-workers compared Reichert AT550 NCT with GAT in population with IOP within the normal range, and showed a close agreement between them. (23) The same comparison was performed in a sample with glaucomatous patients under treatment and the agreement between them had been maintained. (25)

In a Systematic Review and meta-analysis to assess the agreement of different tonometers used in clinical practice with GAT, concluded that NCT and HAT (handheld applanation tonometer) seem to be those who have the closest agreement with GAT. Patients with glaucoma, ocular hypertension and representative of the general population were included. (8)

Ophthalmologists have noticed a poor agreement between NCT and GAT, observing that by using NCT and after comparing with GAT, there is an overestimation of IOP readings and particularly it occurs when the eyes are tearful.

In fact, it had been observed that some patients had a reflex tearing after the first measure using the Keeler Pulsair tonometer, which is a portable and handled NCT tonometer and it was thought that it may affect into the subsequent readings. For this reason, Andrew KC Lam and co-workers used this tonometer to measure IOP on thirty normal subjects, aged from 21 to 30 years, with and without the instillation of artificial tears. Although the study results showed an increase in IOP measures with the instillation of artificial tears, the variation was less than 1mmHg and not clinically significant. (22)

In a previous study, the American Optical Non-contact tonometer (AONCT) was used. It was demonstrated that IOP measures increased with artificial tears. In this study, the increases were statistically significant and as a result of abnormal thick tear film. (22)

From our point of view the first study presents some limitations. First of all , it is important to take into account that in daily practice ophthalmologists measure IOP in an upright position. Moreover, "IOP is higher in the supine position than in upright position" (10). It could be related to episcleral venous pressure, which tends to be constant during the day, but increases in the supine position. (4) So, postural change is a factor to be taken into account when interpreting the measurements. (5) Thus, we think that the results of this study are not concluding and it is important to control the different factors that can modify the IOP.

Secondly, it seems that the aim of that study is to investigate the influence of tears on the cornea -because they take into consideration the retention and distribution of artificial tears on the corneal surface- , and then how affect to tonometric results.

In our opinion, we think that the overestimation of IOP readings using NCT could be due to the presence of a higher volume of tear in the lower tear meniscus. It might cause an optical interference consisting in deviating, by prism effect, the beam of light reflected from the central cornea, therefore misleading and delaying its proper detection by the photocell. The time taken for applanating the cornea is proportional to IOP and that would finally end with an IOP overestimation.

In summary, some previous studies showed that NCT comparing with GAT may overestimate IOP readings, especially when IOP is above the normal range and others suggested that there is a close agreement between them, particularly in normotensive patients. We are interested in investigating the influence of a certain volume of fluid in the lower tear meniscus in the NCT measurements and if NCT maintains the agreement with GAT in the presence and in the absence of a certain volume of fluid in the lower tear meniscus, in patients with a PIO < 21mmHg under those conditions. We think that would be a poor agreement between these methods with the presence of a certain volume of fluid and a close agreement in the absence of this.

3. HYPOTHESIS

1. A certain volume of fluid in the lower tear meniscus of healthy eyes affects on intraocular pressure measurements using the non-contact tonometer, causing an overestimation of tonometric results.
2. There is a poor agreement between intraocular pressure readings using the non-contact tonometer and Goldmann applanation tonometer, in the presence of a certain volume of fluid in the lower tear meniscus of healthy eyes. In contrast, there is a close agreement between these methods in the absence of a certain volume of fluid.

4. OBJECTIVES

1. To research the influence of a certain volume of fluid in the lower tear meniscus on intraocular pressure measurements using the non-contact tonometer in healthy eyes.
2. To investigate the agreement between intraocular pressure measurements of two exploratory techniques -the non-contact tonometer and Goldmann applanation tonometer-, in the presence and absence of a certain volume of fluid in the lower tear meniscus of healthy eyes.

5. METHODOLOGY

5.1 Study design

This study is designed as transversal (cross-sectional) for diagnostic tests of repeated measures.

5.2 Setting and duration

The study will be performed in Centre d' Especialitats Güell (Girona) within a time period of 6 months, approximately.

5.3 Population

The study population will include subjects who will have healthy eyes meeting the inclusion and exclusion criteria. In this study, healthy eyes will be defined as those that will present no ocular pathology. We will study right eyes.

Inclusion criteria:

- ❖ Aged 18 years or more.
- ❖ Visual acuity > 0.5.
- ❖ Normal intraocular pressure (10-21mmHg).
- ❖ Normal lid fissure (9-11mm)

Exclusion criteria:

- ❖ Uncooperative patient in the measurement of IOP.
- ❖ Recent use of topical or systemic drugs.
- ❖ Use of contact lenses.
- ❖ Palpebral pathology such as ectropion, entropion, ptosis, lagophthalmos.
- ❖ Epiphora or lachrymal obstruction.
- ❖ Ocular surface disease such as dry eyes, conjunctivitis or corneal disease.
- ❖ Intraocular disease such as glaucoma, uveitis or retinal disease.
- ❖ Ocular motility disorders such as strabismus.
- ❖ Corneal astigmatism over 3 D.
- ❖ Prior intraocular surgery or ocular trauma.
- ❖ Systemic disease such as dysthyroid ophthalmopathy.
- ❖ Hypersensitivity to components or excipients of COLIRCUSÍ FLUOTEST.

5.4 Sample selection

The sample method used will be consecutive non-probability sampling. The sample selection will be performed in Centre d' Atenció Primària Santa Clara (Girona). A general practitioner (GP) joined to the research team and aware of the inclusion and exclusion criteria will be in charge of selecting those patients who will come to the consulting room and meet the criteria taking into account the clinical history. GP will inform patients about the study and invite them to participate voluntarily, making them sign an informed consent form (**Annex V**).

These patients will be referred to Centre d' Especialitats Güell (Girona) to undergo an ophthalmological examination carried out by an ophthalmologist and an optometrist joined to the research team. This ophthalmological examination will consist in visual acuity, slitlamp examination of the external eye and anterior segment, eye fundus examination, IOP measurement using GAT, topography, and assessment of the ocular motility, palpebral pathology, dry eye, epiphora and lachrymal obstruction. Practising this ophthalmological examination we will be sure that the patients will meet all the inclusion and exclusion criteria.

Once we have ruled out ocular pathology, we will assess that the eye will have a proper lower tear meniscus during the first ten seconds after the instillation COLIRCUSÍ FLUOTEST, which are the eyedrops used in this study. It means that the meniscus should be stable and maintains a height of ≥ 2 mm. We need this height because in a normal defence eyelid fissure of 7-8 mm (for normal non defence is 9-11 mm), 2 mm gets into the area of 3.06 mm of central cornea that NCT analyzes. For this reason, we will take an image of the right eye within the first ten seconds after the instillation of two drops of COLIRCUSÍ FLUOTEST using Spectral OCT (Optical Coherence Tomography) – Cirrus HD-OCT Spectral domain technology, Zeiss carried out by an optometrist. This procedure will be repeated three times in right eye with an interval of 5 minutes between them, obtaining three images of the lower tear meniscus.

If the lower lachrymal meniscus maintains a height of ≥ 2 mm over the three images the patient will be included in the study. Doing that, we will suppose that the lower

tear meniscus will have this height after applying these eyedrops and that all the eyes will have a similar meniscus during the IOP measurements.

5.5 Sample size

The number of subjects necessary to achieve a statistical power of 80% at a level of significance of 0.05 is **125**. This sample size calculation has been determined by using the free trial version of StudySize 3.0 which has been downloaded from the web. We have been calculated it through the reliability test called intraclass correlation coefficient (ICC), two-sided test taking into account that the number of raters will be three, and as there is a close agreement between these methods, especially in normotensive patients (2,14,23,24) who is the population included in this study we will assume a ICC equal to 0,9 (H_0), as well as a ICC equal to 0,85 (H_1) because we think that the agreement between these methods in the presence and in the absence of a certain volume in the lower tear meniscus will be poor and close to the usual agreement, respectively.

5.6 Variables

The study variables of the first objective are the following:

- ❖ Intervention: It will consist in the instillation of two drops of COLIRCUSÍ FLUOTEST in the conjunctival sac (space between the eye and eyelid) in order to obtain a certain volume of fluid in the lower tear meniscus. The lower tear meniscus height will be ≥ 2 mm.
- ❖ Variables of interest: intraocular pressure measurements. They are the tonometric results measured in mmHg that the non-contact tonometer notifies before the instillation of COLIRCUSÍ FLUOTEST and in the absence of lower tear meniscus, and the results obtained immediately after the instillation of COLIRCUSÍ FLUOTEST in the presence of a certain volume of fluid.

It is a continuous quantitative variable.

The study variables of the second objective are the following:

- ❖ Exploratory techniques: non-contact tonometer and Goldmann applanation tonometer.
- ❖ Variables of interest: intraocular pressure readings. They are the tonometric results measured in mmHg that the non-contact tonometer notifies before the instillation of COLIRCUSÍ FLUOTEST and in the absence of lower tear meniscus, the results obtained immediately after the instillation of COLIRCUSÍ FLUOTEST in the presence of a certain volume of fluid, and the tonometric results measured by the Goldmann applanation tonometer.

It is a continuous quantitative variable.

Covariables:

- ❖ Age: years.
- ❖ Gender: male or female.
- ❖ Central corneal thickness: μm . It is known that central corneal thickness (CCT) may affect the accuracy of IOP readings using applanation tonometry, because a major force is required in order to applanate a thicker cornea ($>540\mu\text{m}$) and a minor force for applanate a thinner cornea ($<520\mu\text{m}$), causing an overestimation or underestimation in IOP readings, respectively. It seems that NCT is more affected by CCT than GAT. (12,13) For this reason, we will consider CCT as a confounding variable when we will assess the agreement between them.

5.7 Measure instruments and medication

In this study we will use two types of applanation tonometers to measure intraocular pressure, which are:

- ❖ The Topcon CT-80 Non-Contact Computerized Tonometer (**Image 10,11, Annex II**), which is a NCT. It will be carried out by two optometrists, one for the NCT measures before the eyedrops instillation and a second optometrist after the eyedrops instillation. As NCT is operator independent, the decision of choosing two optometrists is in order to avoid examiner bias by knowledge of previous or later measurements.
- ❖ The HS HAAG-STREIT INTERNATIONAL AT 900® (**Image 5,6, Annex II**), which is a GAT, as a reference in IOP measures. It will be carried out by an experienced ophthalmologist.

We will use COLIRCUSÍ FLUOTEST (**Image 9, Annex II**) as a volume of fluid in the lower tear meniscus. As the information pamphlet says, it is a colouring solution which is used for diagnosis in ocular examinations which require a brief corneal anesthesia, such as tonometry, gonioscopy or electroretinography. It is also be used for foreign bodies removal or other minor ocular interventions. It is composed of sodium fluorescein which stains the tear film, and chlorhydrate oxybuprocaine which has a fast and brief local anesthetic action.

These eyedrops are commonly used for GAT. Although the instillation of COLIRCUSÍ FLUOTEST is not needed in NCT measurements, it might be useful as a volume of fluid in the lower tear meniscus, because it is retained time enough for the measures and it can be used for GAT readings as well.

In addition, we will use pachymetry (OcuScan® RxP Ophthalmic Ultrasound System, Alcon) in order to measure CCT.

5.8 Data collection

Patients will come to the ophthalmological consulting room two times. In the first session, they will come in order to undergo an ophthalmological examination, as stated in the sample selection. Those patients included in the study will return the next day, and the examiners will remind them some recommendations that they will have to follow during the time before coming to the second session. They should do their usual activities and habits, but in order to control some factors that may increase the IOP they should avoid drinking alcohol or large amounts of fluid (500ml or more) two hours before the measuring, they should avoid practising exercise during the previous hours and they should respect a minimum of four hours between waking and coming in to the second session.

The measurements will be taken at similar times in the afternoon, between 14:00 and 16:00 hours, which is the period of the day when IOP is lower and more stable in order to avoid the effect of IOP diurnal variations. (14,23)

NCT measures and GAT measures will be performed in different rooms and the examiners will not know the IOP results obtained with the other tonometer. Moreover, the order between NCT measures and GAT measures will not be randomized. The IOP measurements with the GAT will be always after the measure using NCT, it will be done to prevent a systematic bias due to the aqueous massage effect which may affect NCT measures. (15,16)

The examiners will follow the same technical procedure explained in the introduction and the recommendations and guidelines of manufacturers.

Both applanation tonometers will be correctly calibrated to avoid inaccuracy in the IOP measurements and a systematic error due to the measure method.

Although the methods of measurement will be exposed in the informative document, the examiners will explain briefly the procedure. The patients will be advised to: remain calm, maintaining the position and gaze, leaving the eyes widely open without excessive extension of the lid fissure and avoid blinking, hard lid squeezing or eye movements; breathing normally and avoiding Valsalva's maneuver during the measurements.

Firstly, for the IOP measurement using NCT before the instillation of COLIRCUSÍ FLUOTEST, the lower tear meniscus will be dried with a gauze until no visible, it will be done carefully in order to avoid the reflex tearing. Then, then the first optometrist will measure IOP. Five minutes later, the second optometrist will instil COLIRCUSÍ FLUOTEST in the conjunctival sac and within the first ten seconds the IOP measurement will be taken (before tear break-up).

Following the manufacturer recommendation using the Topcon CT80 NCT (14), four readings will be taken but only the last three readings will be averaged and recorded for statistical analysis. The NCT will do this procedure automatically.

The time difference between the two methods will be 15 minutes in order to allow IOP returning into its undisturbed baseline value.

Measuring IOP with GAT will be performed only after the instillation of COLIRCUSÍ FLUOTEST, because it is not possible to take the measures without the application of these eyedrops. Three measures will be taken and the average will be recorded for statistical analysis. For each measure, the period of contact between the biprism and the cornea will be under five seconds in order to avoid a decrease in IOP due to the aqueous massage effect on repeated applanation measures. (3,14) The tonometer biprism will be cleaned properly after each use.

After IOP measurements, the optometrist will measure the CCT using ultrasonic pachymetry.

The examiners will enter information in a database while the project is being developed.

6. STATISTICAL ANALYSIS

6.1 Normality

Normal distribution of IOP in the general population is Gaussian but is skewed towards right. As noted in the introduction, in the first approximation curve the mean IOP is 16mmHg +/- 2SD, so "normal" IOP is distributed in the range of 11 and 21 mmHg. As subjects included in this study will have an IOP less than 21mmHg, we will consider that this parameter will have a normal distribution.

6.2 Univariate descriptive analysis

All the qualitative variables will be expressed as percentages.

All the continuous quantitative variables will be expressed as means \pm SD.

6.3 Bivariate descriptive analysis

In the case of the first objective, we will use the paired t-test to know the mean IOP value before and after the instillation of COLIRCUSÍ FLUOTEST using the non-contact tonometer and the mean difference (MD) between these values.

In the case of the second objective, we will do a descriptive analysis of the means differences between NCT measures and GAT measures using the Student's t test. Moreover, we will use the intraclass correlation coefficient (ICC) to analyse the agreement between these two exploratory techniques in the presence and the absence of a certain volume of fluid. In addition, the Bland and Altman method will be used in order to graphically represent the agreement.

Moreover, we will do a descriptive analysis of the following variables: age and gender.

We will also describe the results taking in to account the age (<40years and \geq 40years) and gender in order to know if the results remain the same or in contrast, the results change and we should consider these variables as confused factors.

Finally, we will do a descriptive analysis of the central corneal thickness and we will describe the ICC taking into account this variable stratifying the results in three groups (<520 μ m, 520-540 μ m, >540 μ m).

P-values less than 0.05 will be considered statistically significant.

7. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical tenets of the Declaration of Helsinki; all the subjects included in the study will receive an informative document and will sign an informed consent form.

Moreover, it will comply with “Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal”, we will guarantee the confidentiality and the anonymity of all data related with the participants when collecting data and publishing results.

As COLIRCUSÍ FLUOTEST is a drug used for diagnosis in ocular examinations, the study will be conducted in accordance with “Ley 29/2006, de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios”. Moreover, we will inform to AEMPS (Agencia Española de Medicamentos y Productos sanitarios) about the use of COLIRCUSÍ FLUOTEST in our study. The study will be presented to Centre d’Atenció Primària Santa Clara and Centre d’Especialitats Güell in order to receive their consent. The study will be presented to the CEIC (Comitè d’Ètica i Investigació Clínica) of Hospital Universitari Josep Trueta, in order to be evaluated and approved.

8. STUDY LIMITATIONS

One of the shortcomings of this study is that we will use COLIRCUSÍ FLUOTEST, instead of including patients with epiphora or using artificial tears which would be more alike the tear film. The effect that has been observed by ophthalmologists is an overestimation of IOP readings obtained with NCT and comparing with GAT in tearful eyes. We cannot guarantee that the effect that we may observe in this study will be the same as in the presence of epiphora or artificial tears, because although these eyedrops will represent a volume of fluid, perhaps the surface tension properties or other factors are not the same of the tears or artificial tears.

We have decided to use COLIRCUSÍ FLUOTEST because despite the combination of fluorescein and anesthesia is not needed for NCT, these eyedrops are commonly used for GAT measurements and because we investigate also the agreement between NCT and GAT we will want to maintain the same conditions and to use the same product for both methods. Moreover, the effect of topical anesthesia in IOP had been studied and it seems that there is a small but a statistical significant reduction in IOP. The studies showed that the IOP is maintained after the first minute of the instillation of a topical anesthetic. (26) Despite we do not know that COLIRCUSÍ FLUOTEST will have the same effect, for one of its components (chlorhydrate oxybuprocaine), which has a fast and brief local anaesthetic action, we will use these eyedrops in both methods to maintain the same conditions and to avoid a reduction in IOP readings obtained in GAT with the exclusive use of COLIRCUSÍ FLUOTEST in this method.

In addition, we will include patients with a lower tear meniscus that maintain a height of ≥ 2 mm during the first 10 seconds after the instillation of COLIRCUSÍ FLUOTEST, but it will be examined the day before of IOP measurements. We suppose that in the next session, when we take the IOP measurements, the tear meniscus will maintain the same features after the instillation of the eyedrops, but we cannot guarantee it.

Moreover, there are factors that are difficult to control during the IOP measurements such as blinking, hard lid squeezing, eye movements or Valsalva's maneuver. The patient cooperation is very important and although they will receive some recommendations before taking the measures, we will have to assume that these factors may have an effect on tonometric results.

Another important point is that GAT readings are operator dependent, and although the ophthalmologist will have large experience and technical skill, and will operate by the same technical procedure, we should take into account that an intraobserver variability exists. However, in our study, as all GAT measurements will be carried out by the same examiner, interobserver variability will not affect.

In addition, as the sample selection and the methods will be performed in three different sessions and days the patients, we should take into account that patients will participate voluntarily and it could be difficult that they will come in all the three sessions, assuming that the sample selection and the methods may take longer than expected.

Finally, the included patients will have healthy eyes. Therefore, it will be difficult to extrapolate the results in patients with ocular pathology, because we do not know if the effect will be the same in this group.

9. WORK PLAN

Research team:

- ❖ Main researchers (MR): Estefanía Dorado (medical student), Joan Tarrús de Vehí (ophthalmologist, Opht).
- ❖ Researchers: general practitioner (GP), two optometrist (Opt1 and Opt2).

PHASE 0. COORDINATION PHASE (6 months)

ACTIVITY 1. Researchers: MR. The protocol will be developed and presented to the CEIC (Comitè d'Ètica i Investigació Clínica) of Hospital Universitari Josep Trueta, in order to be evaluated and approved. (4 months)

ACTIVITY 2. Researchers: MR, GP, Opt1, Opt2. It will consist in 3 organizational meetings. (1 month)

First meeting. The MR will organize a first meeting with the GP, Opt1 and Opt2 in order to expose the protocol and encourage them to form part of the researcher team, explaining the different tasks that they will have to develop in the study.

Second meeting. The study will be presented to Centre d'Atenció Primària Santa Clara and Centre d'Especialitats Güell in order to receive their consent.

Third meeting. It will consist in explaining in detail the inclusion and exclusion criteria, the measurement instruments (NCT, GAT) and reviewing the technical procedure, the recommendations and guidelines of manufacturers in order to take the measures as the protocol explains and train the examiners involved in the project and how they will have to collect the data.

ACTIVITY 3. Researchers: MR, GP, Opt1, Opt2. Pilot study and organizational meeting. (1 month)

An initial pilot study will be developed to detect problems in the data collection described in the protocol. Before the pilot study, the researcher team will meet in order to discuss the problems that they will notice, suggestions for changes and improvement, elaboration and evaluation of the final protocol.

PHASE 1. SAMPLE SELECTION AND DATA COLLECTION PHASE (6 months)

ACTIVITY 1. Researchers: GP, Opht, Opt1. Sample selection -consecutive non-probability sampling.

The sample selection will be performed by the GP in CAP Santa Clara (Girona), the GP will inform patients about the study and invite to participate voluntarily, delivering a consent informed form that they must sign and referring them to Centre d' Especialitats Güell, Girona to undergo an ophthalmological examination carried out by the Opht and Opt1. This ophthalmological examination will be on Thursdays.

ACTIVITY 2. Researchers: Opht, Opt1, Opt2. Intraocular pressure measurements.

Patients included in the study will be called to return on Wednesday at Centre d' Especialitats Güell, Girona in order to take the IOP measurements using NCT and GAT which will be carried out by the Opht, Opt1 and Opt2. They will enter information in a database while the project is being developed. As the IOP measurements will be taken on Wednesdays, we estimate that we will study approximately 5 patients per week. Therefore, we need approximately 6 months to recruit and study 125 patients. The researchers will communicate their gratitude to the patients for their participation in the study.

ACTIVITY 3. Researchers: Opht, Opt1, Opt2. Maintenance and calibration of the measure instruments.

During the period of data collection, the Opht, Opt1 and Opt2 will check the calibration of the tonometers at least once every two weeks.

ACTIVITY 4. Researchers: MR. Periodic review of the data quality.

A periodic review of data quality will be carried out by the MR in order to know if data is collected correctly and to detect if there are errors that need to be solved.

ACTIVITY 5. Researchers: MR, GP, Opt1, Opt2. Meetings performed during the sample selection and data collection.

During the period of data collection the MR will organize one meeting per month with a total of six meetings. In these meetings the research team may discuss problems that they will have detected, difficulties or concerns related to the study and whether the methodology is developing correctly.

PHASE 3. DATA ANALYSIS AND EVALUATION OF THE RESULTS (1 month)

A statistician will develop the data analysis obtained during the data collection. The MR will organize a meeting with the other researchers in order to interpret and assess the results of the study, discuss and take conclusions.

PHASE 4. ARTICLE ELABORATION AND RESULTS PUBLICATION (3 months)

The research team will elaborate an article in order to publish their investigation in the journal “Archivos de la Sociedad Española de Oftalmología”.

In the future, they will present the study in the annual SEO Congress.

In **Annex V**, you can see the chronogram.

10. BUDGET

PERSONNEL COSTS			
	CATEGORY	COST	TOTAL
	MR	-	-
	GP	-	-
	Opt1	-	-
	Opt2	-	-
	Statistician for data analysis	25h 35€/h	875€
DIAGNOSTIC TESTS AND INSTRUMENTS COSTS			
	ITEM	COST	TOTAL
	Topography	54€ per topography 54 € x 150 patients	8100€
	OCT	42€ per OCT 42 € x 150 patients	6300€
	Pachymetry	37 € per pachymetry 37 € x 125 patients	4625€
	Snellen test, slitlamp, fundus stitlamp lenses, direct ophthalmoscope, NCT, GAT	-	-
MEDICATION COSTS			
	COLIRCUSÍ FLUOTEST	2,15 € (PVL) per jar of 3ml 2,15 € x 24 weeks	51,60€
PUBLICATION COSTS			
Journal "Archivos de la Sociedad Española de Oftalmología"		-	-
PRESENTATION COSTS			
Annual SEO Congress (4 days)		360€ per person 300 € per person (partners) Assistants: MR	660€
Travel expenses	Transport	150€ per person	300€
	Accomodation	240€ per person (4 days)	480€
	Food and miscellania	160€ per person (4 days)	320€
TOTAL			21711,60 €

11. CLINICAL AND HEALTHCARE IMPACT

With this project we wish to provide more information about non-contact tonometry. Currently, when a patient goes to the ophthalmological consulting room first, a nurse examines intraocular pressure using the NCT. Although ophthalmologists take into consideration these tonometric results, often when IOP readings are high they verify them using the gold standard test (Goldmann tonometer) before giving an opinion or a final diagnosis. It is done because poor agreement between these tonometers at high IOP levels is known. In addition, it has been noticed by ophthalmologists that in patients with IOP with tearful eyes, there is an overestimation of IOP readings using NCT after comparing with GAT.

We wish to provide new knowledge about the NCT functioning and discover if a certain volume of fluid in the lower tear meniscus can affect to IOP readings using NCT and if it could be an important factor to take into account when interpreting the IOP measurements, because it could influence the validity of the IOP readings just as with central corneal thickness in applanation tonometry.

If our hypothesis is proved, it could allow further investigations in order to improve the accuracy and precision of the NCT measurements. For instance, how different heights of lower tear meniscus affects to IOP results, it means to create correcting values (nomogram) just as correcting scales as occurs with pachymetry or just take into account the need of drying the lower tear meniscus before taking the measures.

In our study we will include patients with IOP within the normal range in order to be sure that, in case the overestimation of NCT readings comparing to GAT exist, it is not associated with the presence of high IOP levels. But it could be interesting a next study evaluating the same variables in a population with IOP levels above the normal range, because maybe the poor agreement between NCT and GAT could be related with the factor that we are investigating in this study. Therefore, improving the accuracy and precision of NCT help optometrists and nurses who are the most commonly users of this tonometry especially in glaucoma screenings, developing a best work in the detection and adequate referral of patients with high IOP. Moreover, they could

actively engage in the follow-up of glaucomatous patients under treatment, reducing the need of an ophthalmologist for the evaluation of these patients when the intraocular pressure is maintained.

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ANNEX I. Intraocular pressure

Image 1. Theoretical distribution of intraocular pressures in nonglaucoma (N) and glaucoma populations (G). (4)

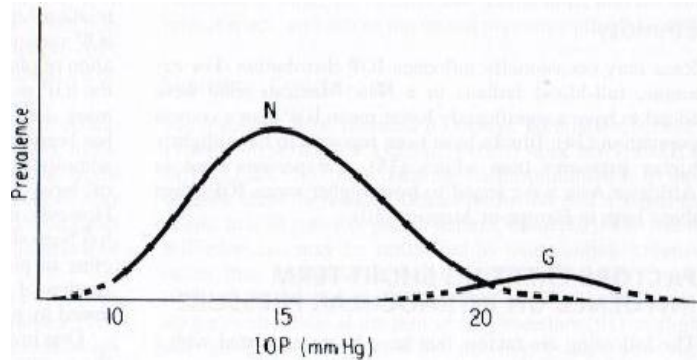


Image 2. Intraocular pressure distribution in the general population. (6)

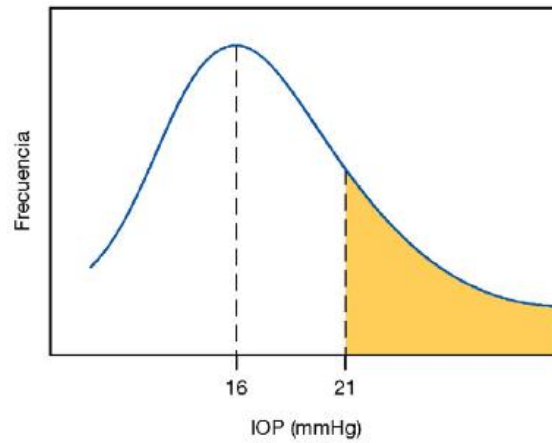


Table 1. Factors that influence intraocular pressure adapted from (4,5)		
Factors	Association	Comments
<i>Demographic¹</i>		
Age	IOP may increase with increasing age	In part, it is due to CV factors (blood pressure, pulse rate, obesity), aqueous humor production and outflow decrease.
Sex	Women may have higher IOP	Between 20 to 40 years, IOP is equal between sexes
Ethnicity	Blacks may have higher IOP	If it is caused by genetic or environmental factors remains unknown.
Heredity	IOP may have a genetic influence	Polygenic effect
<i>Systemic²</i>		
Diurnal variation	In normal individuals, IOP fluctuates an average of 3-6mmHg It depends on fluctuation in the rate of aqueous humor formation (catecholamins), diurnal glucocorticoid cycle.	Diurnal pattern may vary in some individuals, especially those with glaucoma or ocular hypertension. It has important clinical implications in patients with glaucoma
Seasonal variation	IOP is higher during winter months	It is related to the number of hours of light and changes of atmospheric pressure
CV factors	IOP may be increased by: systemic hypertension and elevation of episcleral venous pressure	Other factor that can increase IOP: systemic hyperthermia, obesity, pulse rate, hemoglobin concentration
Exercise	It may increase or decrease IOP, depending on the nature of the activity	↑IOP: straining, playing a wind instrument ↓IOP: prolonged exercise (eg. running or bicycling)
Lifestyle	Factors which are related to increase IOP: obesity, alcohol, smoking, caffeine, lower socioeconomic status	
Postural changes	Going from the upright – setting position to the supine position may raise IOP until 6mmHg	Healthy persons have a compensatory mechanism This may be a problem when IOP in children or mentally-challenged should be measured
Neural factors	It seems that IOP is under neural control: the effect of cholinergic and adrenergic substances modify IOP	
Hormonal factors	Glucocorticoids, diabetes and hypothyroidism may increase IOP Hypertiroidism may decrease IOP	Other hormones which may influence in IOP: GH, aldosterone, vasopressin and MSH
Environmental conditions	Cold air may decrease IOP Reduced gravity increase IOP	
Foods and drugs	Topical cycloplegic agents Systemic agents with cholinergic effects	Raise IOP
	Anesthetic and sedative general agents	Reduce IOP in proportion to depth and time of anesthesia Exceptions: trichloroethylene and ketamine
	Alcohol, marijuana, heroin LSD	Reduce IOP Increases IOP
	Corticoesteroids	See above

		The effect is greater in patients with glaucoma
	Topical prostaglandins	May increase or decrease IOP depending on the dosage used
	Water (large volumes of fluid, >500ml)	Raise IOP
<i>Ocular</i>		
Refractive error¹	Patients with myopia may have higher IOP	IOP is related with axial length
Eye movements²	Eye movements against mechanical resistance may rise IOP	
Eyelid closure²	IOP may increase due to: blinking, hard lid squeezing, lid fissure widening, up-gaze, Grave's infiltrative ophthalmopathy, forcible eyelid closure.	
Inflammation²	In general, if the eye is inflamed IOP is reduced	If outflow is more affected than inflow structures, IOP may raise
Intraocular conditions²	IOP may be reduced in anterior uveitis and rhegmatogenous retinal detachment	
Surgery²	After ocular surgery IOP is reduced	If outflow structures are affected, IOP may raise
<p>Factors which have long-term influence on IOP¹: it means that they can influence IOP throughout the lifetime of the individual.</p> <p>Factors which have short-term influence on IOP²: it means that they can influence IOP lasting from seconds to months.</p>		

ANNEX II. Instruments for measuring IOP

Table 2. Types of tonometers (4,5)	
<p>APPLANATION TONOMETERS “By measuring the force necessary to flatten a small and standard area of the cornea” Shape of deformation: simple flattening</p>	<p>Goldmann tonometer Maklakow tonometer Perkins tonometer Draeger tonometer MacKay and Tono-Pen tonometer Pneumatic tonometer</p> <p>Non-contact tonometer The Ocuton tonometer</p>
<p>INDENTATION TONOMETERS “By measuring the amount of deformation or indentation of the globe in response to a standard weight (force) applied to the cornea” Shape of deformation: truncated cone</p>	<p>Schiøtz tonometer/ electronic Schiøtz tonometer Impact-rebound tonometer Transpalpebral tonometry</p>

Image 3. Corneal deformation: A (indentation tonometer), B (applanation tonometer).(4)

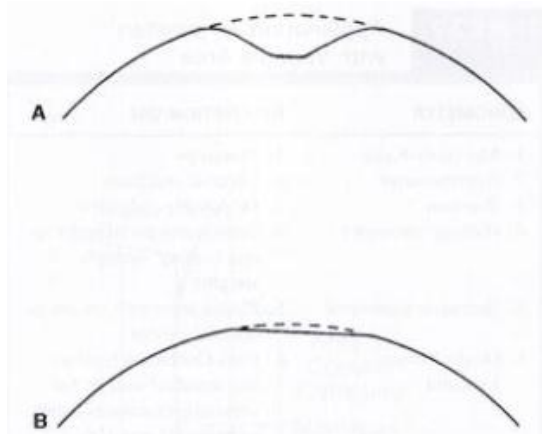


Image 4. A. The Imbert-Flick law ($W=P_t \times A$). B. Modification of Imbert-Flick law ($W+S=P_t \times A_1+B$). (4)(6)

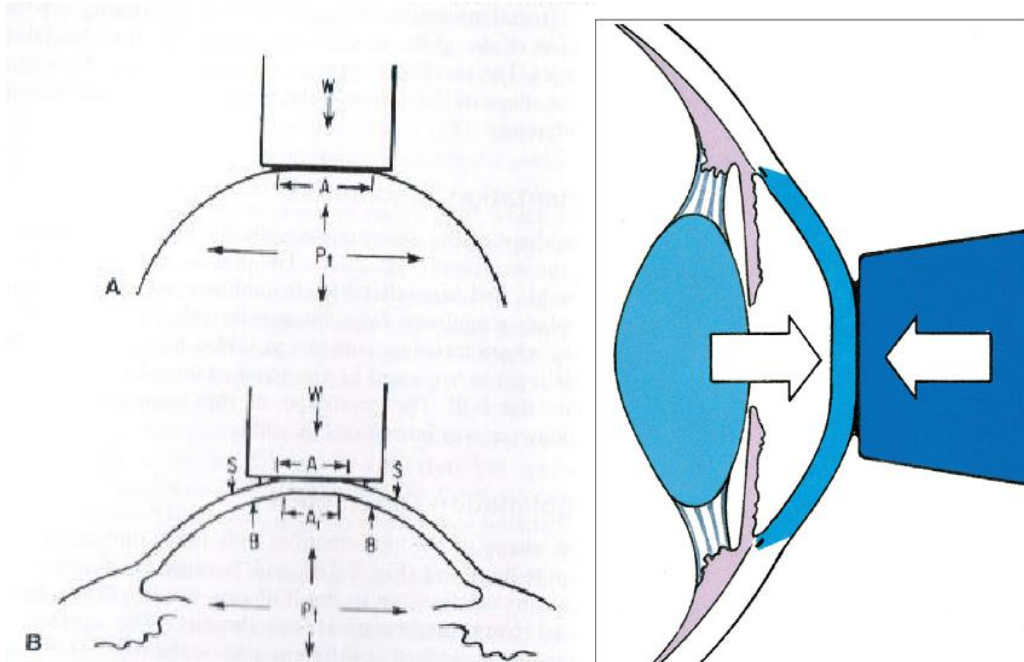
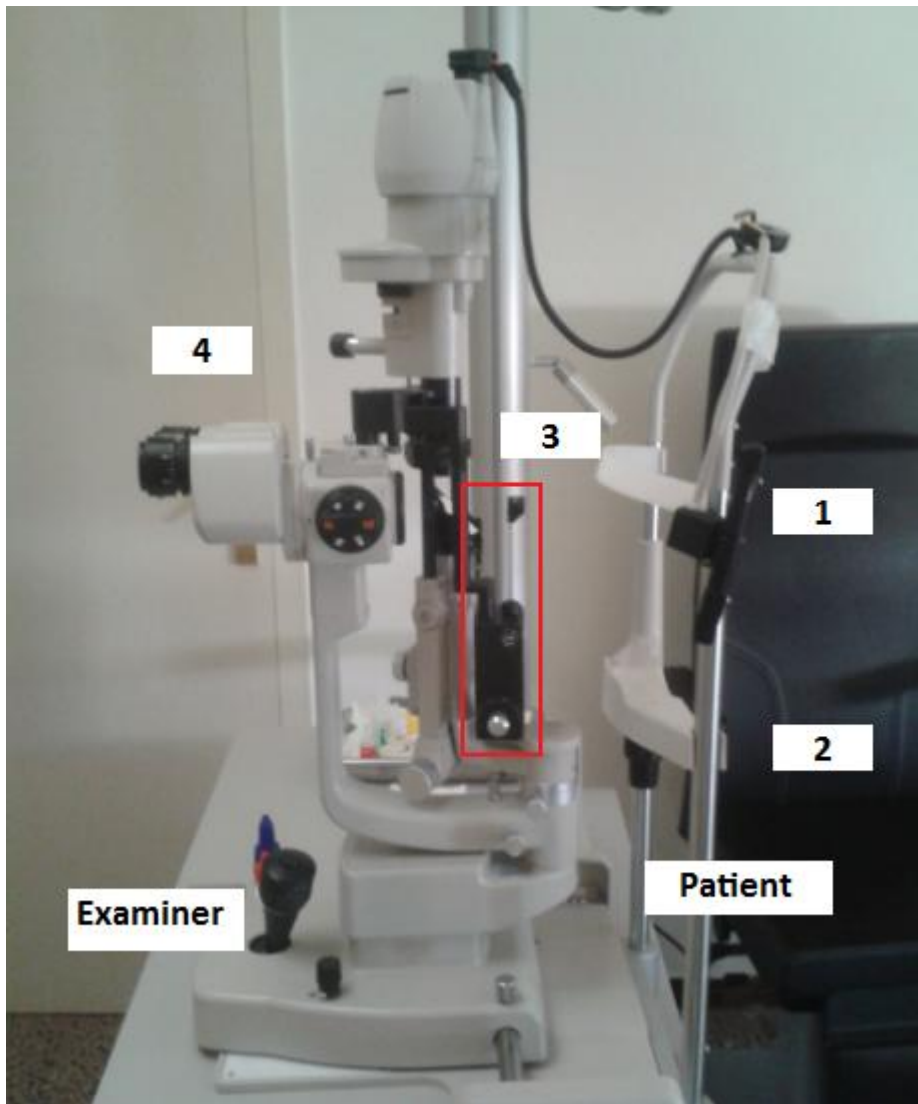
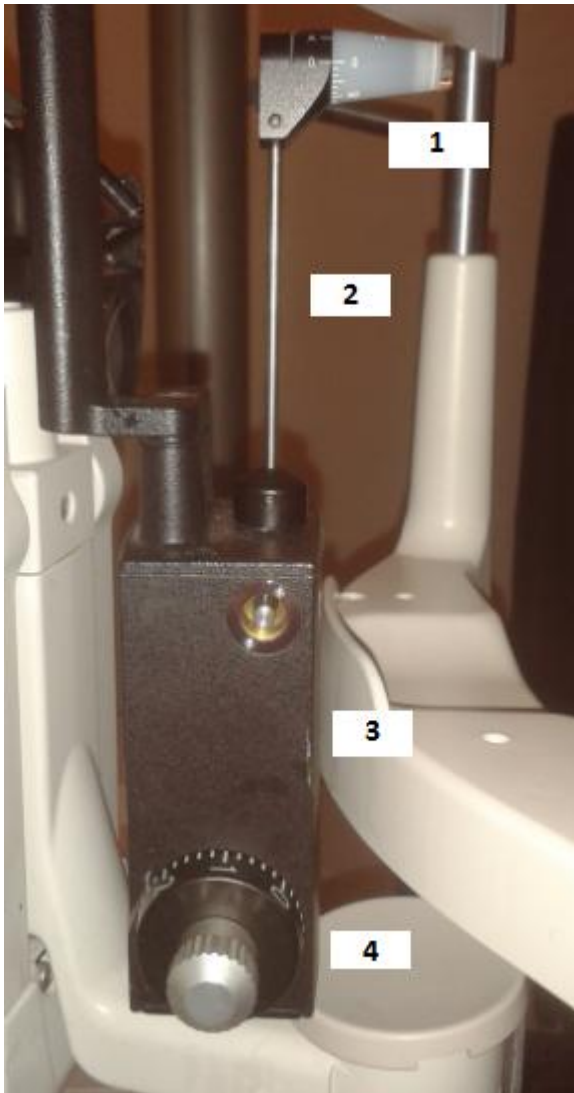


Image 5. Goldmann applanation tonometer mounted on a slit-lamp. Photograph made in Centre d'Especialitats Güell (Girona).



1.Forehead bar 2.Chin rest 3.Goldmann applanation tonometer 4. Direction of examiner's view.

Image 6. Goldmann applanation tonometer. HS HAAG-STREIT INTERNATIONAL AT 900®. Photographs made in Centre d'Espécialitats Güell (Girona).



1. Biprism

2. Rod

3. Housing

4. Adjustment knob

Illumination with a cobalt blue light

Image 7. The biprism in contact with the cornea. (6)



Image 8. Semicircles stained with fluorescein. (6)

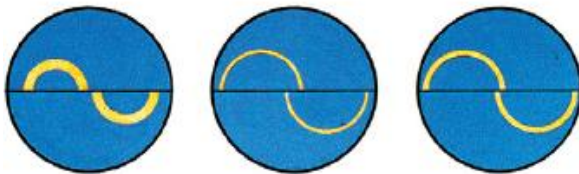


Image 9. COLIRCUSÍ FLUOTEST. Photograph made in Centre d'Especialitats Güell (Girona).



Table 3. Sources of error by using GAT	
Causes of underestimation	Comments
Inappropriate fluorescein staining of the tear film	It occurs when too much time passes between the application of fluorescein and the IOP measurement. The reading of IOP should be within the first minute or immediately after the instillation of fluorescein in order to avoid the error. (5) If there is so much fluorescein, it can cause an overestimation of IOP. (2)
Repeated tonometry	It has been described an IOP reduction effect produced by subsequent applanation measures. It is caused by an aqueous massage effect which may consist in an IOP decrease production or an increase of aqueous humor outflow due to the compression of the anterior chamber. (15,16)
CCT (central corneal thickness)	Thin corneas: <520µm (e.g. glaucomatous eyes, after refractive surgery). (6,10)
Corneal curvature	For every 3D of with-the-rule astigmatism, there is 1mmHg of underestimation. (5)
Causes of overestimation	Comments
Wide tear meniscus	The tear meniscus is visualized at the margin of contact between cornea and biprism. If the tear meniscus is wide, it can cause an overestimation of IOP. (4)
Semicircles (thickness should be 0.25-0.3mm)	If the semicircles are too narrow or wide, then the IOP may be underestimated or overestimated. (5) Solution if too narrow: blinking two or three times in order to fill the fluorescein or apply more fluorescein. Solution if too wide: the eyelids and the prism should be drying with a gauze. If there is an inadequate alignment with different sizes, the IOP could be overestimated. (4,5)
CCT	Thick corneas: >540µm (e.g. ocular hypertension, corneal edema). (4,5,10)
Corneal curvature	For every 3D of against-the-rule astigmatism, there is 1mmHg of overestimation. (5)
Others	<ol style="list-style-type: none"> 1. Elevating the eyes >15° above the horizontal. (5) 2. Excessive extension of the lid fissure. (5) 3. Squeezing on the eyelids or globes. (5) 4. Valsalva maneuver during the measurement: it can cause an overestimation of IOP reading as a result of an artificial increase on IOP. (10)
Other potential error of GAT	<ol style="list-style-type: none"> 1. A scarred, irregular cornea may deform the fluorescein semicircles, and consequently the IOP estimation can be difficult. (4,5) 2. Prolonged contact: it can damage the cornea and produces inappropriate readings. Moreover, it can decrease IOP due to the aqueous massage effect. (4) 3. Interobserver variability: 0-3mmHg. (1,5) 4. Intraobserver variability: up to 2mmHg. (1) 5. Incorrect calibration. (6)

Image 10. Topcon CT-80 Non-Contact Computerized Tonometer . Photograph made in Centre d'Especialitats Güell (Girona).

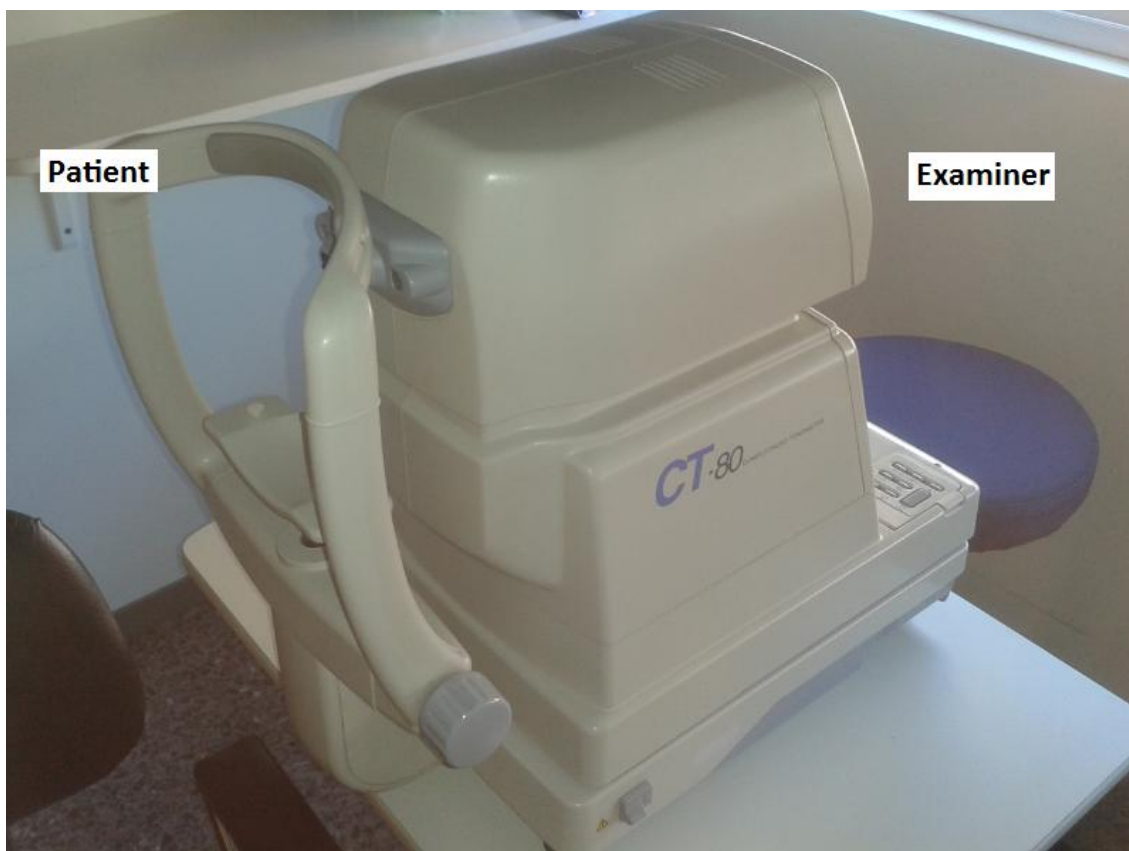


Image 11. Parts of the non-contact tonometer. Photographs made in Centre d'Especialitats Güell (Girona).

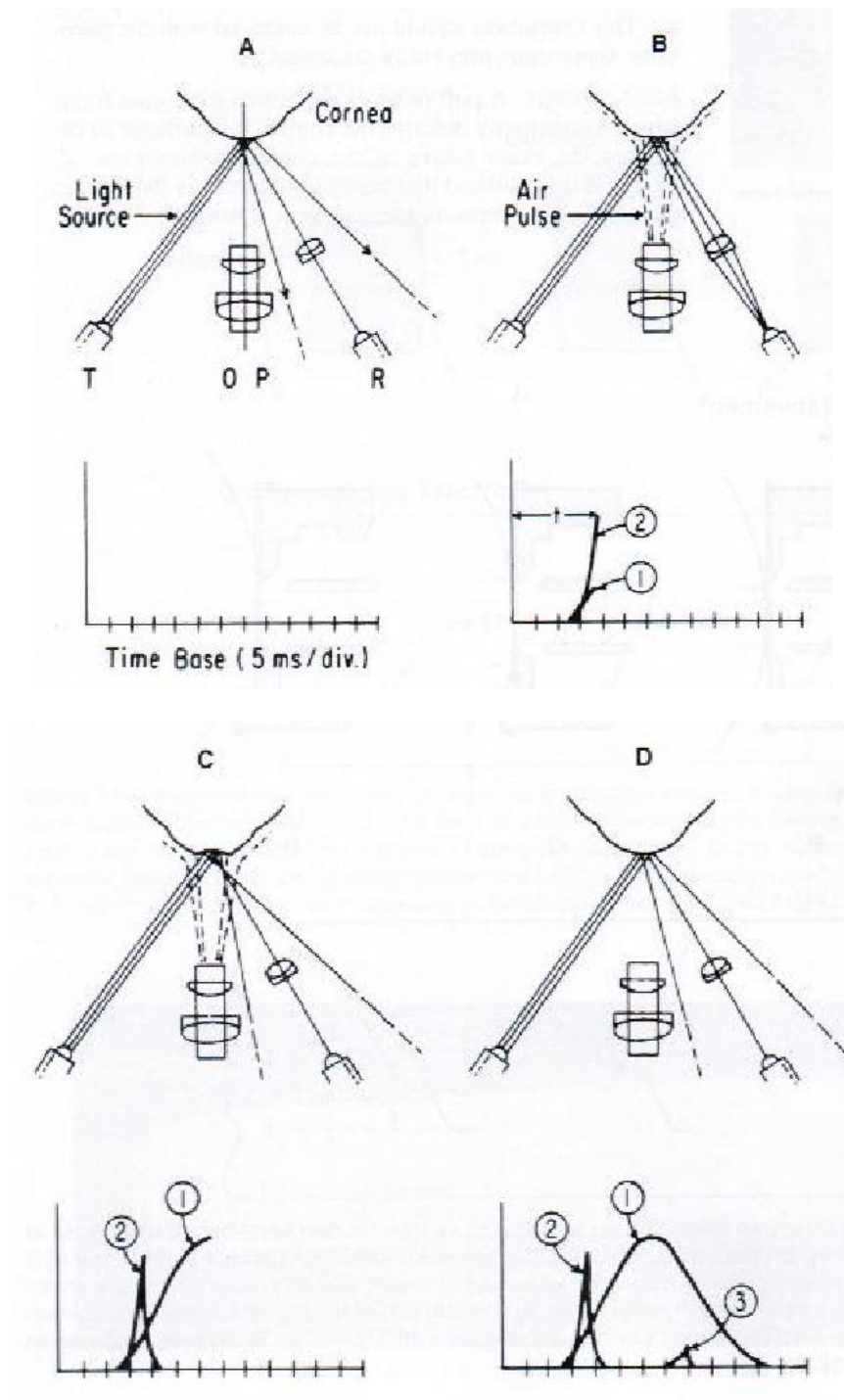


1. Forehead bar 2. Chin rest. 3. Puff of air exit and beam of light exit and entrance (pneumatic system and optoelectronic applanation monitoring system)



Alignment or optical system

Image 12. Non contact tonometer functioning. Photograph made in Centre d'Especialitats Güell (Girona). Transmitter(T), Receiver(R), Optical system(O), Pneumatic system(P), time(t), air puff(1), light rays(2), another light peak(3)



ANNEX III. The lachrymal functional unit

Image 13. The lachrymal drainage system. (17)

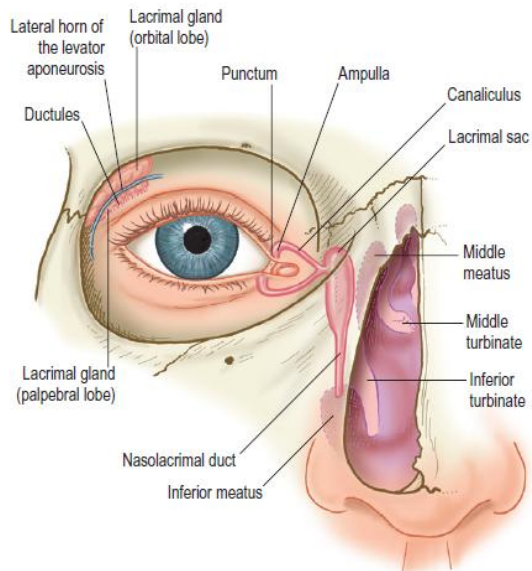


Image 14. The three layers of tear film. (6)

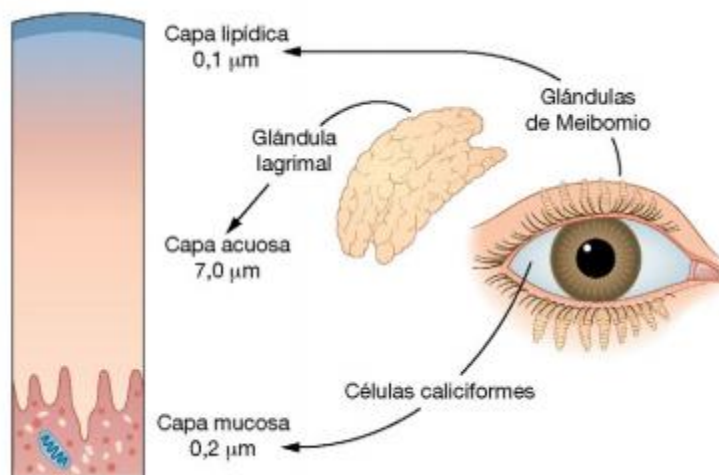


Image 15. Slitlamp photograph with fluorescein staining, lachrymal meniscus is visualized (green line). (17)

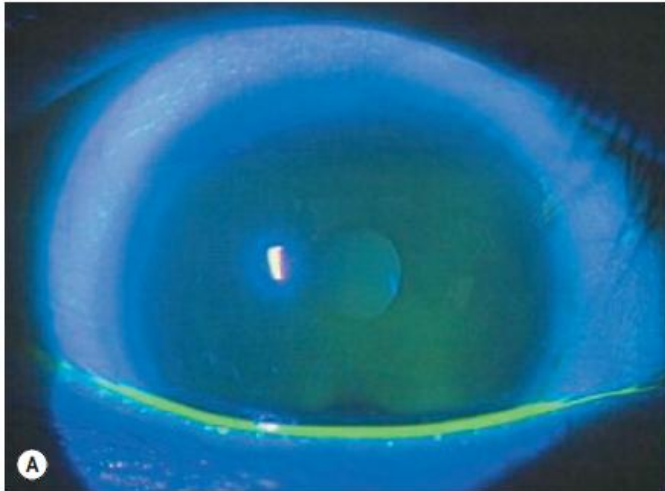


Image 16. Tear meniscus measurements with Spectral OCT. (21)

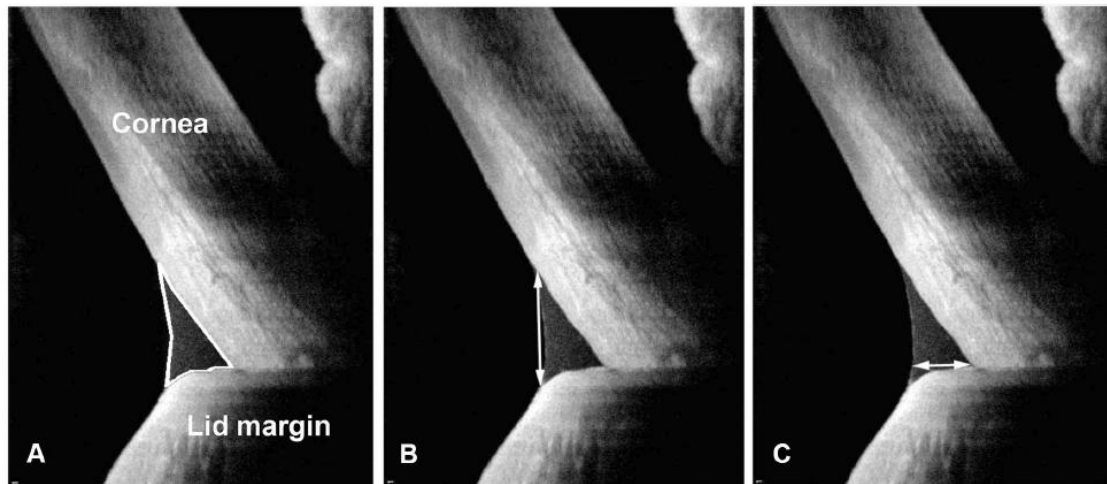


FIGURE 1. Tear meniscus measurement with Spectral OCT. A, Cross-section area (TMA). B, Height (TMH). C, Depth (TMD).

ANNEX IV. Chronogram

		2014												2015														
PHASES		S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D											
<u>0. COORDINATION PHASE</u>	Responsibles	[Blue shaded area]																										
Activity 1	MR	[Light blue shaded area]																										
Activity 2	MR, GP, Opt1, Opt2						[Light blue shaded area]																					
Activity 3	MR, GP, Opt1, Opt2																											
<u>1. SAMPLE SELECTION AND DATA COLLECTION</u>		[Orange shaded area]																										
Activity 1	GP, Opht, Opt1																											
Activity 2	Opht, Opt1, Opt2																											
Activity 3	Opht, Opt1, Opt2																											
Activity 4	MR																											
Activity 5	MR, GP, Opt1, Opt2																											
<u>3. DATA ANALYSIS AND EVALUATION OF THE RESULTS</u>	Statistician, MR, GP, Opt1, Opt2																											
<u>4. ARTICLE ELABORATION AND RESULTS PUBLICATION</u>	MR, GP, Opt1, Opt2																											

ANNEX V. Informed consent form

Consentiment informat per a la participació en l'estudi de la tonometria de no contacte

Informació general:

Aquest consentiment va dirigit als pacients del Centre d'Atenció Primària Santa Clara, Girona per tal de participar en un estudi sobre tècniques diagnòstiques en oftalmologia. A continuació, se li explicarà en què consisteix aquest estudi. Es prega que llegeixi atentament aquest document i que per qualsevol dubte, el personal sanitari que l'atendrà i que forma part de l'equip investigador restarà a la seva disposició i respondran a aquests.

Per tal de dur a terme l'estudi, necessitem la seva autorització a través de la signatura del consentiment informat.

Objectius:

L'objectiu de l'estudi és valorar la influència que té la presència d'un volum de fluid en el menisc lacrimal inferior, en la mesura de la pressió intraocular realitzant una tècnica diagnòstica, anomenada tonometria de no contacte o d'aire. Així com valorar la concordança d'aquesta tècnica amb la tonometria de Goldmann.

Procediments:

Aquestes tonometries són dos mètodes que es basen en l'aplanació de la còrnia per tal de mesurar la pressió intraocular de l'ull. La tonometria de no contacte emet un flux d'aire per tal d'aplanar la còrnia, pot ser una mica molest sobretot pel soroll que emet, però innocu. Aquesta tècnica la realitzaran dos optometristes. La tonometria de Goldmann utilitza un prisma que en contacte amb la còrnia i aplicant una petita força l'aplana. Aquesta tècnica la realitzarà l'oftalmòleg.

A més, serà necessària la instil·lació de dos gotes de COLIRCUSÍ FLUOTEST, un col·liri compost per fluoresceïna sòdica i oxibuprocaina clorhidrat i els següents excipients: clorobutanol, polividona, edetat sòdic, àcid bòric i aigua purificada. Es tracta d'una solució colorant pel diagnòstic en oftalmologia amb acció anestèsica local ràpida i de breu duració. Per tant, no sentirà dolor.

El procés de selecció de participants en l'estudi s'inicia en el Centre d'Atenció Primària Santa Clara (Girona), on el metge de família li explicarà en què consisteix l'estudi i la voluntarietat de la participació, així com li entregarà el present consentiment informat, que haurà de signar per tal de formar part d'aquest. Ha de saber que un cop estigui d'acord amb la participació, serà derivat al Centre d'Especialitats Güell, Girona (Girona)

un dimarts al matí per tal de realitzar una valoració oftalmològica duta a terme per l'oftalmòleg i l'optometrista. Aquesta valoració es fa per tal de descartar certa patologia ocular que ens puguin influir en l'estudi, ja que volem estudiar ulls sans. Ha de saber que un cop finalitzada aquesta valoració, serà quan es decidirà si pot formar part de l'estudi o no. En el cas que ho autoritzi, haurà de tornar el següent dia (dimecres matí) per tal de realitzar les mesures de la pressió intraocular.

Aquestes mesures es realitzaran entre les 14.00h i 16.00h. Abans d'assistir a aquesta sessió, es recomana: que segueixi realitzant les seves activitats i hàbits habituals, però eviti beure alcohol o grans quantitats de líquid (500ml o més) dos hores abans de la mesura, eviti practicar exercici durant les hores prèvies, així com deixar un mínim de 4h entre que s'aixeca al matí i ve a la segona sessió.

Beneficis i riscos:

Ha de saber que es tracten d'instruments que s'utilitzen en la pràctica clínica diària i realitzades per professionals amb experiència, per tant no tenen perquè causar cap mena de dany.

No obstant, està descrit que amb el col·liri que se li aplicarà, pot experimentar una irritació passatgera, inflamació o envermelliment corneal i molt rarament, pot aparèixer una reacció hiperal·lèrgica corneal amb queratitis epitelial difusa. Si prèviament ha tingut algun problema amb aquest col·liri, preguem que ens ho faci saber.

També, està descrit el risc d'infecció a través del prisma del tonòmetre de Goldmann. No obstant, sempre després del seu ús i entre usos es neteja adequadament amb solucions esterilitzants.

No rebrà cap aportació econòmica per la participació.

Confidencialitat:

Li garantim la confidencialitat i anonimat de les seves dades personals, complint amb el que diu la "Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal". Les dades recollides seran només amb finalitat d'investigació.

Li agraïm que formi part d'aquest estudi sobre tècniques diagnòstiques en oftalmologia.

Si renuncia a participar en l'estudi o si preveu que no es pot comprometre a assistir a totes les sessions esmentades, preguem que ens ho faci saber. Això no suposarà cap càstig ni pèrdues de benefici per vostè.

Declaració del consentiment:

He comprés tota la informació sobre l'estudi que se m'ha facilitat en un llenguatge clar i senzill, així com les explicacions sobre els procediments que se'm realitzaran pel fet de participar en aquest. Que les meves dades personals seran tractades amb total confidencialitat i anonimat, i que aquestes tenen com a objectiu la investigació científica. Tanmateix, manifesto haver obtingut la informació sobre els dubtes que se m'han plantejat.

També, he comprés que la participació és voluntària i que tinc la possibilitat de revocar en qualsevol moment el consentiment prestat, sense la necessitat de donar cap explicació i de demanar l'eliminació de les meves dades personals, sense que això suposi cap problema en la meva atenció sanitària posterior.

Per tot això, manifesto de forma acreditativa està satisfet amb tota la informació rebuda.

Autorització:

Sr/Srade.....anys
d'edat i DNIAUTORITZO la meva participació en l'estudi.

Data:

Signatura:

Revocació:

Sr/Srade.....anys
d'edat i DNI REVOCO el consentiment prestat.

Data:

Signatura:

Metge que ha informat al pacient

Servei:

Nom i cognoms:

Núm. Col.legiat:

Signatura:

Consentimiento informado para la participación en el estudio de la tonometría de no contacto

Información general:

Este consentimiento va dirigido a los pacientes del Centre d'Atenció Primària Santa Clara (Girona), para participar en un estudio sobre técnicas diagnósticas en oftalmología. A continuación, se le explicará en qué consiste dicho estudio. Se ruega que lea atentamente este documento i que para cualquier duda, el personal sanitario que lo atenderá y que forma parte del equipo investigador restará a su disposición y responderá a estos sin ningún problema.

Con tal de llevar a cabo el estudio, necesitamos su autorización a través de la firma del consentimiento informado.

Objetivos:

El objetivo de este estudio es valorar la influencia que tiene la presencia de un volumen de fluido en el menisco lagrimal inferior, en las medidas de la presión intraocular realizando una técnica diagnóstica, llamada tonometría de no contacto o de aire. Así como valorar la concordancia de esta técnica con la tonometría de Goldmann.

Procedimientos:

Estas tonometrías son dos métodos que se basan en la aplanación de la córnea con tal de medir la presión intraocular del ojo. La tonometría de no contacto emite un chorro de aire para aplanar la córnea, puede resultar un poco molesto sobre todo por el ruido que emite, pero inocuo. Esta técnica la realizarán dos optometristas. La tonometría de Goldmann utiliza un prisma que en contacto con la córnea y aplicando una pequeña fuerza la aplanan. Esta técnica la realizará el oftalmólogo.

Además, será necesaria la instilación de dos gotas de COLIRCUSÍ FLUOTEST, un colirio compuesto por fluoresceína sódica y oxibuprocaina clorhidrato y los siguientes excipientes: clorobutanol, polividona, edetato sódico, ácido bórico y agua purificada. Se trata de una solución colorante para el diagnóstico en oftalmología con acción anestésica local rápida y de breve duración. Por lo tanto, no sentirá dolor.

El proceso de selección de participantes en el estudio se inicia en el Centro de Atención Primaria Santa Clara (Girona), donde el médico de familia le explicará en qué consiste dicho estudio y la voluntariedad de la participación, así como le entregará el presente consentimiento informado que deberá firmar con tal de formar parte de éste. Tiene

que saber que una vez esté de acuerdo con la participación, será derivado al Centre d'Especialitats Güell (Girona), un martes por la mañana para realizar una valoración oftalmológica que llevará a cabo el oftalmólogo y la optometrista. Esta valoración se hace con tal de descartar cierta patología ocular que nos pueda influir en el estudio, ya que queremos estudiar ojos sanos. Tiene que saber que una vez finalizada esta valoración, será cuando se decidirá si puede formar parte del estudio o no. En el caso que lo autorice, deberá volver al siguiente día (miércoles por la mañana) para realizar las medidas de la presión intraocular.

Estas medidas se realizarán entre las 14.00h y 16.00h. Antes de asistir a esta sesión, se recomienda: que siga con sus actividades y hábitos habituales, pero evite beber alcohol o grandes cantidades de líquido (500ml o más) dos horas antes de la medida, evite practicar ejercicio durante las horas previas, así como dejar un mínimo de 4h entre que se levanta por la mañana y va a la segunda sesión.

Beneficios y riesgos:

Tiene que saber que se tratan de instrumentos que se utilizan en la práctica clínica diaria y realizados por profesionales con experiencia, por lo tanto no tienen porque causar ningún daño.

No obstante, está descrito que con el colirio que se le aplicará, puede experimentar una irritación pasajera, inflamación o enrojecimiento corneal y muy raramente, puede aparecer una reacción hiperalérgica corneal con queratitis epitelial difusa. Si previamente ha tenido algún problema con este colirio, le rogamos que nos lo haga saber.

También, está descrito el riesgo de transmitir infecciones a través del prisma del tonómetro de Goldmann. No obstante, siempre después de su uso y entre usos se limpia adecuadamente con soluciones esterilizantes.

No recibirá ninguna aportación económica por la participación.

Confidencialidad:

Le garantizamos la confidencialidad y anonimato de sus datos personales, cumpliendo con lo que dice la "Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal".

Los datos recogidos serán sólo con finalidad de investigación.

Le agradecemos que forme parte de este estudio sobre técnicas diagnósticas en oftalmología.

Si renuncia a participar en el estudio o si prevé que no se puede comprometer a asistir a todas las sesiones comentadas, le rogamos que nos lo haga saber. Esto no supondrá ningún castigo ni pérdidas de beneficio para usted.

Declaración del consentimiento:

He comprendido toda la información sobre el estudio que se me ha facilitado con un lenguaje claro y sencillo, así como las explicaciones sobre los procedimientos que se me realizarán por el hecho de participar en éste. Que mis datos personales serán tratados con total confidencialidad y anonimato, y que éstos tienen como objetivo la investigación científica. Además, manifiesto haber obtenido la información sobre las dudas que se me han planteado.

También, he comprendido que la participación es voluntaria y que tengo la posibilidad de revocar en cualquier momento el consentimiento prestado, sin la necesidad de dar ninguna explicación y de pedir la eliminación de mis datos personales, sin que esto suponga ningún problema en mi atención sanitaria posterior.

Por todo esto, manifiesto de forma acreditativa estar satisfecho con la información recibida.

Autorización:

Sr/Sra de años de edad y DNIAUTORIZO mi participación en el estudio.

Fecha: Firma:

Revocación:

Sr/Srade años de edad y DNIREVOCO el consentimiento prestado.

Fecha: Firma:

Médico que ha informado al paciente

Servicio:

Nombre y apellidos:

Nº de colegiado: Firma: