Diplomarbeit

Are the results of the Contact Lens Sensor Triggerfish® influenced by light?

eingereicht von

Maximilian Mächler

zur Erlangung des akademischen Grades

Doktor der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Augenheilkunde

unter der Anleitung von

Univ.-Prof. Dr. Christoph Faschinger

Graz, 04.08.2016

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 04.08.2016 *Maximilian Mächler eh*

Acknowledgment

I wish to express my sincere gratitude to Professor Dr. Christoph Faschinger, who gave me the opportunity to conduct and compose this paper. I would like to thank you for your expert advice and encouragement throughout the working process, as well as for your time and patience whenever I needed support. It would not have been possible to perform the experiments and to write this paper without your help, your fundamental ideas and perpetual input.

I would like to thank my parents Heinrich and Petra for always being there when I needed you, for your advice and guidance throughout my life, for being my rolemodels and heroes and for your unconditional love.

Furthermore I would like to thank Veronika for accompanying me through five years of studying, for being able to answer all my medical questions out of memory, for travelling the world with me, for supporting me, for always reminding me what is most important in life and for making me feel at home wherever you are.

Additionally I express my deepest thanks to my family and my friends for your continual support and your companionship throughout my life. Without you I would not be who I am today.

Finally I would like to extend my acknowledgments to the Medical University of Graz for providing my education and qualifications.

Abstract – German

Einleitung: Das Glaukom ist eines der häufigsten Krankheitsbilder in der Augenheilkunde, wobei der Augeninnendruck den wichtigsten therapierbaren Risikofaktor darstellt. Weltweit erblinden etwa acht Millionen Menschen pro Jahr durch glaukomatöse Veränderungen. Trotz dieser epidemiologischen Bedeutung bleiben über die Hälfte der Patienten undiagnostiziert.

Die Firma SENSIMED hat im Jahr 2009 eine neue diagnostische Möglichkeit entwickelt um Veränderungen im Profil des Augeninnendrucks über 24-Stunden hinweg aufzuzeichnen. Eine spezielle Kontaktlinse wird auf die Hornhaut aufgebracht, welche Veränderungen des intraokulären Volumens pseudo-kontinuierlich misst. Wie alle neuen Methoden, muss auch diese auf Ihre Wertigkeit hin untersucht werden. Studien zeigten, dass die entwickelte Linse anfällig für Störungen sein könnte und dadurch die Möglichkeit von Artefakten gegeben sei. Manche der aufgezeichneten Fluktuationen sind möglicherweise nicht auf den Augeninnendruck zurückzuführen. Unser Ziel war es einen Versuchsaufbau zu schaffen, durch welchen wir den Einfluss von Licht auf die Linse testen können. Des Weiteren wollten wir einen Einblick in die Literatur bezüglich des klinischen Nutzens der Linse geben.

Material und Methoden: Die Triggerfish genannte Linse besteht aus Silikon und beinhaltet Dehnungsmessstreifen, welche Änderungen in der Krümmung der Kornea, die durch den Augeninnendruck mitbeinflusst wird, feststellen. In unserem Studiendesign wurde die Linse während der Messzeit mit unterschiedlichen Arten und Helligkeiten von Licht beschienen. Die Beleuchtungsstärken und die Temperatur wurden währenddessen stetig gemessen und die 24-Stunden Triggerfish-Profile wurden ausgewertet.

Resultate: Insgesamt führten wir acht Testläufe mit jeweils verschiedener Lichtquelle, Lichtstärke und Beleuchtungszeit durch. In sieben von acht Tests zeigte sich nachts, bei Lux-Zahlen gegen null, ein sehr ruhiges, mit wenigen Ausreißern versehenes Profil. Hingegen zeigte das Profil während der aktiven Beleuchtungszeit starke Ausreißer und mehr Fluktuationen. Trotz dieser Beobachtung war es uns nicht möglich eine sichere Korrelation zwischen der Lichtstärke und den Artefakten festzustellen. Auf der anderen Seite zeigte sich jedoch, dass die Temperatur durchaus Einfluss auf das Profil zu nehmen scheint. Diese Erkenntnis wurde bereits in anderen Publikationen bemerkt.

Schlussfolgerung: Die Triggerfish-Linse wird höchstwahrscheinlich nicht durch die Stärke des Lichts einer einwirkenden Lichtquelle beeinflusst. Jedoch scheint es ein gewisses Störpotential durch Licht zu geben. Es zeigte sich weiters, dass Temperaturänderungen mit Fluktuationen im 24-Stunden Profil zu einem gewissen Grad korrelieren.

Abstract – English

Introduction: Glaucoma is one of the most common diseases in ophthalmology with intraocular pressure (IOP) as its most important treatable risk factor. Over eight million people per year are losing their eyesight due to this condition. Despite this over 50% of glaucoma patients are still undiagnosed.

The company Sensimed announced a new method in 2009 to record and estimate fluctuations in IOP over a 24-hour period. By placing a Contact Lens Sensor (CLS) onto the eye, changes in intraocular volume can be measured pseudo-continuously. However, validity has yet to be evaluated. Some studies showed that the new device may be prone to noise and artifacts in its profile and that it shows certain 'fluctuations', which cannot be explained. We therefore sought to examine the influence of light on the CLS. Furthermore we analyzed current literature regarding the usability of the new device.

Material and methods: The CLS called Triggerfish features a soft contact lens with implemented strain gauges to measure changes in corneal curvature, which were found to correlate with IOP.

We developed a study design in which the CLS was shined on by different kind of light sources with different brightnesses during its measurement. Illuminance and temperature were recorded throughout the process and the 24-hour TF profiles were analyzed.

Results: We did eight test runs, each with different sources of light, brightnesses and intervals. In seven out of eight tests the night periods, during which close to complete darkness was recorded, showed a rather quiet profile. In contrast, profiles recorded during the daytime, when ambient light was present, showed various spikes and fluctuations. However, it was not possible to find a certain correlation between illuminance and disturbances in the 24-hour profile. We found that temperature has an ambiguous influence on the profile, which has already been stated in recent literature.

Conclusion: The CLS is not influenced by light intensity per se, although there are findings supporting the assumption that light might be a factor in creating noise to some degree. Temperature is influencing the profile to a certain point and might be responsible for some of the known artifacts.

Table of Contents

Abbreviations

ASIC	application-specific integrated circuit
ATP	adenosine triphosphate
CAI	carboanhydrase inhbitor
CCT	central corneal thickness
CLS	Contact Lens Sensor
C/D ratio	cup/disc ratio
DCT	dynamic contour tonometry
GAT	Goldmann applanation tonometry
HCO_3	hydrogen carbonate, *also bicarbonate*
IOP	intraocular pressure
ISNT	inferior, superior, nasal, temporal
ITC	iridotrabecular contact
LED	light-emitting diode
NICE	National Institute for Health and Care Excellence
NRR	neuroretinal rim
mV eq	millivolt equivalent, *arbitrary unit*
NTG	normal tension glaucoma
PAS	peripheral anterior synechiae
PACG	primary angle-closure glaucoma
POAG	primary open-angle glaucoma
PXS	pseudoexfoliation syndrome
OHT	ocular hypertension
OCT	optical coherence tomography
RNFL	retinal nerve fiber layer
TF	Triggerfish®
UBM	ultrasound biomicroscopy
VAS	visual analogue scale

Table of Figures

1 Introduction

The purpose of this study was to evaluate the possible influence of daylight and artificial light on the Triggerfish® (TF) Contact Lens Sensor profile and was inspired by questions raised in two previously published studies by De Smedt et al (1) and Mansouri and Shaarawy (2).

The TF Contact Lens Sensor (CLS) is a soft contact lens, which is applied to the eye and is capable of pseudo-continuously measuring the changes of ocular volume dimensions of the patient. It was developed by the Swiss company SENSIMED. The output of the CLS is said to strongly correlate with the intraocular pressure (IOP) and the device is designed and marketed to be used as a diagnostic tool in patients suffering from glaucoma.

However, there are some anomalies or artifacts in the results, which causes are yet to be detected and which complicate a proper implementation into clinical practice.

Therefore we developed a study design to evaluate the possible influence of light to any degree on the TF sensor output.

Within this section of our paper we will give information on the main domain of application for the TF sensor, which is in patients suffering from glaucoma or ocular hypertension, and we will also evaluate the current state of research regarding the possible causes for before-mentioned artifacts in the data output.

1.1 *Primary field of application: Glaucoma*

The primary field of application for the CLS is in glaucoma suspects and patients with established glaucoma.

The website of the company SENSIMED (3) states its goal as to ‘improve the overall management of glaucoma by enabling highly personalised treatment programs along with the effective monitoring of the success of those treatments’. (3)

1.1.1 Definition

Glaucoma is either defined as a collective term for different diseases of the eye, associated with an enlarged excavatio disci nervi optici and retinal nerve fiber loss found mostly in individuals with increased intraocular pressure (4) or also as a ‘diverse group of disorders … [characterized by a] … progressive optic neuropathy that is associated with visual field loss … and in which IOP is a key modifiable factor’ (5: p.307).

The disease can be classified either by it being congenital or acquired. Furthermore it can be distinguished by the pathophysiological mechanics leading to an impairment of aqueous outflow: the open-angle or angle-closure type.

Differentiation can also be made between primary and secondary glaucoma, whereas in the latter an identifiable disorder or a preceding disease is responsible for the onset of glaucoma. (5)

1.1.2 Epidemiology

The global prevalence of glaucoma, for a population which is aged between 40 and 80 years, is about 3,5% (6), with nearly half of them (5) being possibly undiagnosed.

Since the average age of the global population is continuously increasing, it is very likely that the incidence of glaucoma will also rise. The estimated number is that there will be around 80 million people suffering from glaucoma in 2020. (7)

There is a rather great variety in gender and different ethnicities.

In estimations made for 2010 (8), women comprised for 59% of all glaucoma cases. When further subdivided 55% of open-angle glaucoma patients were female and in angle closure glaucoma even 70% of persons afflicted were women.

Not only gender is a factor in the probability of developing glaucoma, there is also a great imbalance between different ethnicities.
On the one hand primary open-angle glaucoma (POAG) is most common in white, Hispanic and black individuals. (5) However, there is a significant disparity in distribution even between these different ethnicities. The age-adjusted prevalence rate of POAG was found to be four to five times higher in African Americans than it is in European Americans. Furthermore the highest prevalence can be found in the black population of the Caribbean. (8)
On the other hand primary angle closure constitution applies to nearly half of all glaucoma cases and is mostly found in Asian individuals (5), although the highest incidence rate is among Inuit people (8).
Glaucoma is the second leading cause for blindness, just after cataract, with approximately eight to nine million people becoming blind because of glaucoma in 2010. (8) It is also second in causing blindness in developed countries, with the consequences of diabetes mellitus being the leading cause. (9)
4.5 million people became blind globally because of POAG and 3.9 million due to primary angle-closure glaucoma (PACG). For 2020 these numbers will rise up to 5.9 and 5.3 million, respectively. (8)

1.1.3 Anatomy and physiology

Fundamental to the pathophysiology of glaucoma is the physiology of IOP as the main modifiable factor in its progress. The balance of aqueous humour production and its outflow mainly determine the IOP. Aqueous humour/fluid or also intraocular fluid derives from plasma and emerges from capillaries as an ultrafiltrate into the stroma of the ciliary processes. Secretion into the posterior chamber happens along an osmotic gradient. (5)
This is a passive flow triggered by said osmotic gradient, which is mainly established by active transport of sodium and chlorid into the posterior chamber. Furthermore the enzyme carbonic anhydrase is also playing a key role in the maintenance of the osmotic gradient by providing substrates, especially for the Cl/HCO_3 antiporter. (10)
The active secretion of these solutes across the dual-layered ciliary epithelium, for which Adenosine triphosphate (ATP) is needed, is influenced by the sympathetic

nervous system. Activated beta-2-receptors increase secretion and activation of alpha-2-receptors decreases the active transport of aqueous humour. (5)
The aqueous fluid is quite similar to the cerebrospinal fluid in its composition, with the main components being electrolytes, glucose and amino acids. It is secreted approximately at 0.15 ml/h, supplies the lens and the cornea and underlies continuous replacement. (10)
Aqueous fluid flows from the posterior chamber into the anterior chamber, whereas it has to pass the pupil (Figure 1). From there the outflow of intraocular fluid happens via three different routes (5):

- Trabecular outflow (90%): Aqueous fluid flows through the trabecular meshwork (Figure 1), which acts as a form of sieve at the angle of the anterior chamber, and enters Schlemm's canal, which is connected to episcleral veins. The resistance of the trabecular meshwork is essential to the proportion of aqueous fluid production and outflow and therefore establishes the IOP. This outflow route is pressure sensitive, which means that an increase in IOP will lead to increased outflow under physiological conditions.
- Uveoscleral drainage (10%): A small portion of the intraocular fluid enters the ciliary body again and is drained through the veins inside the ciliary body, choroidea and sclera (Figure 1).
- Outflow via the Iris: The smallest portion of the aqueous fluid drains via the iris.

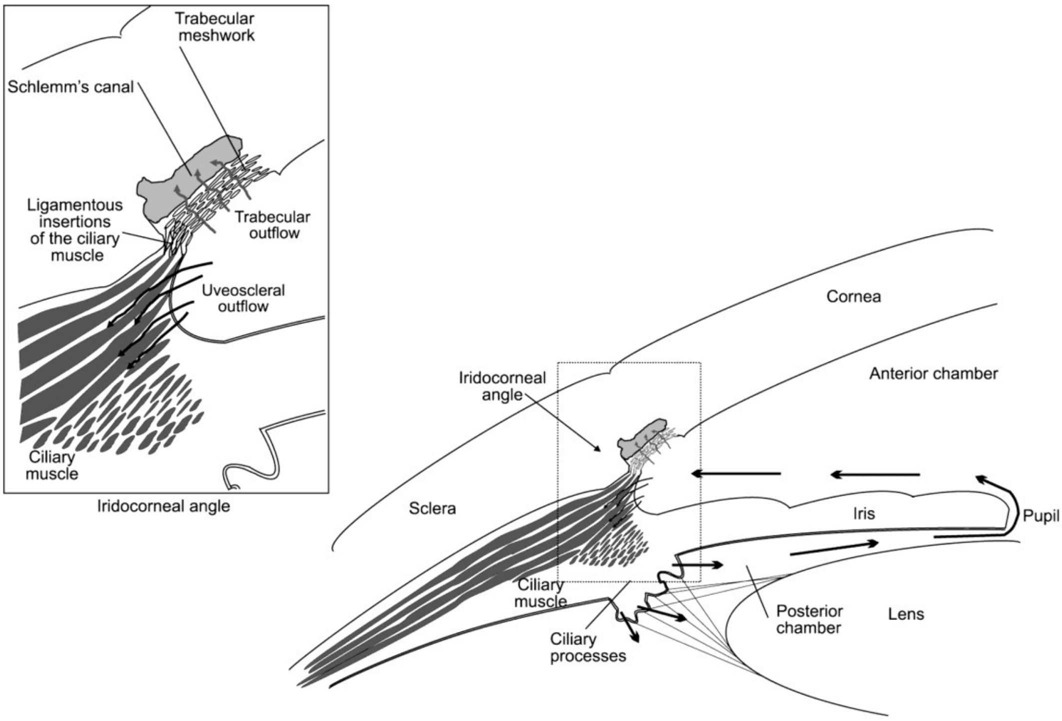


Figure 1: Physiological flow of aqueous fluid and anatomical scheme of anterior and posterior chamber (11: p.206).

The structures, which are most sensitive to chronically increased IOP, are the retina and the optic nerve. Axons of retinal ganglion cells converge on the optic disc to form the optic nerve. These fibers pass through the lamina cribrosa, which is a perforated connective tissue membrane and synapse in the thalamus (lateral geniculate nucleus) to build the visual system. The optic nerve head, which corresponds to the physiological blind spot in the visual field, has a diameter of about 1.5 mm and has a rather great width variance in individuals. The point where the axons eventually converge to build the optic nerve forms a depression in the disc, referred to as the cup (Figure 2). The pink tissue between the border of the cup and the inner margin of the disc is referred to as neuroretinal rim. Besides the essential component of a functioning microcirculation also neurotransmitters, such as glutamate, and other trophic factors are crucial for the survival of retinal nerve cells. (5, 12)

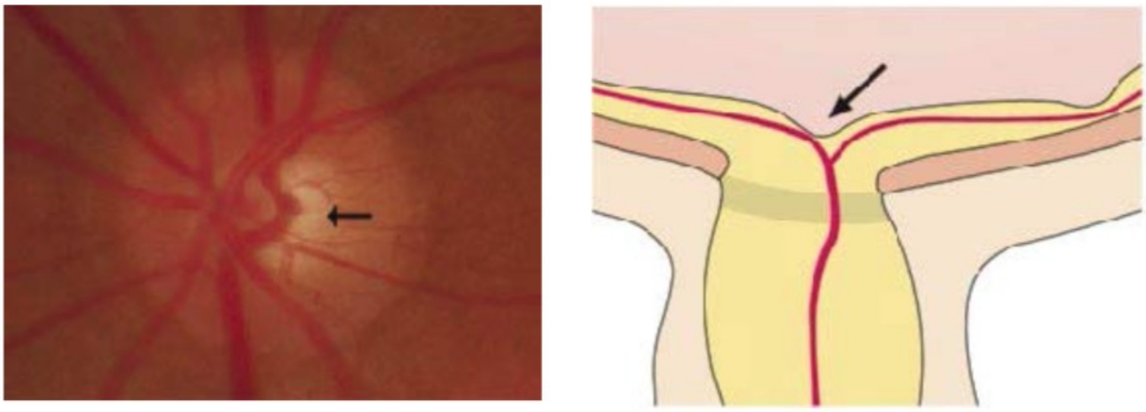


Figure 2: Funduscopy of a healthy eye, including a figure of the optic cup (9: p.237).
The arrow indicates the cup in both pictures. The cup forms a small, white depression in the center of the optic disc, surrounded by the pink to orange tissue of the neuroretinal rim.

The pathophysiology of glaucoma can easily be explained with these before-mentioned physiological basics in mind and always comes down to a degeneration of retinal cells and their nerve fibers, which causes the glaucomatous symptoms.

1.1.4 Intraocular pressure

The intraocular pressure (IOP) is mainly determined by the volume of aqueous fluid and therefore by the balance between production of intraocular fluid and the outflow. The outflow of aqueous humour in turn, is influenced by the resistance in the trabecular meshwork and the episcleral venous pressure. To define physiological limits, the normal range of IOP was set in between 11 – 21 mmHg, at least for Caucasian population. (5)

It is estimated that about 4 – 10% of the population older than 40 years have an IOP over 21 mmHg, but do not show any glaucomatous changes. This condition is referred to as ocular hypertension (OHT). (5)

A large, multicentric trial (Ocular Hypertension Treatment Study) summarized in 'Kanski's Clinical Ophthalmology' (5), showed that patients suffering from OHT have a higher risk of developing glaucoma when compared to healthy subjects, with the IOP being the most important risk factor besides the age and central corneal thickness (CCT). The risk of suffering from glaucoma increases with increased IOP, age and with lower CCT. There are two explanations for the last mentioned fact. On the one hand lower CCT means higher risk because IOP is underestimated in common tonometry, especially in Goldmann applanation tonometry. On the other hand there might be associated factors in other anatomical structures such as a thinning of the lamina cribrosa.

Out of those three risk factors IOP plays the most crucial role in the progression of glaucomatous disease, as well as in its treatment, since it is the only modifiable factor.

The normal IOP pattern over a 24-hour period underlies a certain fluctuation, which is caused by physiological variation depending on the daytime, the heartbeat, blood pressure and respiration. The normal pattern seems to have a peak in the early morning hours and its lowest values in the afternoon and evening, which could be explained by the fact that the greatest amount of aqueous fluid is produced in the early morning. (5)
Some studies (13-15) also suggested that there could be a nightly increase in IOP, which is especially high in glaucomatous patients. Due to the fact that a continuous 24-hour IOP profile is quite difficult to assess, given the current diagnostic tools, such as the Goldmann applanation tonometry (GAT), these study groups used the TF CLS to evaluate the nightly changes of the dimension of ocular volume.
It is currently discussed whether these fluctuations have or have no impact on the progression of glaucomatous disease. A review done by Singh and Shrivastava (16) in 2009 compared the published literature at that time and came to the conclusion that: '… there is no conclusive evidence that IOP fluctuation/variation are independent risk factors for glaucoma progression. … A major factor limiting all analyses … is the inability to continuously measure IOP …' (16: p.84). The TF CLS is advertised to offer such a possibility, to continuously measure values correlating to the IOP profile. Tan et al (17) did a study in 2015 using the CLS and concluded that IOP fluctuations play a significant role in the progress of glaucoma.
The well recognized ophthalmological text book 'Kanski's Clinical Ophthalmology' (5) also summarizes in its latest issue that: 'Glaucomatous eyes exhibit greater than normal fluctuations, the extent of which is directly proportional to the likelihood of progressive visual field damage…' (5: p.307).
In the end the IOP, regardless of its fluctuations, stands as the most important modifiable factor in the treatment of glaucoma and is therefore also the most evaluated marker in the diagnosis of disease.

1.1.5 Diagnosis of glaucoma

The NICE (National Institute for Health and Care Excellence) (18) provides state-of-the-art guidelines for the NHS in England and Wales and states five main diagnostic pathways for people suffering from or suspected with POAG or OHT. These are: IOP measurement by GAT, pachymetry, gonioscopy, perimetry and assessment of the optic nerve.

The next section will especially be focused on different tonometry modalities since these have to be known to reasonably form an opinion on the value of the TF CLS. The other above-mentioned diagnostic tools will be introduced for the sake of completeness.

1.1.5.1 Tonometry

There are different methods for evaluating the IOP in a patient's eye. The most common modality is the Goldmann applanation tonometry (GAT). Its mechanics are based on the Imbert-Flick principle, which states that pressure (P) inside a sphere equals the force (F), which is used to flatten the sphere's surface divided by the area of the flattened zone (A); $P=F/A$. Based on this principle a Goldmann prism is used to flatten a predetermined area of 3.06 mm diameter of the bulbus with a measurable force applied to it, therefore making it possible to calculate the pressure, more specifically the IOP, from the known variables. The mentioned predetermined diameter of the flattened area was found to be ideal, regarding other factors like corneal rigidity and capillarity of the tear film cancelling each other out in that case and therefore allowing an optimal accuracy in measurements. The examination is done in a seated position and the patient's head has to be placed in a resting position. The device can be attached to the slit lamp and the GAT is strictly reserved to health care professionals and cannot be done in a domestic setting. Although the GAT can still be referred to as gold standard, there are some limitations, which have to be considered in its use. Beside some user-dependent problems and bias in the administration of the GAT, the most problematic source of error is the variation of central corneal thickness (CCT). While the calculations for the proper use of the GAT were made with the assumption of an average CCT of 520 µm, it has to be stated that different factors can lead to a slight deviation from this figure. (5)

A meta-analysis published in 2000 by Doughty and Zaman (19) found that the average CCT in healthy subjects ranges at 536 µm with a standard deviation of 31 µm. Furthermore they examined the influence of CCT especially on the evaluation of IOP by GAT and found that a 10% difference in CCT from a baseline of 535 µm results in 3,4 ± 0,9 mmHg variance in IOP. Thinner CCT results therefore in a lower IOP value. This phenomenon was found to play a much bigger role in patients suffering from ocular chronic diseases (especially POAG, OHT, normal tension glaucoma (NTG) and diabetes), than in healthy subjects. The study authors therefore suggested to make adjustments in these patients. The corrections were advised to be 2 or 3 mmHg for a 50 µm difference in CCT from a baseline of 535 µm.

Corneas tend to be thicker in patients suffering from OHT and thinner in NTG, additionally surgical interventions are altering the surface of the cornea and IOP is generally underestimated in these patients. Other factors influencing the outcome of GAT are different pathologies like corneal edema (underestimation of IOP) or astigmatism. Furthermore a wide margin between systolic and diastolic pulse pressure in ocular perfusion leads to rather large oscillations in interpreted values of the examination, which make it difficult to determine the true figure. Additionally pathophysiological factors like an iatrogenic obstruction in venous return and therefore an increased venous pressure (e.g. a tight collar, etc.) may lead to overestimation of IOP. (5)

There are several other forms of tonometry summarized in the most recent issue of 'Kanski's Clinical Ophthalmology' (5).

The pneumotonometry uses the same principle as the GAT, with the difference being that the area of the cornea is not compressed by a prism, but rather by a jet of air.

There is another device using the mechanism of the pneumotonometer in the ocular response analyzer. With two sequential measurements the so-called corneal hysteresis is assessed, which is thought to be a superior marker for the progression of glaucoma and is derived from geometrical and viscoelastic attributes of the cornea.

Another device using the initial idea of GAT is the portable applanation tonometry, also Perkins tonometer, which uses a Goldmann prism and a portable light source. It is mainly used in bed-bound and anaesthetized patients.

The electronic identation/applanation tonometer is also a portable option for evaluation of IOP. It has a probe tip, which simultaneously measures and applies the force to the cornea.
A device quite easy to use and even usable by the patients themselves is the rebound tonometry, which uses a small plastic ball wielded towards the cornea. The deceleration of the ball is proportional to the IOP.
A rather new device is the DCT (dynamic contour tonometry), which uses a surface matching the normal contour of the cornea and not a prism to flatten the surface of the cornea. The pressure applied is then just measured by a pressure sensor. Studies actually showed that this modality may provide a more accurate option in comparison to GAT. Additionally the DCT is relatively independent of corneal biomechanical factors.
There are also reports on implantable tonometers, but none of it has yet made it into everyday clinical use.
Although there are several alternatives to GAT, it still remains the gold standard of IOP measurement.

One of the problems with current devices is, that it is quite challenging to obtain 24-hour IOP profiles. As stated before, the IOP undergoes fluctuations during a normal day. Additionally it is suspected (20-22) that the highest IOP, and therefore the most relevant values, can be found outside of office hours.
The recording of a 24-hour profile could help detecting both, fluctuations and outside office hours IOP peaks. However, the current possibilities to obtain a 24-hour profile are restricted due to the need of a sleeping laboratory, which is quite expensive and inconvenient for the patient. The examinations are usually carried out with GAT, Perkins tonometry, or other conventional tonometry modalities. The patient needs to be awake while these measurements are performed, therefore disturbing the physiological day and night rhythm. (20)
Another option is to obtain the IOP with self-tonometry devices by the patients themselves. However, this requires good compliance of the patient and especially older patients have problems with the technical aspect of self-tonometry. Furthermore it does not provide a solution for obtaining undisturbed measurements during the night period. (20)

There have been discussions about implantable sensors continuously measuring the IOP. Besides uncertainty regarding ethical aspects, cost efficiency and evaluation of the potential target population, no device emerged onto the market for clinical routine yet. (23)

The device we are doing our study on, the TF CLS, offers a new option in the evaluation of intraocular volume changes, which uses a different approach and mechanics then all other modalities. Especially the potential ability to record a 24-hour pattern of IOP related values would be groundbreaking. If it turns out to be a valuable tool in the treatment of diseases it could revolutionize the diagnostics and follow-up in glaucoma.

1.1.5.2 Pachymetry

Pachymetry measures the central corneal thickness (CCT) either by optical or ultrasonic methods. (5) As mentioned before the CCT is a crucial aspect in the evaluation of IOP and the diagnosis of glaucoma.

1.1.5.3 Gonioscopy

Gonioscopy is used to evaluate the angle of the anterior chamber by the use of an optical instrument. There are other options like optical coherence tomography (OCT) or high-frequency ultrasound biomicroscopy (UBM) to assess the anterior chamber. It is suggested to use these modalities as an additional help and not to replace conventional gonioscopy. (5)
The goniolens used in gonioscopy eliminates total internal reflection (cornea – tear film – air), following the physical laws of deflection of light rays passing through two media with different refractive index, by having a similar refractive index as the cornea itself. The use of the lens (cornea – tear film – goniolens) makes it therefore possible to visualize the anterior chamber either directly or indirectly reflected via mirrors. The aim is to display the angle structures and to evaluate the angle width, which is especially important in the differentiation between POAG and PACG. (5)

1.1.5.4 Perimetry

Perimetry is basically used to determine the visual field of a patient and therefore the functionality of the retinal cells and the optic nerve. If there are any scotomas, which are areas with reduced or total loss of vision, a possible damage of the optic neural pathway on any level is highly likely. There are different testing algorithms used for different pathologies, with the glaucoma pattern especially observing the central and paracentral visual field, since most defects in glaucoma happen to be found within 25 degrees of the fixation point. (5)

1.1.5.5 Evaluation of the optic nerve

The optic nerve head can be examined by fundoscopy or fundus photography. The most important terms regarding the evaluation of the optic nerve should be explained within this section. (5)

The neuroretinal rim (NRR) is the tissue between the outer line of the cup and the most eccentric margin of the disc. Usually the NRR follows the 'ISNT-rule', which states that the inferior rim is the broadest, followed by the superior, nasal and temporal part.

The cup/disc ratio (C/D ratio) describes the proportion of the vertical diameter of the cup to the vertical diameter of the disc. Only 2% of population show a C/D ratio of 0.7 or greater. Asymmetries of 0.2 or more between both eyes should be further evaluated.

The optic disc size is another substantial parameter in judging the C/D ratio and is additionally a prognostic factor on its own. In theory large discs are thought to be more sensitive than discs with smaller diameter. The normal vertical diameter in white population is 1.5 – 1.7 mm.

Glaucomatous changes include different appearances of the disc and the cup itself like increasing cup size (Figure 3) or notching of the disc, additionally to other non-specific showings (haemorrhages in the disc, bayoneting (Figure 3), vein collaterals, etc.). Furthermore peripapillary changes in the tissue surrounding the optic nerve head could be another marker for early damages in glaucomatous patients. The retinal nerve fiber layer (RNFL) can be damaged as well, which can be seen in slit lamp examinations or in optical coherence tomography (OCT).

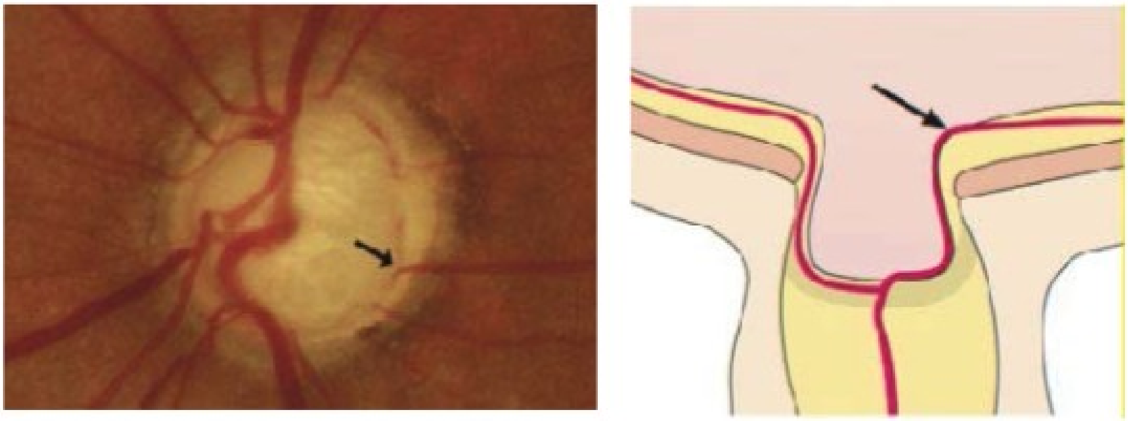


Figure 3: Funduscopy of a glaucomatous eye, including a figure of the optic cup (9: p.239). Enlargement of the cup and even the disk itself is one of the main findings in glaucomatous eyes. The arrow indicates bayoneting of a vessel, meaning that the vessel shows a sharp angle when descending into the cup. The picture is especially impressive when compared to the picture of a healthy subject (**Figure 2**).

1.1.6 Treatment of glaucoma

In this section the available treatment options will be concisely introduced to build a general comprehension of glaucomatous diseases.

1.1.6.1 Medical treatment

1.1.6.1.1 Prostaglandin derivates

Prostaglandins (Latanoprost, Travoprost, Bimatoprost, Tafluprost) are mainly lowering the IOP via enhancing the uveoscleral aqueous outflow and are typically chosen for first-line therapy. Prostaglandins are administered topically and are usually used once a day. The most common adverse side effects are conjunctivial hyperaemia and hyperpigmentation of eyelashes, periorbital skin and even the iris, whereas systemic side effects, including headaches, are very rare. (5)

1.1.6.1.2 Beta-blockers

Topical beta-blockers (Timolol, Betaxolol, Levobunolol, Carteolol, Metipranolol) reduce IOP by decreasing the amount of aqueous fluid produced by blocking adrenergic receptors in the ciliary epithelium. In some cases the effectiveness of the drug decreases with time (tachyphylaxis), especially when added to an already administered systemic beta-blocker. The drug should not be taken in the evening, since it may negatively influence the eyes perfusion by lowering the local perfusion pressure and since aqueous fluid production is rather low during the nighttime anyway. Beta-blockers are sometimes chosen as first-line therapy due to the cosmetic concerns of using prostaglandins. Ocular side effects are rare and may include allergy or punctate keratitis. Systemic adverse events are also quite seldomly reported, but can even become life threatening conditions such as brochospasm, especially in patients suffering from asthma. Additionally it has been reported that the use of topical beta-blockers can have systemic cardiovascular effects (bradycardia, worsening of heart failure, hypotension or blocks in the hearts conduction system) and even increases cardiovascular mortality. Other side effects may include sleep disorders, mental health problems and other vegetative effects. (5)

1.1.6.1.3 Alpha-2 agonists

Alpha-2 agonists (Brimonidine, Apraclonidine) are, similar to beta-blockers, also decreasing the aqueous fluid production via taking effect on the ciliary epithelium. Additionally they also increase aqueous outflow via the uveoscleral pathway and are discussed to have a neuroprotective effect. Alpha-2 agonists are able to cross the blood-brain barrier causing mental side effects and severe hypertension. Alpha-2 agonists have therefore to be used with caution, especially in young patients, patients with vascular insufficiency and in patients using MAO-inhibitors. (5)

1.1.6.1.4 Carbonic anhydrase inhibitors (CAI)

These agents (Dorzolamide, Brinzolamide) lower secretion of aqueous fluid by inhibiting one of the key enzymes in its production. CAIs are either used three times a day as a monotherapy, or twice a day as an adjunctive treatment. Topical CAI agents should not be combined with systemic CAIs. Renal impairment is rare but possible, as well as allergic reactions, especially since CAIs are chemically related to sulfonamide antibiotics. These side effects become even more important when systemic CAIs (Acetazolamide, Dichlorphenamide, Methazolamide) are used for therapy of acute glaucoma. Important side effects in the systemic use of CAIs include angle closure, paraesthesia, hypokalemia, gastrointestinal symptoms and bone marrow suppression. (5)

1.1.6.1.5 Cholinergic Agonists

These drugs are also referred to as miotics (Pilocarpine, Carbachol) and are nowadays especially used in angle closure glaucoma. Contraction of the sphincter pupillae opens the angle in theory and therefore promotes aqueous outflow. Local side effects include miosis, myopic shift and worsening of visual defects. Systemic side effects are rare and include typical cholinergic side effects (confusion, bradycardia, bronchospasm, gastrointestinal and urinary symptoms). (5)

1.1.6.1.6 Osmotic agents

Osmotic agents such as Mannitol, Glycerol and Isosorbide are limited to acute situations where an immediate decrease of IOP has to be achieved, which is not possible by other means. Side effects include cardiovascular overload with its related symptoms and urinary retention. (5)

1.1.6.1.7 Combined preparations

Combined preparations of two topical agents like beta-blockers, prostaglandine-derivates, CAIs, alpha-2 blockers or miotics are available to increase compliance and for patients convenience. (5)

1.1.6.2 Surgical treatment

1.1.6.2.1 Laser therapy

There are different treatment options available in glaucoma patients using laser (5).

In laser trabeculoplasty the aim is to enhance the aqueous fluid outflow within the trabecular meshwork by the use of laser beams. Laser trabeculoplasty is indicated in different open-angle configurations and especially when failure or a lack of compliance of medical therapy is present. It can be established as adjunctive therapy and is increasingly discussed as primary therapeutic option. Laser iridotomy on the one hand is used in similar fashion in angle closure configurations on the iris rather than the trabecualar meshwork due to the different pathophysiological mechanism.

Laser iridoplasty on the other hand is performed to create a larger anterior chamber by causing contractions in the iris. It is commonly used in acute angle closure to achieve immediate relief.

Diode laser cycloablation aims to destroy parts of the secretory ciliary epithelium and therefore to reduce the production of aqueous fluid. It is mainly used in patients with end-stage secondary glaucoma and poor visual ability, especially to reduce pain.

1.1.6.2.2 Trabeculectomy

Surgical treatment comes second after medical and laser therapy have failed, were insufficient or have at least been considered and decided to not be suitable. Trabeculectomy is the current standard and most used surgical procedure for glaucoma surgery, especially for POAG. It targets a faster drainage of aqueous fluid and therefore a decrease of IOP. Historically it was first performed to create drainage of aqueous fluid through the canal of Schlemm by excision of parts of the trabecular meshwork. Already back then it was discovered that a sub-conjunctival bleb formed after the surgery was completed. The assumption was made that drainage occurred through the sub-conjunctival space, although the exact mechanisms were not and are still not understood fully today. The technique used nowadays was already described over 50 years ago and still stands valid, although some improvements have been made and different styles emerged. The basic principle of this surgical procedure is that a small pocket under the conjunctiva is formed and treated with topical chemotherapeutics or other antimitotic agents to achieve fibrosis and persistence of the bleb. A sclerotomy is done and is later sealed again with a scleral tissue flap to enter the anterior chamber and to obtain a passage for aqueous fluid to flow to and drain via the sub-conjunctival space. (5, 24)

There is another surgical option, which preserves the trabecular meshwork and is therefore called non-penetrating filtration surgery. In this technique overfiltration, which is a possible side effect of trabeculectomy, is reduced by not entering the anterior chamber. A scleral flap is excised as far as leaving behind a thin layer of trabeculum and/or Descemet-membrane, which is the basal membrane of the cornea (25), through which aqueous fluid can diffuse into the sub-conjunctival space. (5)

Drainage shunts are another alternative to common trabeculectomy. The aim is to implant a tube, some even containing pressure sensitive valves, to create drainage of aqueous fluid. (5)

1.1.7 Classification of glaucoma

The main differentiation in primary types of glaucoma is made between primary open-angle glaucoma (POAG) and primary angle closure glaucoma (PACG). Additionally there is a condition named ocular hypertension, which may be a precursor for manifest glaucoma and was already mentioned before. Furthermore there is the term of normal-tension glaucoma (NTG). Secondary glaucoma types have to be differentiated from the above. (5)

1.1.7.1 POAG

1.1.7.1.1 Definition

To be defined as POAG the patient has to be found to have (5):

- an IOP of > 21 mmHg at some stage
- glaucomatous optic nerve damage (not due to secondary glaucoma or a non-glaucomatous cause) and retinal nerve fiber loss
- an open anterior chamber angle
- characteristic visual field loss

1.1.7.1.2 Pathophysiology

As the name already suggests this type is characterized by its open anterior chamber angle, meaning that no obstruction can be seen in clinical examination. However, there is an elevation in the outflow resistance within the trabecular meshwork with a frequently observed consecutive raise in IOP. (5)
The increase in IOP, especially if chronically increased, causes degeneration of retinal ganglion cells and retinal nerve fiber loss with decreasing width of the neuroretinal rim and evenly enlargement of the cup becoming the first detectable signs in fundoscopy. (12)

Direct mechanical damage, which is especially high at the passage of nerve fibers coming through the lamina cribrosa, and ischemia, caused by the compression of vessels supplying the optic nerve, are the two main mechanisms leading to cell death. Interestingly it can be observed that not only retinal cells are damaged, but that also nerve cells in the lateral geniculate nucleus and along the visual system, as far back as to the visual cortex, get impaired. Furthermore it was found that retinal cells are going down rather through apoptosis than necrosis. Both statements suggest that it is not just the direct influence of increased pressure or ischemia, but also the rearrangement and alterations in the environment of the cells leading to their death. The current theory states that after an initial injury astrocytes and glial cells begin to proliferate, as well as the extracellular matrix of the lamina cribrosa being rearranged. All of this leads to a reduction in axoplasmatic flow causing not just an insufficiency in supply of nutrients, but also a shortcoming in the removal of metabolic end products, increased oxidative stress and the initiation of an immune response. Furthermore a reduced supply of neurotransmitters and a trophic insufficiency are doing their part. This factors result in degeneration of retinal and other nerve cells, a remodeling of the optic nerve head as described above and consecutive typical glaucomatous symptoms. (5, 12)

1.1.7.1.3 Risk factors

The most important risk factor is IOP, since it is also the only treatable factor in progression of primary glaucoma. Furthermore age, race and family history play a role in the likelihood of developing POAG. Additionally there has been found that some gene defects are likely to be associated with the familial clustering of POAG. Myopic eyes are associated with a higher incidence as well as diabetes and vascular diseases are thought to be linked to a higher risk of being inflicted with POAG. (5)

1.1.7.1.4 Prognosis

Patients suffering from POAG have a rather good prognosis, since most of them will not become blind. The prognosis varies within the time of diagnosis, the visual damage already present at diagnosis and the compliance in therapy. For white population the chance of becoming blind on both eyes when suffering from POAG ranges around 5 – 10%. (5)

1.1.7.2 PACG

1.1.7.2.1 Definition

The defining configuration in angle closure glaucoma is that the iris occludes the trabecular meshwork by forming an iridotrabecular contact (ITC), therefore limiting the aqueous fluid outflow. The progress of disease is expressed in three different stages: primary angle closure suspect, primary angle closure and primary angle-closure glaucoma. The distinction between those types is mainly based on severity of gonioscopy findings (especially ITC or peripheral anterior synechiae (PAS) between the iris and the trabecular meshwork), results of perimetry, status of the optic nerve and retinal nerve fibers and the IOP. Although the cause of obstruction lies not within the trabecular meshwork it can also degenerate with chronic angle-closure configuration and become an additional factor. (5)

1.1.7.2.2 Pathophysiology

There are different mechanisms leading to the development of angle closure. Basically the obstruction in aqueous outflow is not within the trabecular meshwork, as it is in POAG, but within the physiological pathway of aqueous fluid prior to this section. A relative pupillary block originates from a higher pressure in the posterior chamber when compared to the anterior chamber. This results from anatomical variations in most cases, where a rather shallow anterior chamber is present. The resulting failure of normal aqueous fluid flow and the consequently protrusion of the iris leads to closure of the chamber angle. An acute pupillary block can be caused by mydriasis either functionally or pharmacologically triggered, and can lead to extreme IOP values, which make immediate relief vital. Reduction of IOP by any means resolves the bowing of the iris, as far as there are no other pathologies causing an angle closure. A non-pupillary block is caused by anatomical variations of the iris, such as the plateau iris. The configuration of a plateau iris is defined as a rather flat plane of the iris, which automatically narrows the angle recess. In some cases it is rather hard to determine the specific pathomechanism since features of both before-mentioned mechanisms are present. Furthermore some patients show signs of both open angle glaucoma and angle-closure glaucoma, and the way of pathophysiology is therefore referred to as combined mechanism. (5, 9)

1.1.7.2.3 Risk factors

Risk factors include the age, gender and race, as referred to before. Family history and genetic reasons are not fully discovered yet, but there are signs of increased prevalence in affected families. Furthermore subjects with hypermetropic eyes are more likely to develop pupillary blocks, just as a short axial length of the eye means a shallow anterior chamber and therefore higher risk of angle closure. (5)

1.1.7.2.4 Prognosis

PACG is rather uncommon in Caucasian population and therefore most data on outcome is gathered in Asian patients. However, the data is still inconclusive, but assumptions are that PACG leads to more cases of visual field loss than POAG and therefore has a worse prognosis. (26)

1.1.7.3 NTG

1.1.7.3.1 Definition

NTG is a special case of POAG, in which IOP is elevated, but within its physiological range. Nevertheless patients show signs of damage of the optic nerve. This could mean that in those patients other factors than IOP alone are decisive for progression of disease and optic nerve damage. 30% of Caucasians and up to 60% of Japanese patients suffering from POAG may have normal IOP readings at time of initial diagnosis. In the end the distinction between NTG and POAG is solely based upon the obtained IOP values. Therefore extended evaluation of IOP should be considered, especially when just taking singular readings. Additionally it was found that some NTG patients show IOP spikes elevated upon its normal limits during the nighttime. (5)

1.1.7.3.2 Pathophysiology

The pathophysiological pathway of NTG is still not thoroughly explained. There are theories about vascular dysfunction, anomalies in the structure of nerve tissue or autoimmune diseases causing NTG. Additionally it was found that CCT is lower in patients diagnosed with NTG when compared to subjects suffering from POAG. This could mean that there is raised intraocular volume, which is damaging the optic nerve, but due to the thinner cornea the measured IOP remains within its normal range. (5)

1.1.7.4 Secondary glaucoma

1.1.7.4.1 Secondary open angle glaucoma

Secondary causes for open angle glaucoma can be divided into pre-trabecular, trabecular and post-trabecular obstruction. (5)

Pre-trabecular obstruction is caused by a membrane covering the trabecular meshwork, as in the process of extensive neovascularization or proliferation of fibrovascular tissue.

The reason for trabecular blockage is that some kind of material clogs the trabecular meshwork. Pigment, red blood cells, proteins and other material can cause blockage and consecutive degeneration of the trabecular meshwork.

Pseudoexfoliation syndrome (PXS) can also cause a trabecular obstruction and secondary open angle glaucoma. PXS is mostly seen in women over the age of 50 and is most common in Scandinavian countries and different parts of Africa with a prevalence of up to 5% for risk population. In PXS, pseudoexfoliative material, a fibrillary amyloid-like substance, is produced in abnormal cell metabolism. The material is deposited throughout the body and not just in the eye, therefore making it a systemic disease. It can be become relevant in ophthalmology when creating a trabecular blockage.

Elevated venous pressure, for whatever reason, is responsible for post-trabecular obstruction.

1.1.7.4.2 Secondary angle-closure glaucoma

In angle-closure glaucoma it has to be distinguished between secondary changes leading to pupillary block or not. Seclusio pupillae with extended synechiae after iridocyclitis, a subluxated lens and other rare occurrences lead to secondary angle-closure glaucoma with papillary block on the one hand. On the other hand secondary PAS due to inflammation, neoplastic changes and others can lead to secondary angle-closure glaucoma without pupillary block. (5)

1.2 *Current state of research regarding the evaluation of source of artifacts in TF output signal*

As mentioned in the section above, there is a great need for new diagnostic tools in the treatment of glaucoma. The TF CLS is addressing these needs and is therefore a very welcome alternative to conventional diagnostic methods. However, as with every new device, it has to be tested for its quality and especially its validity. Since some study groups potentially found artifacts in the output signal of the CLS, it has to be investigated which could be the triggering factors.

This was also the purpose of the trial, which we will write about in this paper. In the following section, we want to evaluate the current state of research regarding the source of artifacts in the CLS output.

The inventor of the TF lens Matteo Leonardi (27), already stated that the CLS also records the ocular pulsation (Figure 4), which can be distinguished rather clearly from the dimensional changes of ocular volume in its profile. The movements of the eyeball and blinking (Figure 4) are also causing known artifacts in the profile. Furthermore changes in biomechanical characteristics of the eyeball, like the central corneal thickness (CCT), the corneal diameter and the rigidity of the sclera, could influence to the output signal. (27, 28)

Faschinger and his team from the Department of Ophthalmology at the Medical University of Graz did several studies (29-33) regarding the TF contact lens. During their work they also came across the phenomenon that the CLS profile shows artifacts, which could not be attributed to blinking, ocular pulsation or movement artifacts. They already described this finding in their first CLS related publication made (29). There was no explanation in published data to be found, which could identify a reason for some of the spikes in the profile (Figure 4).

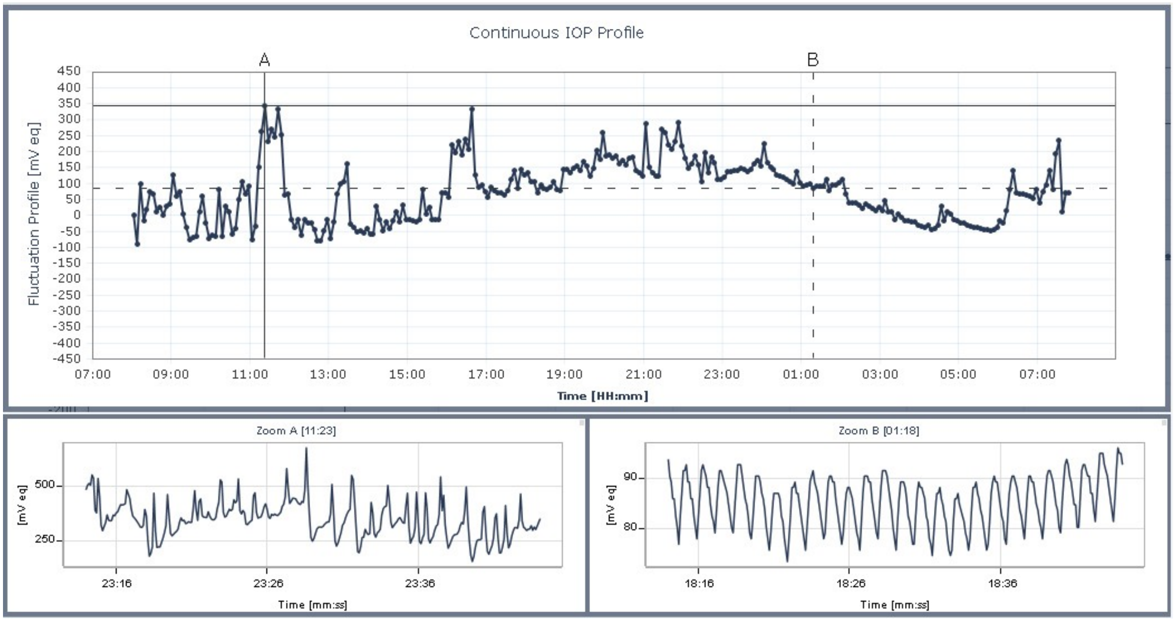


Figure 4: 'Spikes' in a Triggerfish profile
The y-axis shows the arbitrary unit mV eq, whereas the x-axis shows the time. The picture on the bottom left (Zoom A) shows approximately 30 seconds of the profile, were the spikes are representing the movements of the eye lids. The picture on the bottom right (Zoom B) shows a profile during night when eyes are closed. The quite regular fluctuations in Zoom B represent the ocular perfusion. The picture on top (Continuous IOP Profile) shows the whole 24-hour profile. The cause for those rather long lasting spikes shown at around 11am – 12pm and 4pm – 5pm in this picture remains unclear.
This is a profile obtained from an actual patient, courtesy of Prof. Faschinger.

There are rather large and prolonged spikes to be seen in the 24-hour profile depicted in Figure 4. Those spikes cannot be attributed to any of the above-mentioned factors and are to long lasting and regular to be put aside as mere noise.

Faschinger et al (30) summarized all the possible factors for these artifacts in listing movements of lid and eye, the prolonged period of wearing the CLS and especially during night time, movements of the CLS, changes in biomechanical characteristics and also changes in temperature or exposure to light. Since there were no studies made focusing on the factors temperature and light they sought to examine the influence of temperature on the CLS profile in one of their trials. (30)

In theory there should not be any influence at all, since the CLS includes compensating passive gauges in its structure, just as explained in section 2.1. To proof this principle, Leonardi, the inventor of the CLS, previously showed that there are just minimal changes in the profile within a range of 30°C (18°-45°C). (34)

In the trial done by Faschinger et al (30) the CLS profile did show significant changes due to the changes in temperature induced by a water bath thermostat. Those changes did not show any numerical relation, but there was a tendency of decreasing mV eq with increasing temperature and vice versa. The authors concluded that these changes may result out of the fact that the compensating gauges in the Wheatstone bridge are simply not able to compensate.

However, this is not an explanation why the results of this trial differed from the findings of Leonardis experiment.

To put the question of influence of temperature into relation to its importance, Faschinger et al mentioned several studies proofing that there are significant changes (around 1°C) in the surface temperature of the cornea during the day. There can even be a wider range (up to 3°C), especially when there is a bigger difference between inside and outside ambient temperature.

In the end, Faschinger et al concluded that there are always some up- or downward spikes to be found in the TF profiles, which cannot be sufficiently explained until today.

One of the first publications mentioning the TF CLS was written by Sit (35) from the Department of Ophthalmology at the Mayo Clinic in 2008. This paper already mentions several limitations and possible reasons for measurement noise in the obtained IOP profile. Among others light is also mentioned as potentially contributing factor. In his publication Sit cites a study done by Anjou, which suggests that light could be an important factor in the variance of circadian IOP rhythm in rabbits. Furthermore Sit mentions the difficulty to measure the IOP with the same accuracy in open and in closed eyes. In those two states the ocular surface features different environment in light exposure as well as in temperature and surface tension.

De Smedt et al (1) conducted a study on tolerability and functionality of the TF CLS in 2012 where they examined the results of the TF profile obtained in ten healthy subjects. The test persons had to keep track of their daily activities and had to record them inside a logbook. The authors described an occasional short-term drop of the profile during the daytime. This drop correlated to time periods where subjects carried out outdoor activities, which exposed them to sunlight. The question if light could influence the results of the profile was raised in the discussion. The authors of this study suggested that further studies with a larger study population should be done to investigate the impact of light on the TF CLS.

The before-mentioned findings were partly validated by Mansouri and Shaarawy (2) who described similar observations by almost using the same phrasing: ‘A characteristic short-term signal drop is occasionally noticed and correlates well with exposure to sunlight during outdoor activities’ (2: p.2).

Due to the fact that even after these mentioned trials (1, 2, 30, 35) the question still remains open, we decided to set up a experimental study examining the influence of light on the output of the CLS, which we will explain in the following section.

2 Material and Methods

2.1 The device: SENSIMED Triggerfish® Contact Lens Sensor

2.1.1 Overall

The device we used for our study was the Triggerfish® (TF) Sensor, constructed by the Swiss company SENSIMED. Its purpose is to continuously measure and record the changes of ocular volume dimensions over a period of 24-hours. The sensor records for 30 seconds every 5 minutes, creating 300 data points during this 5-minute span, which leads to 288 measurements over a 24-hour time span. (36)

This as continuous or at least pseudo-continuous considered measurement, in contrast to the static measurements of conventional devices like the Goldmann tonometry, is a ground breaking new approach towards diagnosis, evaluation and surveillance of glaucoma.

The principle is quite easy, as a soft, disposable, single-use, silicone contact lens, available in three base curves (steep, medium and flat), is used, which has a micro-sensor embedded to capture circumferential changes at the corneoscleral area. The signal is detected by an antenna, which is placed around the orbita. The antenna can just be attached to the bare skin like a patch. It receives the data wirelessly from the contact lens. Conventional glasses cannot be used during the measurement since every metal in close proximity to the antenna and the lens could interfere with data transmission. The antenna is connected to a portable recorder via a thin, flexible cable. The recorder can be worn underneath the clothes in a small pocket, which does not interfere with any daily activity. At the end of the 24-hour long time period, the data is transferred via Bluetooth to a computer using the SENSIMED software (Figure 5), where it can be analyzed. The output value of the profile is an arbitrary unit labelled mv eq (millivolt equivalent) and is provided on the y-axis of the profile. Time is provided on the x-axis. The data collected over 24-hours is displayed as a whole in the main window and two 30-second periods of measurement can be analyzed and compared separately in subordinated windows. It is also possible to combine two data profiles, to evaluate the changes between the two curves. (37)

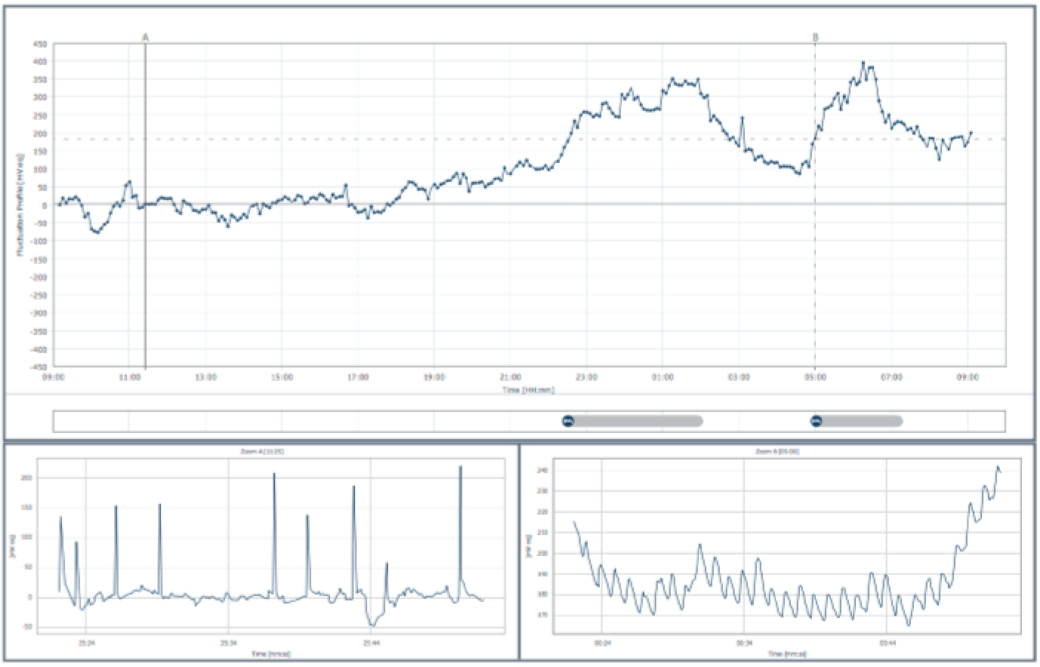


Figure 5: profile of the obtained data from a 24-hour measurement cycle displayed via the SENSIMED software (36).
Even in this picture, which is displayed on the SENSIMED website, fluctuations and small spikes can be seen in the 24-hour profile (graph on top). It remains open if this represents the actual IOP or if these fluctuations are artifacts.

The whole installation offers a non-invasive, practical and fairly good tolerable system to perform before-mentioned 24-hour measurements. It can be easily attached and detached by healthcare professionals and is suitable for an outpatient use, so that patients do not have to be hospitalized while performing the examination. (37)
The SENSIMED TF Contact Lens Sensor was approved by European authorities in 2009 receiving the Class IIa device CE-mark and was from then on available for clinical use. (38) The device was also approved by the U.S. Food and Drug Administration (FDA) in 2016. (39)

2.1.2 Basic principle and technical details behind the TF system

The idea of the TF contact lens lays in the principle of spherical deformation in the corneal curvature, which is assumed to be a direct result of changes in IOP. Hjortdal and Jense (40) conducted a study in 1995, which focused on the biomechanics of the human cornea. As part of it, the connection to IOP changes was also evaluated. Another study, conducted by Lam and Douthwaite in 1997 (41), examined the relation of IOP and changes in corneal curvature more in detail. The constructors of the contact lens however, analyzed the two previous

mentioned papers and various other studies, which focused on the correlation between IOP and the changes in corneal curvature, and Leonardi et al (42) summarized as follows: ‘an IOP change of 1 mm Hg causes a change of central cornealradius [sic!] of curvature of approximately 3 µm (over a typical radius of 7.8 mm)’ (42: p.3114).
On this assumption they evaluated the idea of a soft contact lens, which embeds strain gauges in a Wheatstone bridge configuration to measure changes in electric resistance.

Strain is the principle of the deformation, more specific a change in length, of a specimen due to a force applied to the specimen. Strain can be either positive (extensile) or negative (compressive) and it is basically a dimensionless unit, although it can be expressed in units of length measurement. In reality the dimension of strain is usually very small and therefore expressed as percentage, parts per million or microstrain, which is e x 10^{-6}, equaling 1 µm/m. There are several methods to measure strain, but the most common is to use a strain gauge (or also gage), which changes its electrical resistance in proportion to the amount of strain applied to the gauge. Those strain gauges can be arranged in the Wheatstone bridge, which means that there are four resistive arms (R_{1-4}), to which a Voltage (V_{EX}) is applied across the bridge (Figure 6). (43)

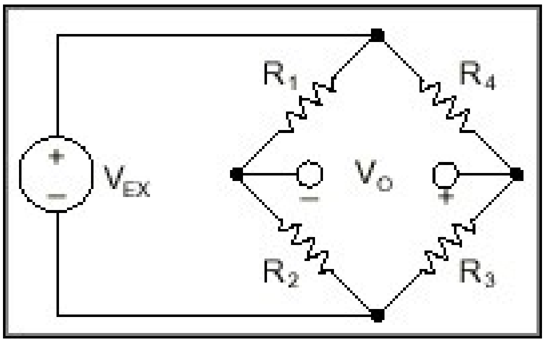


Figure 6: Wheatstone bridge (43).

R1 and R2 compose a voltage divider circuit, just as R3 and R4. The output Voltage (V_O) is dependent on the difference of resistance of either of the two voltage divider circuits. If the proportion of R1/R2 equals R3/R4 the output voltage is zero and the bridge is referred to as balanced. This also means, that any change of resistance in any of one of the four arms results in an output voltage

other than zero, and therefore in an unbalanced bridge. If R_{1-3} are resistances of known resistance and R_4 is the active strain gauge, the changing resistance of R_4 can be measured via the change in V_O. This principle is used to measure the strain in the active strain gauge. One problem however, is that the resistance of the strain gauge can also be altered by other means than just a mechanical force applying to it. The biggest factor here is temperature, as it leads to change in the resistance of the strain gauge. Firstly this problem is addressed by choosing materials, which minimize the effect of temperature on their structure. Secondly there is the possibility to use two strain gauges in the bridge, made out of the same material. The second strain gauge is placed transverse to the active strain gauge, to limit its effects on the active strain gauge. Since temperature affects both strain gauges in the same way, the ratio between both gauges does not change, and therefore also V_O does not change. (44)
This principle was applied in the TF Contact Lens Sensor prototype where the gauges were inserted into a soft lens just as shown in the following figure (Figure 7).

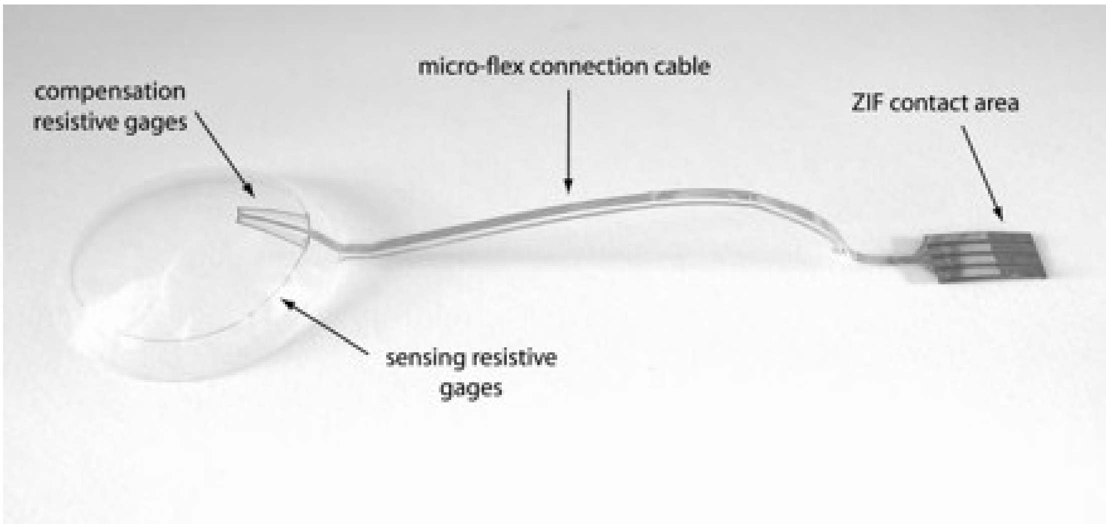


Figure 7: Prototype of the TF contact lens (42: p.3114).

There are several other forces interfering with the inserted lens, such as the atmospheric pressure on the lens, the hydrostatic pressure of tear film which acts against the lens, the surface tension resulting out of the cohesive forces between the molecules of the tear fluid and the adhesive forces between the tear fluid and the surface of the contact lens, gravity of the weight of the lens itself and the lid force, which acts on the lens each and every blink. The interaction between all those factors decides the fit of the lens when applied to the eye. In an ideal setting the lens is surrounded by tear film and therefore can adjust to any force acting on it while floating on the corneal surface. Due to this the lens will find a stable, but slightly eccentric position after every blink. (42)

The soft lens will follow every corneal deformation and Leonardi et al (42) have found that in this scenario the lens will solely have circumferential strain applied to it. Therefore the sensing strain gauges are constructed in a spherical ring around the center of the lens with a diameter of 11,5 mm, which is thought to be the average diameter of the cornea and therefore will place the ring close to the sclero-corneal junction zone, which is believed to show the most deformation with IOP changes. The compensating gauges, for compensation of any temperature-induced alteration of the sensing gauges, are placed radially, so that the strain affecting it is minimized (Figure 8).

The lens itself is made out of silicone, because silicone on the one hand possesses a very good oxygen permeability and on the other hand does not absorb water very good (0,2% in weight), which means that it is quite insensitive to the hydration level of its surroundings. Information gained from the platinum-titanium sensing gauges (V_O) is processed as mV eq and transferred via a microprocessor and a gold-antenna, which is used for transmitting of data and wireless power (Figure 8). This wireless approach was one of the key challenges to be solved within the development and therefore an application-specific integrated circuit (ASIC) was developed. This device was specifically designed by SENSIMED and it would lead too far to explain the working mechanics of this system in depth within this paper.

The whole system consisting of the gauges, antenna and microprocessor integrated in the silicone lens with a thickness of 400 µm in the center and 100 µm at the borders of the lens, is referred to as ‘Contact Lens Sensor’ (CLS). A loop antenna, which can be administered around the orbita of the patient and which is connected to the portable recorder unit, receives the data (10 Hz) and also provides the energy, via a magnetic field at 27 MHz for the CLS (Figure 9). (27)

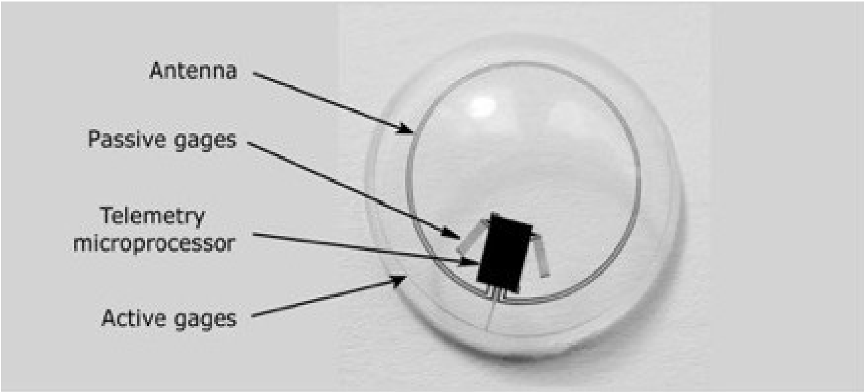
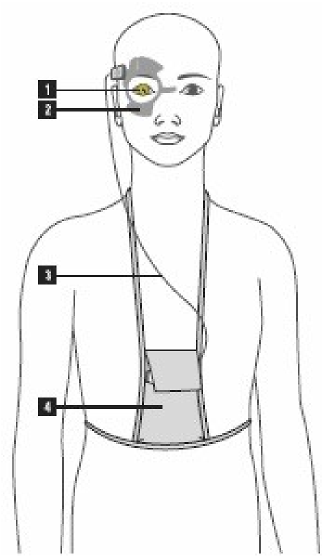


Figure 8: TF contact lens (27: p.434).



1. **TF contact lense**
2. **TF antenna**
3. **Connection to portable recorder**
4. **Portable recorder**

Figure 9: Full equipment (37).

2.1.3 Correlation between IOP and data output of the CLS (first in-vitro studies)

There have been several studies during the developmental process, showing how the data, received from the CLS, is correlating to the actual IOP of the eye. Representative for the outcome, the results of the study conducted by Leonardi et al in 2009 (27) are mentioned in this paper. The study group developed a model, in which the CLS was attached to enucleated pig eyes, which were cannulated to create an artificial IOP via saline instillation. To measure the IOP, a pressure sensor in the silicone tube containing the saline was used (Figure 10).

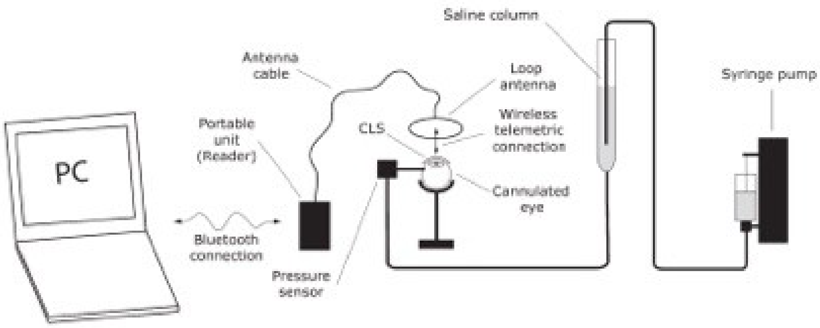


Figure 10: Study design of Leonardi et al (27: p.435).

The IOP was changed between 11 and 14 mmHg dynamically, within an interval of four seconds, in the first experiment. This scheme was supposed to simulate a physiological ocular pulse amplitude, which is about 3 mmHg and is centered at approximately 12,5 mmHg. The data was evaluated from both, the pressure sensor and the CLS, and it showed that there was a good correlation between those two parameters (Figure 11). The slight time delay was explained due to the fluidic resistance of saline circulating in the liquid circuit.

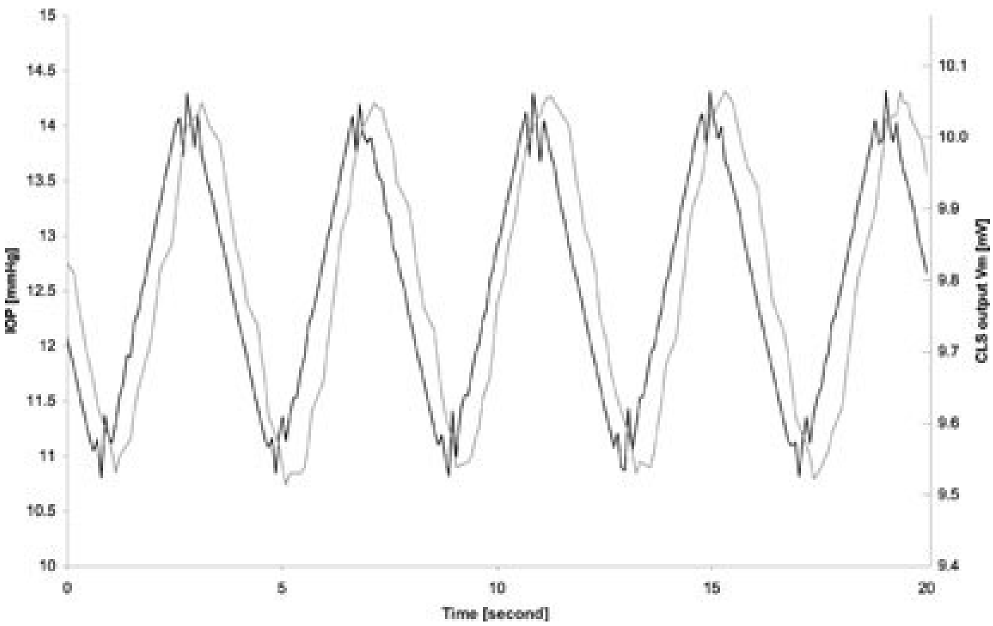


Figure 11: Correlation between IOP and CLS in a 3 mmHg range (27: p.435).
The CLS output (right y-axis), meassured in mV, correlates to the IOP (left y-axis), within a 20-second period and in a range of 3 mmHg changes, centering around 12,5 mmHg.

The second experiment featured static steps of 1 mmHg from 20 mmHg up to 30 mmHg, which was chosen because this range of IOP is widely encountered in patients suffering from glaucoma.

Whereas the mean IOP of the general population is around 16 mmHg, with a range from 11 – 21 mmHg, an IOP over 21 mmHg is considered as ocular hypertension and is associated with a higher risk of developing glaucoma. (5)
Just as in the first experiment, the graphs of IOP and the CLS output correlate (Figure 12).

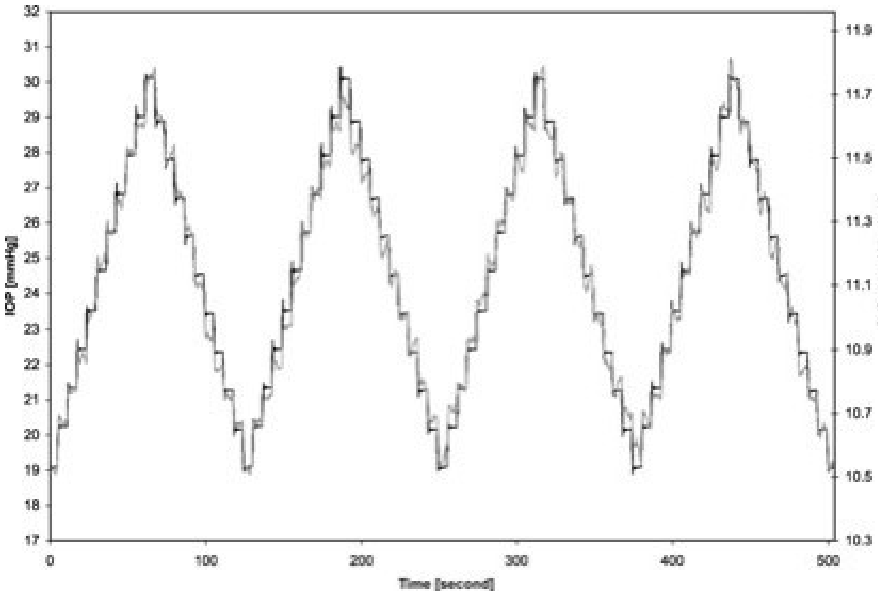


Figure 12: Correlation between IOP and CLS in a range from 20 to 30 mmHg (27: p.436)
The CLS output (right y-axis), measured in mV, correlates to the IOP (left y-axis), within a 500-second period and in a amplitude of 10 mmHg, ranging from 20 mmHg to 30 mmHg.

As a conclusion out of studying the behavior of the CLS on enucleated pig eyes Leonardi et al stated that: 'The results presented in this article show that the device is sufficiently sensitive to measure a signal equivalent to the human ocular pulsation and follows IOP variations in a reproducible way, in static and dynamic mode.' (27: p.436).
Additionally they found that: 'Hydration of the lens will not affect the measurement because we chose silicone, which does not absorb water.' (27: p.436), which is a vital statement for our study, since we decided to use the TF lens embedded in a fluid solution.

2.2 Experimental set-up

The test set-up was in some parts alike to the method used by Faschinger et al (30) in their effort to evaluate the influence of temperature on the TF CLS.

In our experimental set-up we used eight new TF CLS to obtain 24-hour measurements. This consequentially led to eight test runs, since the unique serial number of each lens has to be entered in order to start the measurement. This ensures that each lens, which is designed as a single-use product, is just used in one patient.

We removed the lens from its original glass container, where it was stored immersed in a fluid, but left it placed inside the original plastic protective case. The CLS was placed into a plastic box with its convex side facing upwards. We filled the plastic box with 0.9% NaCl-solution just that much that the lens was fully covered by fluid. It was then ensured that the lens was versatile and floating (Figure 14).

The antenna was attached approximately 1 – 1.5 cm above the CLS, taking care that it was placed well above the level of fluid, to prevent it getting in contact with the liquid and to ensure an orderly data transmission (Figure 14). The antenna was attached to the recording device and the software was started after entering the serial number. It was ensured that the measurement started properly, which is indicated by three LEDs on the recorder.

In order to determine the influence of temperature of the solution on the TF profile, we used the EBI310 USB temperature data logger by EBRO® with a measuring range of -30 °C to +75 °C and a sensitivity of ±0.2 °C within a range of -30 °C to +30°C and of ±0.5 °C beyond this range. (45)

One of two temperature probes was placed inside the box, with at least 10 cm distance to the lens, and the other probe as well as the data logger itself with a third internal probe, was placed beside to measure room temperature (Figure 13). The data logger was set to measure temperature in an interval of one minute over the full course of 24-hours.

To quantify the illuminance (luminous flux per unit area) we used the digital lux meter MS – 1500 by VOLTCRAFT®.

The lux meter was calibrated each time as recommended by the manufacturer before manual measurements were performed. Time points of measurements were determined by the test protocol.
The lens was shined on according to the protocol either by artificial light emitted by a conventional light bulb or a cold light bulb, or by sunlight.
It was ensured that the room was not entered during the measurements for whatever reason, besides rearranging the set-up (switching on/off the lights, opening/closing shutters) and taking measurements (lux meter). Additionally it was taken care that there were no vibrations applied to the experimental field in order to prevent any noise in the profile derived from movement of the lens.
All actions taken were documented inside a logbook.

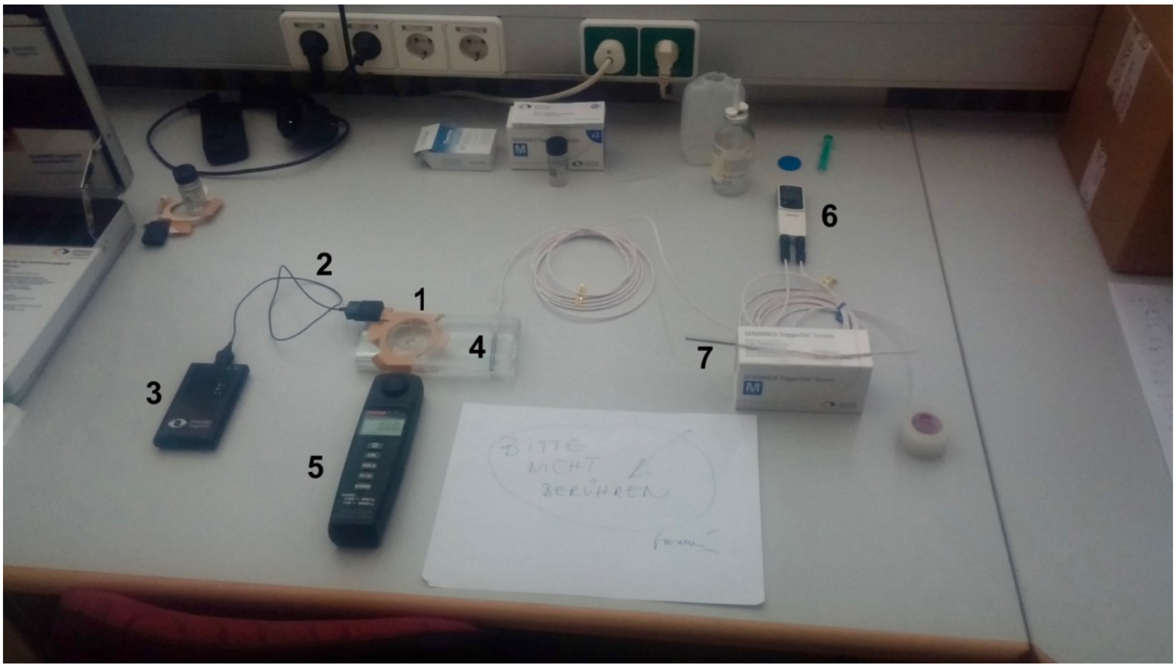


Figure 13: The general set-up of the experiment
1 – the antenna with the CLS in its middle; 2 – connecting cable to the recorder; 3 – recorder; 4 – plastic box filled with NaCl-solution and temperature probe; 5 – lux meter; 6 – temperature data logger; 7 – second external temperature probe

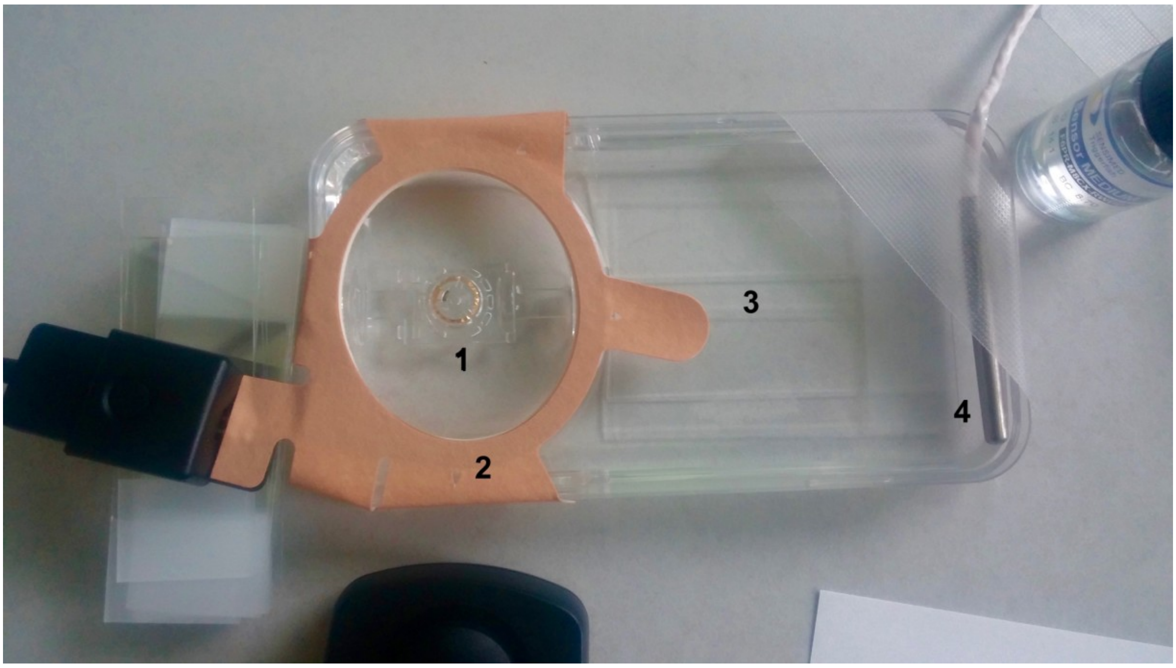


Figure 14: CLS set-up
1 – CLS in its original plastic cage, slightly submerged and floating; 2 – antenna; 3 – plastic box filled with NaCl solution; 4 – temperature probe inserted into the solution

2.3 Test protocol

The assumption, on which our experiment is based on, is that the exposure to light or to other connected confounding factors, is influencing the output signal of the CLS.

Since it is asked for that patients undergo their daily activities while wearing the TF CLS, it is highly likely that they will encounter direct sunlight or that they will spend part of their day in a room, which is lit by artificial light sources.

Our experiment is therefore set to examine the influence of natural sunlight or of different artificial light sources, with the possible confounding factor of an established electromagnetic field in the second case, on the TF profile.

The basic principle of our protocol was therefore to create different exposures to light during the 24-hour measurement period of the CLS. To obtain objective values the illuminance was measured every hour if no light was used and every 30 minutes if the room was illuminated by artificial light or sunlight.

The room we did our experiments in had its windows facing eastward, so that the CLS was not influenced by direct sunlight during noon and afternoon.

In trial number **one** (Figure 15) we started the measurement at 9am. The curtains to the room remained open until 8pm so that sunlight could pass through. Additionally we switched on artificial light sources for specific time periods during that span. A neon lamp, which was attached on the ceiling of the room, was switched on from 11am until 1pm. A desk lamp, with a conventional energy – saving lamp and placed close to the experimental set-up, was switched on from 6pm until 9pm (Figure 16). The desk lamp was rearranged after 30 minutes, since an evident raise of temperature of the fluid was noticed. From 9pm until 7am the room was kept dark, with the sun going down at 7:57pm and the sunrise at 5:53am. From 7am until the end of measurement at 9am the curtains were opened again.

Figure 15: Set-up for the first test run

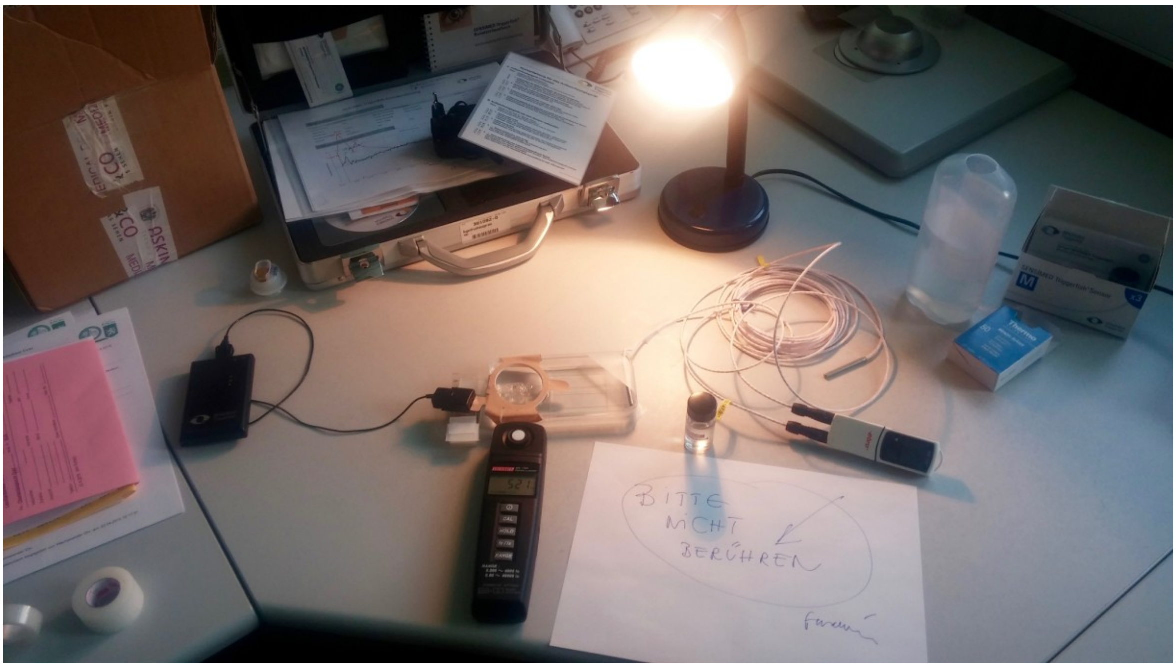


Figure 16: First test with desk lamp switched on

In the **second** trial we started the measurement at 8:10am. The curtains to the room remained open until 8pm. The neon lamp was switched on from 11am until 1pm and from 6pm until 9pm. From 9pm until 7am the room was kept dark, with the sunset at 8:03pm and the sunrise at 5:46am. At 7am the curtains were opened and the measurement stopped at 8:10am.

In the **third** trial we started the measurement at 8:41am. The curtains remained closed throughout the test cycle. The neon lamp was switched on from 12pm until 3:30pm and from 6pm until 9pm. The sun set at 8:21pm and rose at 5:25am. The measurement stopped at 8:41am the next day.

In trials **four** and **five** the same procedures as in experiment **three** were performed. Measurements were started at 8:53am and 7:35am, respectively. The curtains to the room remained closed throughout both experiments. The neon lamp was switched on from 12pm until 3:30pm in trial **four** and until 3pm in trial **five**. The lamp was then again turned on from 7pm until 9pm in both experiments alike. In trial **four** the sun set at 9:11pm and the sun rose at 5:17am. The sun set at 9:31pm and the sunrise was recorded at 5:05am on the day of trial **five**.

For trial **six** we tried to limit the variations of temperature throughout the test phase by placing the lens inside a polystyrene box (Figure 17). The test was started at 8:45am and the curtains and the box were opened for two hours at a time, starting from 10am until 12pm, from 2pm until 4pm and from 6pm until 8pm. In between those times the curtains and the polystrene box were closed. The sun went down at 8:55pm and rose at 5:09am. The curtains remained closed until the end of the measurement.

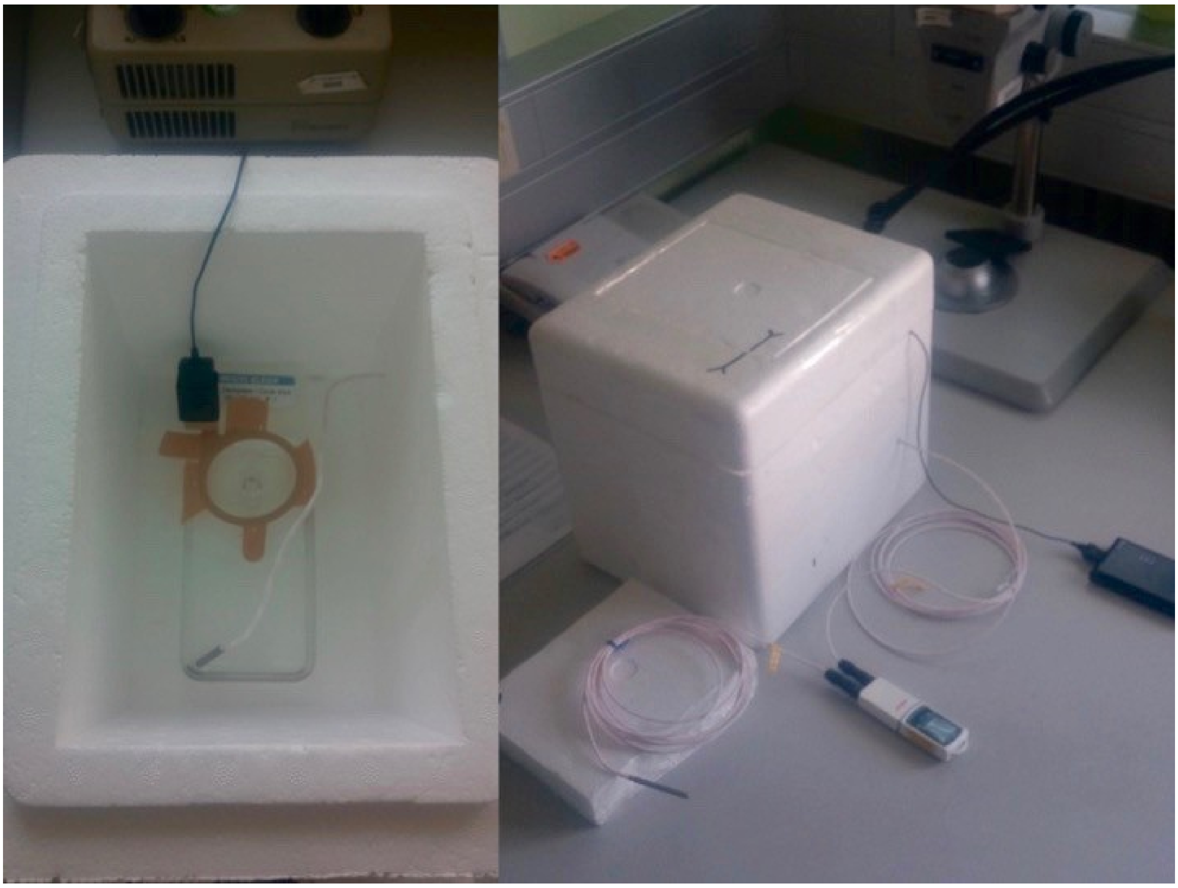


Figure 17: CLS placed inside a polystrene box
The CLS was placed inside a polystrene box, using the same set-up as in the other tests. The box could be closed during the dark periods of the experiment. To obtain lux the lux meter was placed inside a second box, identical to this one, which was arranged right next to the one containing the CLS during measurement points.

Trial **seven** was done in similar fashion with curtains and box opened from 11am until 1pm, 3pm to 5pm and 7pm to 9pm. On this day the sun set at 8:52pm and rose again at 5:14am.

For test **eight** a cold-light emitting lamp was used (Figure 18). The lens was set up without the use of a polystrene box and the curtains remained closed throughout the whole run.

The test was started at 11:45am and the cold-light lamp was turned on from 2pm until 4:30pm, 6pm to 7:30pm, 9pm until 10:30pm and on the next day from 8:30am to 10:30am. The sun set at 5:59pm and rose again at 7:25am.

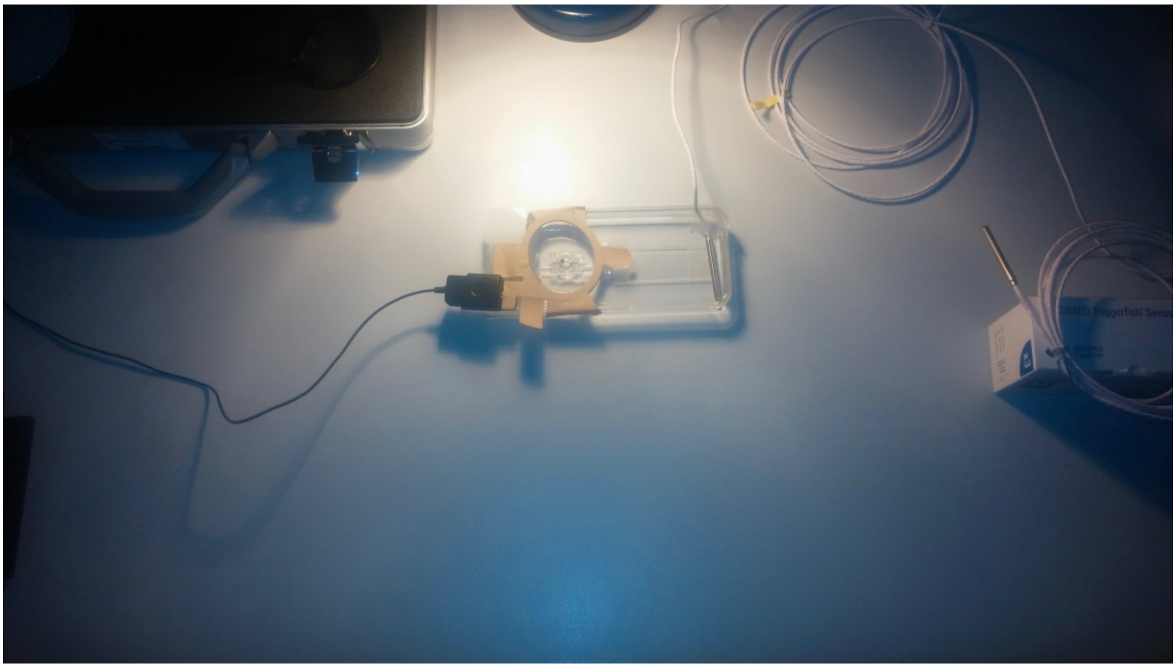


Figure 18: CLS set-up shined on by cold-light light source

2.4 Measurements and data analysis

All measurements and all arrangements were documented in a logbook. Illuminance was measured using the lux meter. Measurements were taken every hour and up to every 30 minutes when artificial light was turned on or the shutters were opened for sunlight to illuminate the room.

The temperature was automatically measured by the temperature data logger.

The obtained data was transferred to a laptop by using the USB port of the data logger. This data could be assessed as a PDF-file, was read with the Winlog.basic software created by the company EBRO® or was converted into an Excel-file. To read the TF profile the TF software (SENSIMED version 2) has to be used. Since the values cannot be transferred into an Excel-file automatically, we had to transfer the figures manually.

To analyse the data we used descriptive statistic with numerical description of the data, together with graphical depiction of every test run.

The figures obtained of the TF profile given as millivolt equivalents (mV eq), temperature in °C and illuminance given in lux (lx), are all classified as continuous metric values.

Evaluation of statistical data in graphic form was done by using MS Office Excel.

3 Results

All eight of the performed examinations showed useable data, although two CLS measurements were incomplete. Test **four** showed a disruption of measurement from 4:30pm until 9pm and the measurement in test **six** was interrupted from 4pm until 6pm. Both interruptions resolved and readings were resumed after the antenna was exchanged.

Temperature and lux measurements were carried out after the protocol and resulted in excellent workable data.

3.1 Test 1

In test **one**, where natural and artificial light sources were used, the TF profile showed a mean value of -3.78 mV eq (min -14.30 mV eq; max 4.10 mV eq; median -3.60 mV eq; SD: 2.91 mV eq; skewness: -0.622). The lux meter showed an average of 870 lx (min 0 lx; max 2772 lx; median 472 lx; SD: 871 lx; skewness 0.994). The temperature measurement showed a mean of 21.6°C (min 20.2 °C; max 22.8 °C; range 2.6 °C; median 21.5 °C; SD: 0.56 °C; skewness: 0.098).

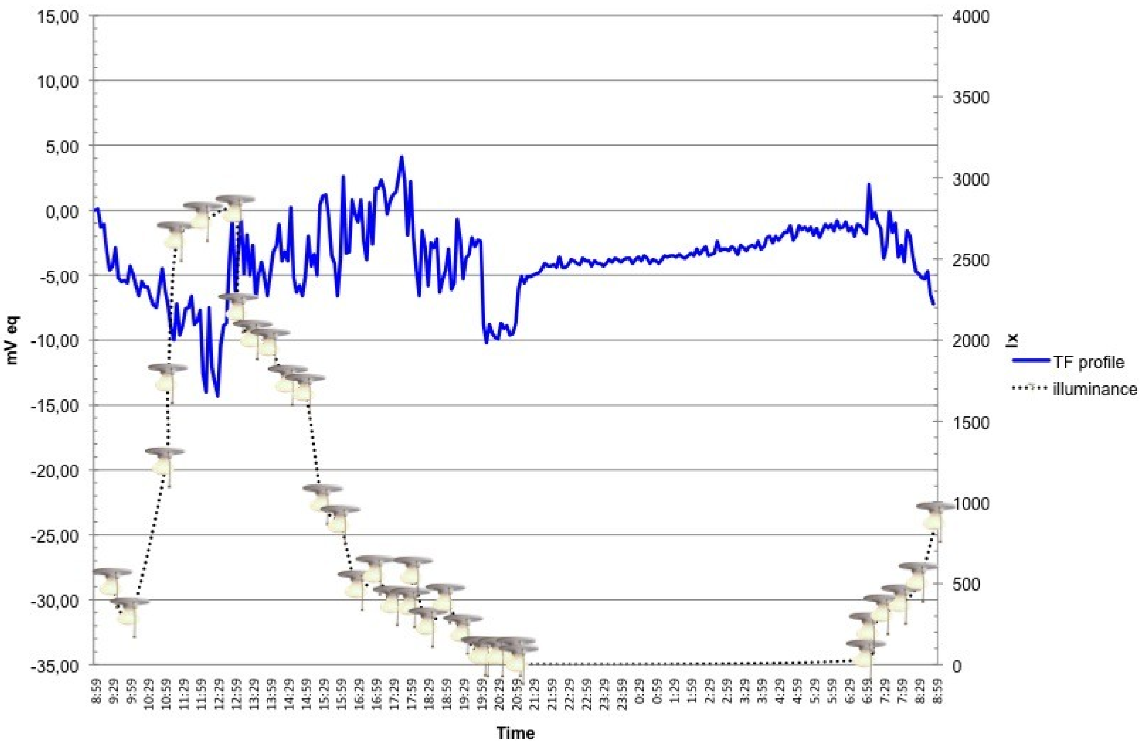


Figure 19: Test 1 – TF profile vs. illuminance
The black dotted line shows the progress of illuminance in lux (y-axis, right) and the light bulbs represent the exact measurement time points. The blue line shows the profile obtained by the CLS in mV eq (y-axis, left). Time is shown on the x-axis.

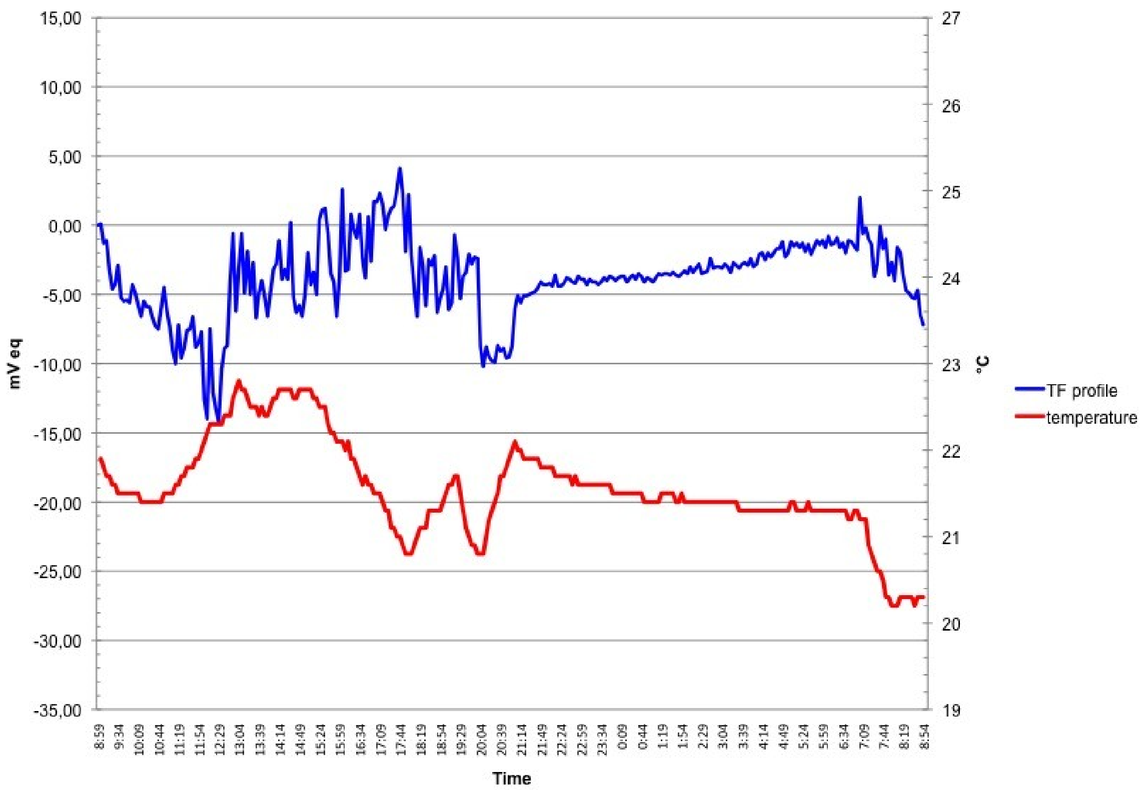


Figure 20: Test 1 – TF profile vs. temperature
The red graph shows the progress of temperature in °C (y-axis, right), whereas the blue line shows the profile obtained by the CLS in mV eq (y-axis, left). Time is shown on the x-axis.

3.2 Test 2

In the **second** test also natural and artificial light was used. The 24-hour profile obtained by the CLS showed a mean value of -2.34 mV eq (min -12.50 mV eq; max 4.80 mV eq; median -1.75 mV eq; SD: 3.58 mV eq; skewness: -0.772). The average value of lux was 1058 lx (min 0 lx; max 3380 lx; median 676 lx; SD: 865 lx; skewness 1.136). The temperature showed a mean of 22.3°C (min 20.9 °C; max 23.5 °C; range 2.6 °C; median 22.4 °C; SD: 0.74 °C; skewness: -0.039).

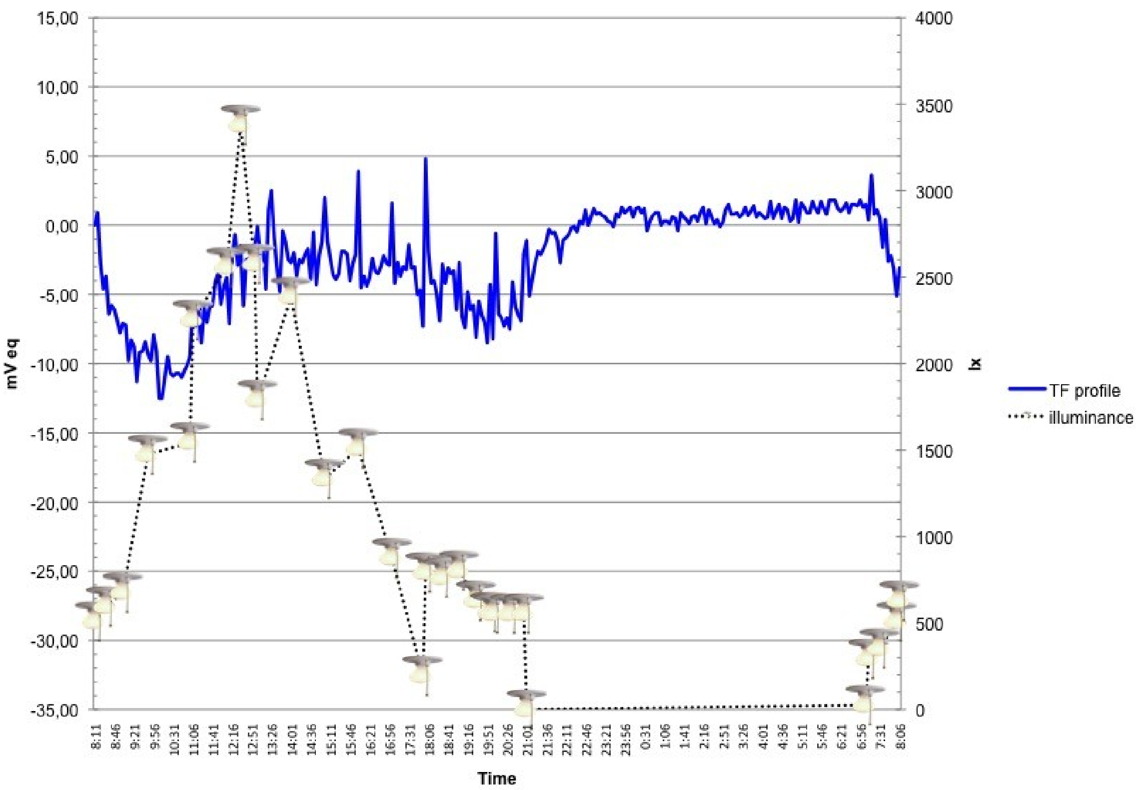


Figure 21: Test 2 – TF profile vs. illuminance

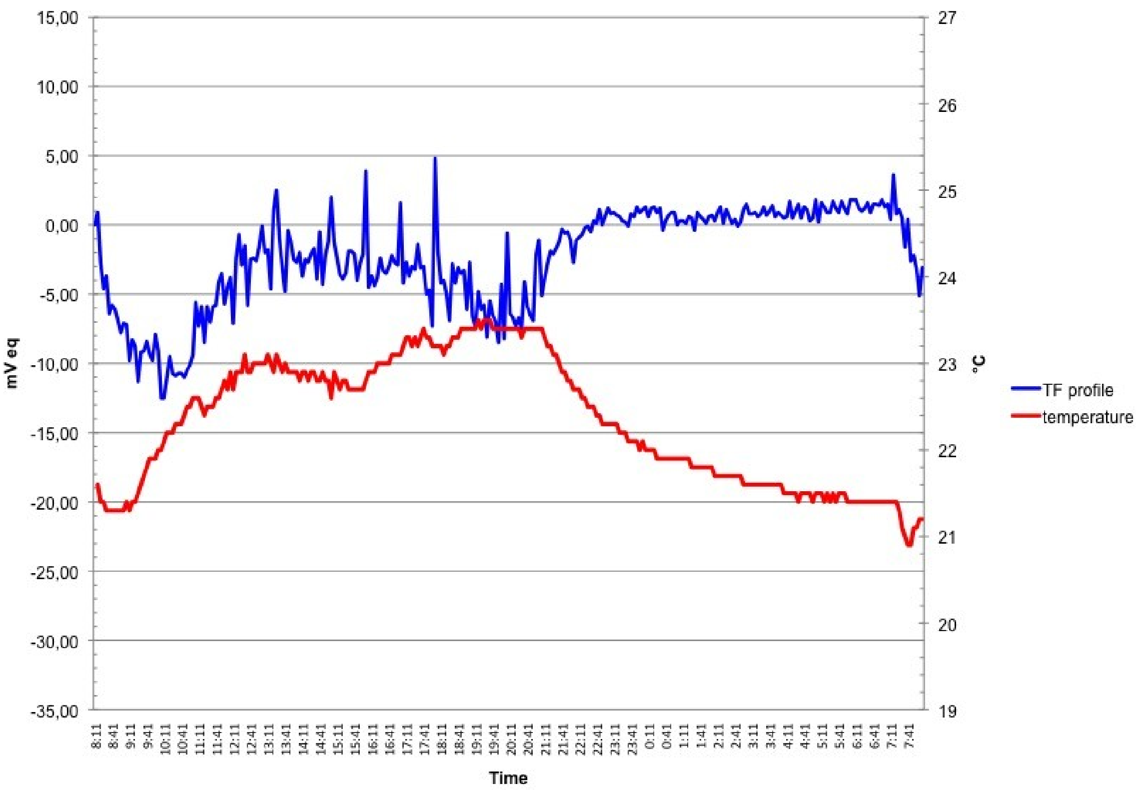


Figure 22: Test 2 – TF profile vs. temperature

3.3 Test 3

Test number **three** featured just artificial light and showed a mean mV eq value of -6.97 mV eq (min -10.50 mV eq; max 2.50 mV eq; median -7.00 mV eq; SD: 1.70 mV eq; skewness: 1.069). The average value of illuminance was 211 lx (min 0 lx; max 438 lx; median 31 lx; SD: 202 lx; skewness 0.084). Temperature showed a mean of 22.4°C (min 21.6 °C; max 23.8 °C; range 2.2 °C; median 22.5 °C; SD: 0.50 °C; skewness: 0.142).

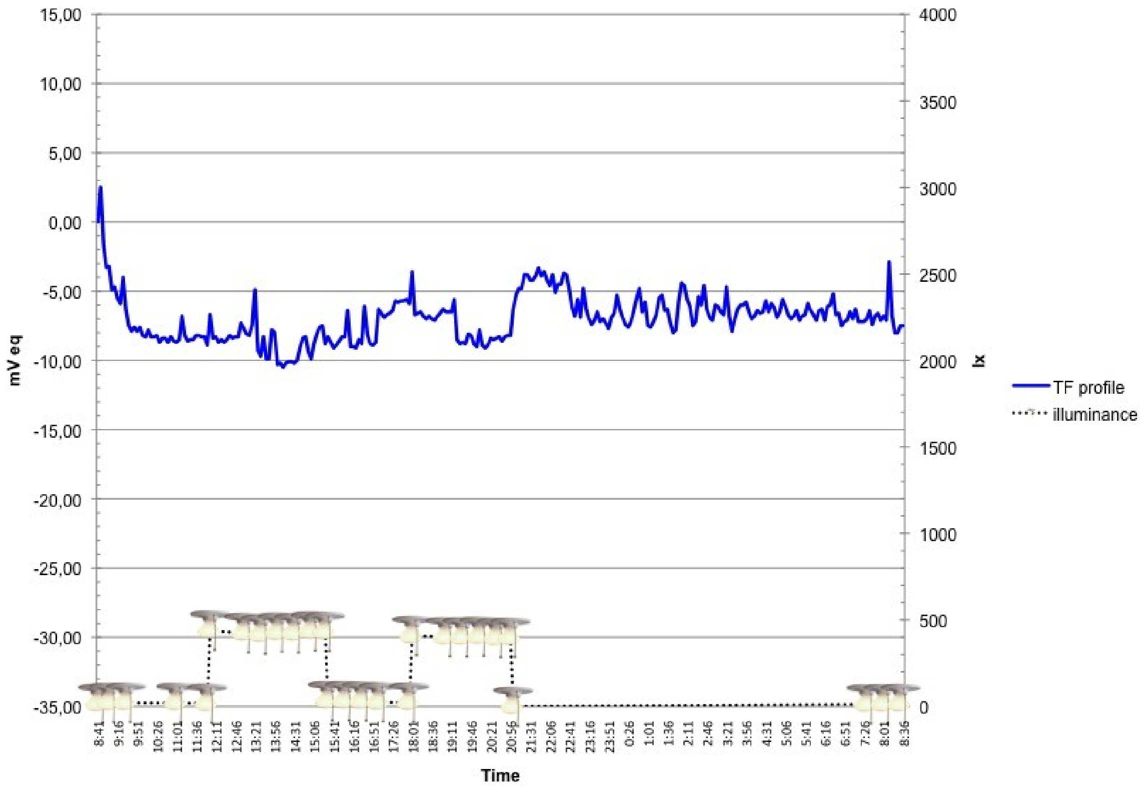


Figure 23: Test 3 – TF profile vs. illuminance

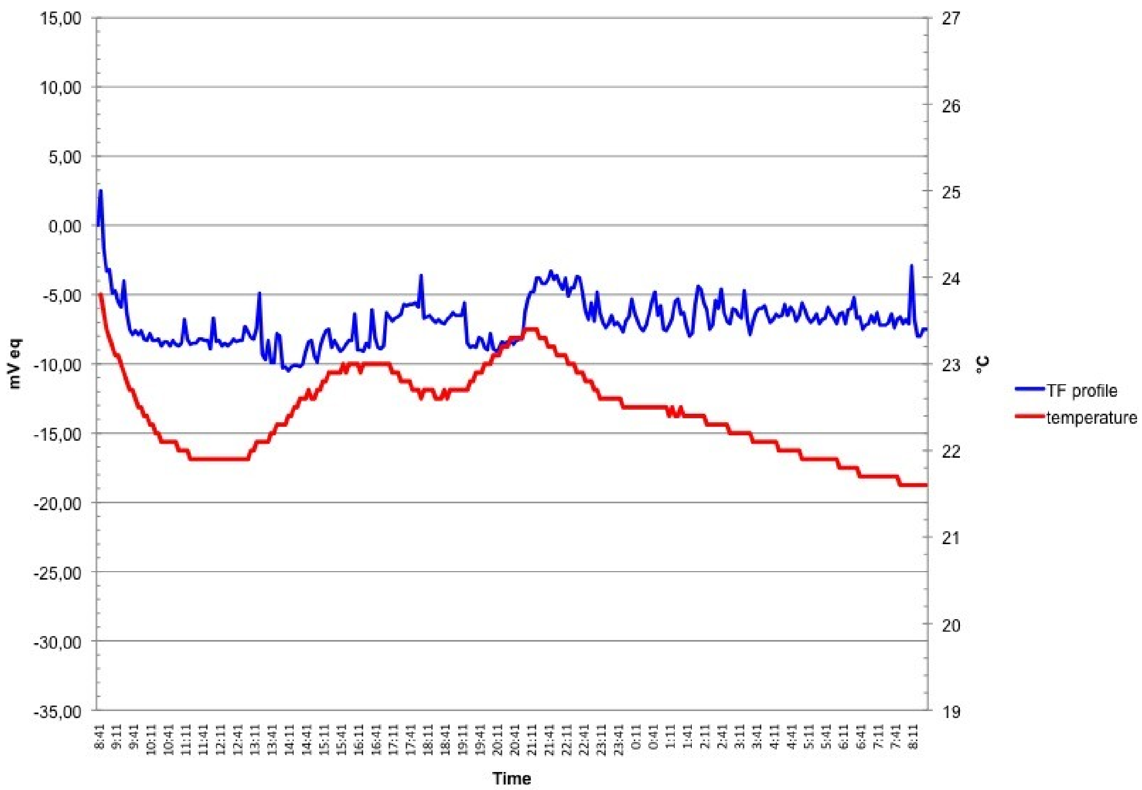


Figure 24: Test 3 – TF profile vs. temperature

3.4 Test 4

The **fourth** test was also done with just the neon light as an artificial light source. During this measurement period it came to a problem with the data transmission of the CLS. The measurement paused from 4pm until 9pm and resumed when the antenna was exchanged.

The remaining data of the experiment showed a mean mV eq value in the TF profile of -3.49 mV eq (min -9.95 mV eq; max 9.85 mV eq; median -3.82 mV eq; SD: 2.83 mV eq; skewness: 0.831). The mean lux value was 158 lx (min 0 lx; max 430 lx; median 20 lx; SD: 194 lx; skewness 0.553). Temperature of the solution showed a mean of 21.6°C (min 20.8 °C; max 23.1 °C; range 2.3 °C; median 21.5 °C; SD: 0.50 °C; skewness: 0.446).

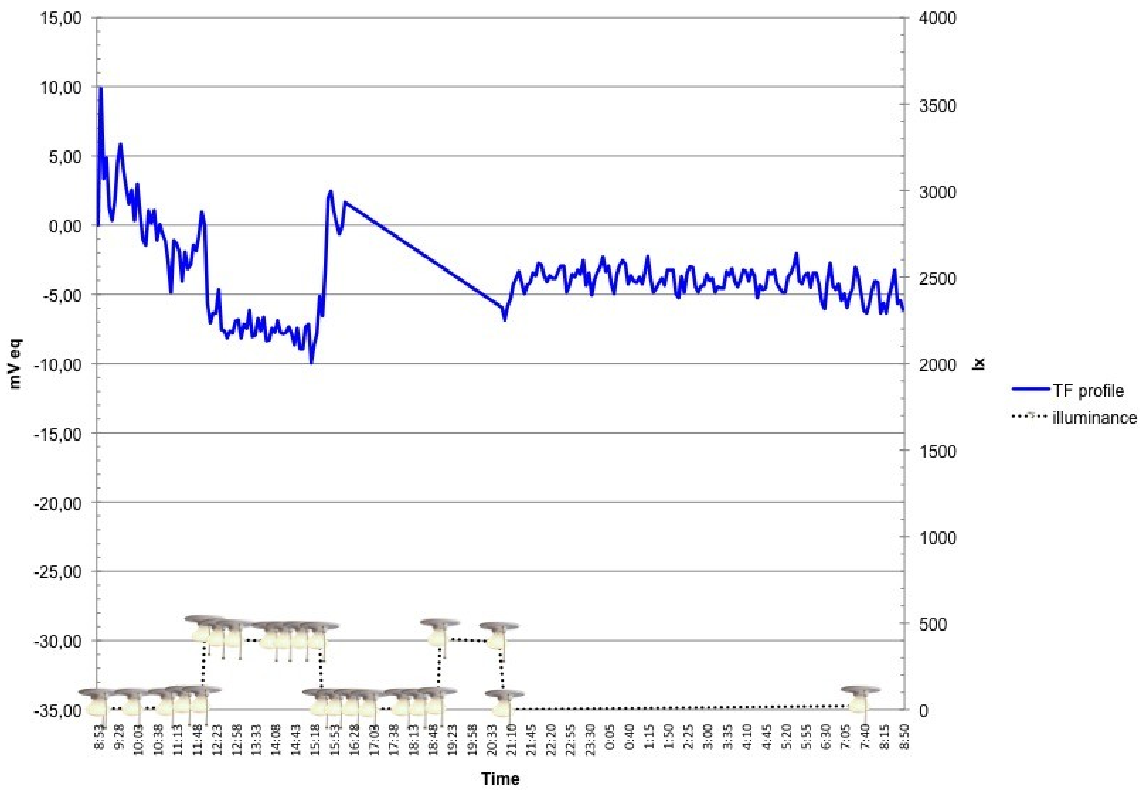


Figure 25: Test 4 – TF profile vs. illuminance

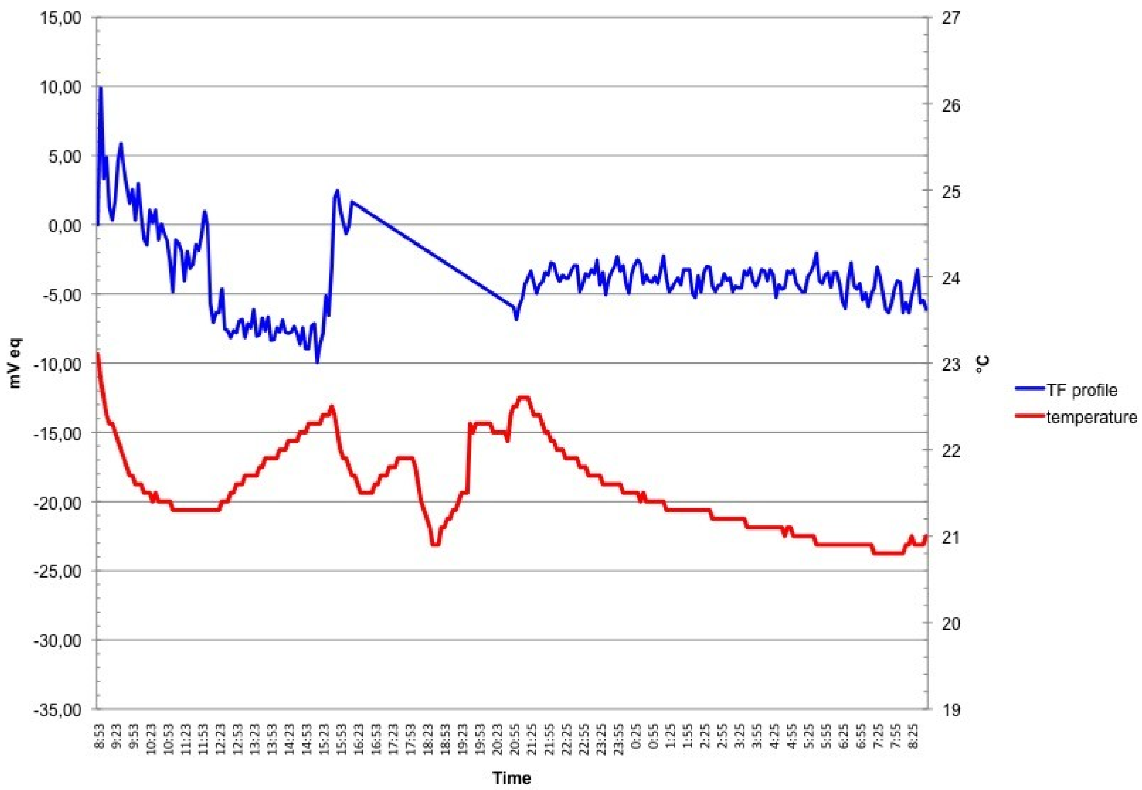


Figure 26: Test 4 – TF profile vs. temperature

3.5 Test 5

Test **five** was carried out in the same way as the previous run. The results were a TF profile with a mean of -22.90 mV eq (min -33.60 mV eq; max 0.00 mV eq; median -22.30 mV eq; SD: 5.16 mV eq; skewness: 0.104). The mean illuminance was 189 lx (min 0 lx; max 447 lx; median 44 lx; SD: 187 lx; skewness 0.316). The temperature showed a mean of 24.9°C (min 24.3 °C; max 25.5 °C; range 1.2 °C; median 25.0 °C; SD: 0.32 °C; skewness: -0.071).

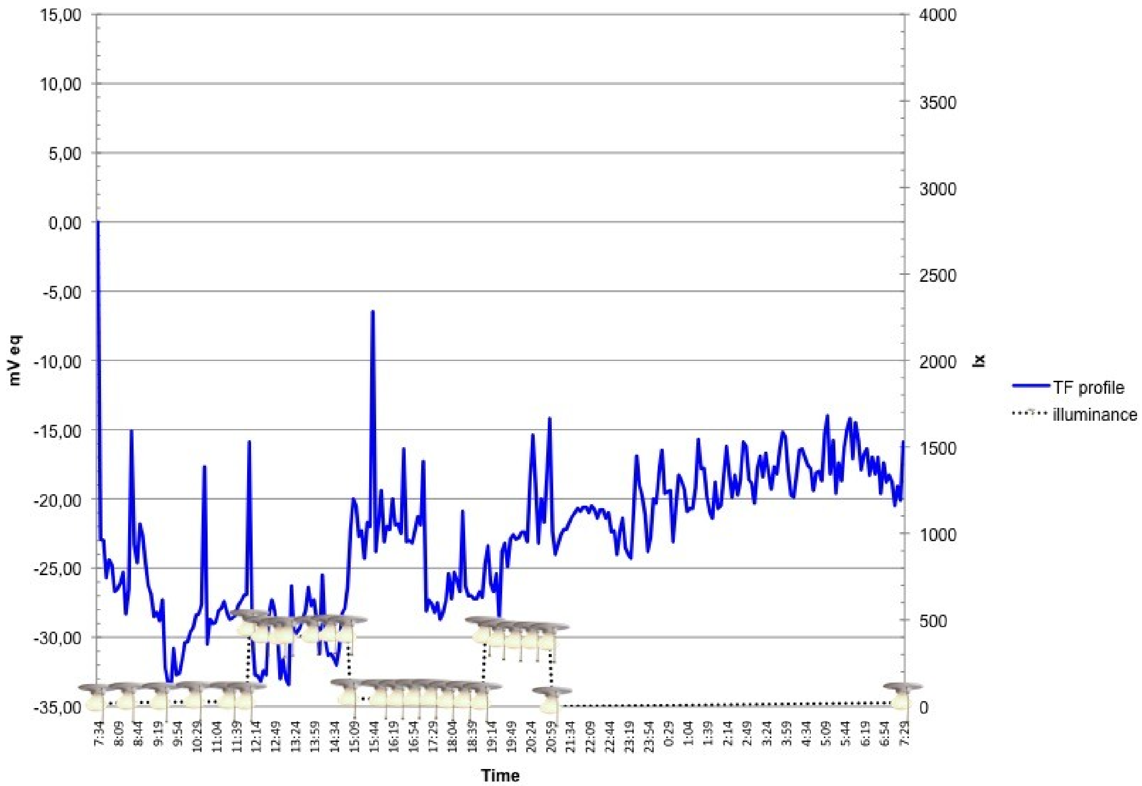


Figure 27: Test 5 – TF profile vs. illuminance

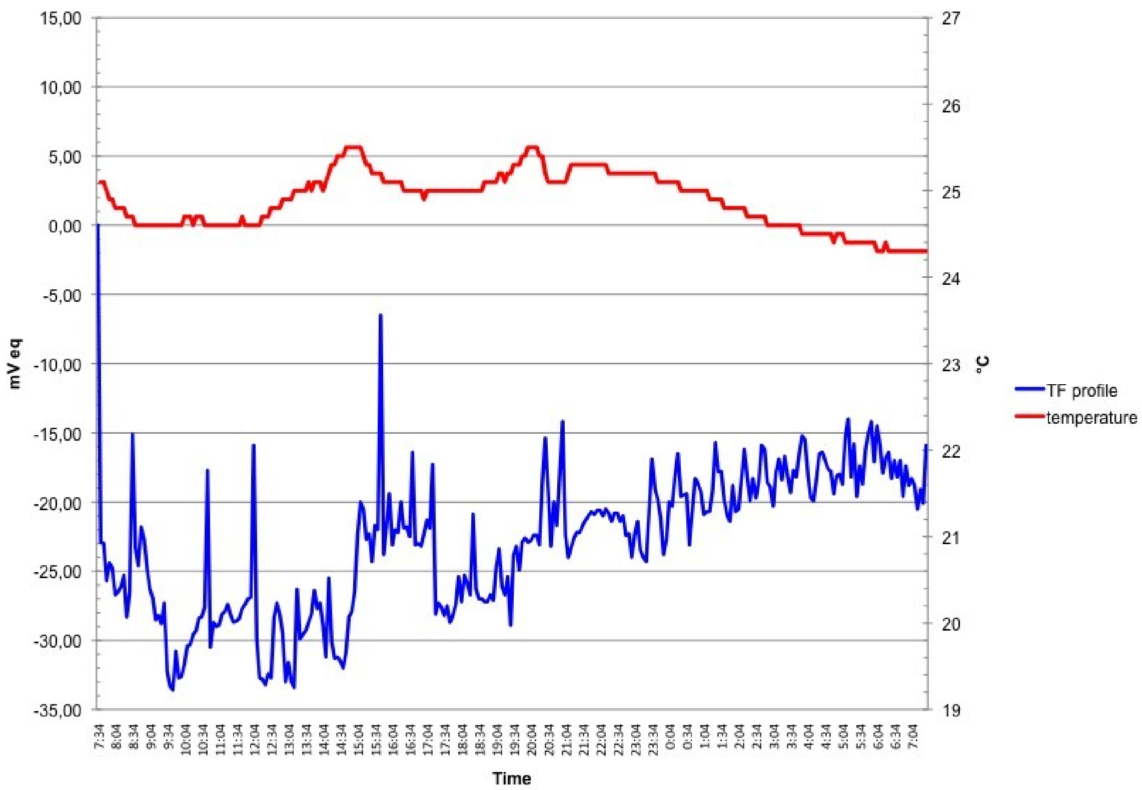


Figure 28: Test 5 – TF profile vs. temperature

3.6 Test 6

The **sixth** test run was the first one to be carried out with the polystrene box to keep temperature fluctuations within a lower range. Natural light was used for this experiment. There was a pause of two hours, from 4pm until 6pm, in the measurements of the CLS. The problem resolved after switching to a new antenna.

The TF profile showed a mean of -6.39 mV eq (min -8.60 mV eq; max 5.80 mV eq; median -7.60 mV eq; SD: 2.45 mV eq; skewness: 1.597). Illuminance showed a mean of 247 lx (min 0 lx; max 799 lx; median 29 lx; SD: 300 lx; skewness 0.745). Temperature averaged at 26.2°C (min 24.6 °C; max 26.9 °C; range 2.3 °C; median 26.4 °C; SD: 0.62 °C; skewness: -0.816).

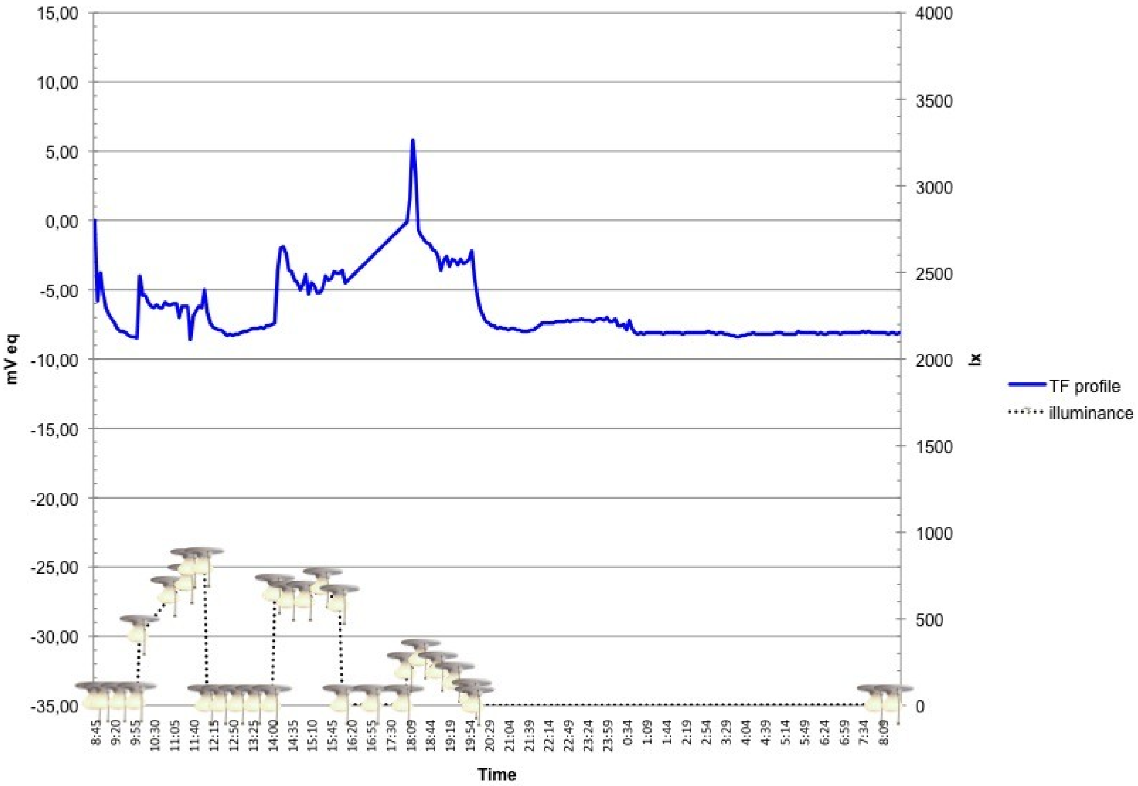


Figure 29: Test 6 – TF profile vs. illuminance

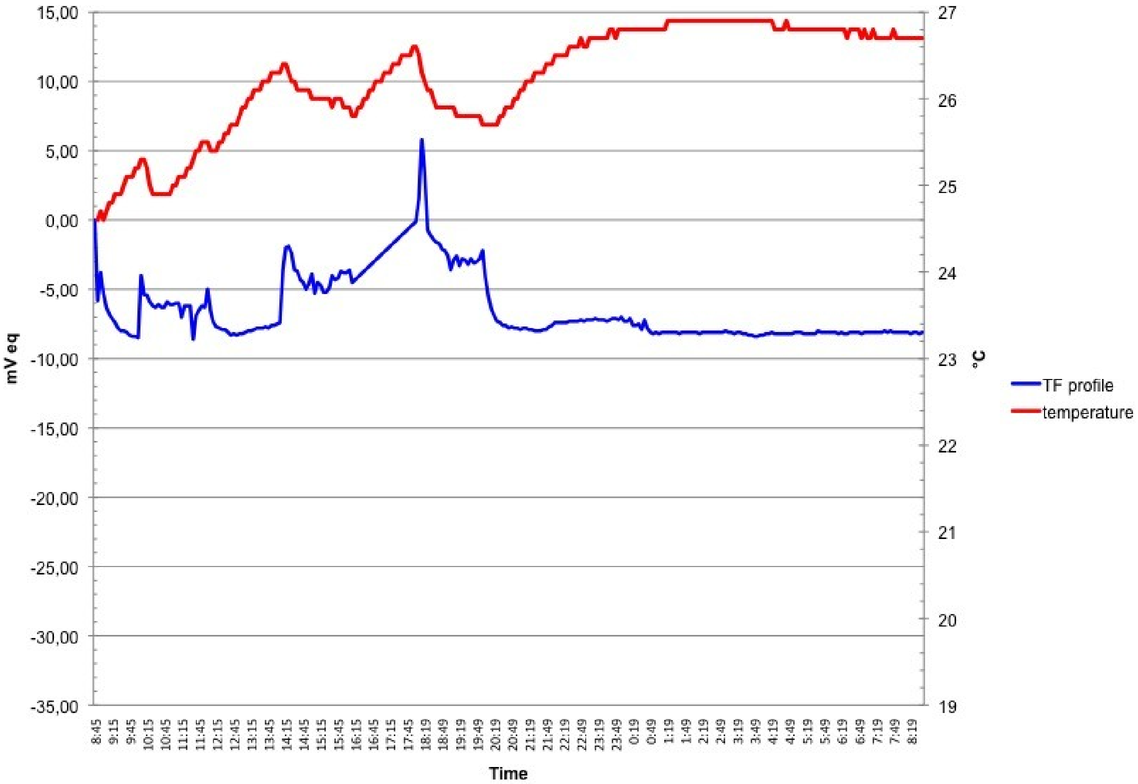


Figure 30: Test 6 – TF profile vs. temperature

3.7 Test 7

Test run **seven** was done in similar fashion to test **six**. Again there was an interruption in measurements of not only the CLS, but also the temperature profile. The interrupted period went on for the last two hours of measurement and stretched from 7am until 8:55am on the second day of the experiment.

The remaining showings revealed a mean in the CLS profile of -22.90 mV eq (min -28.20 mV eq; max 0.00 mV eq; median -24.00 mV eq; SD: 4.18 mV eq; skewness: 1.504). Illuminance averaged at 312 lx (min 0 lx; max 1179 lx; median 16 lx; SD: 419 lx; skewness 0.933). Solutions temperature had a mean of 24.5°C (min 22.1 °C; max 25.8 °C; range 3.7 °C; median 24.6 °C; SD: 0.96 °C; skewness: -0.439).

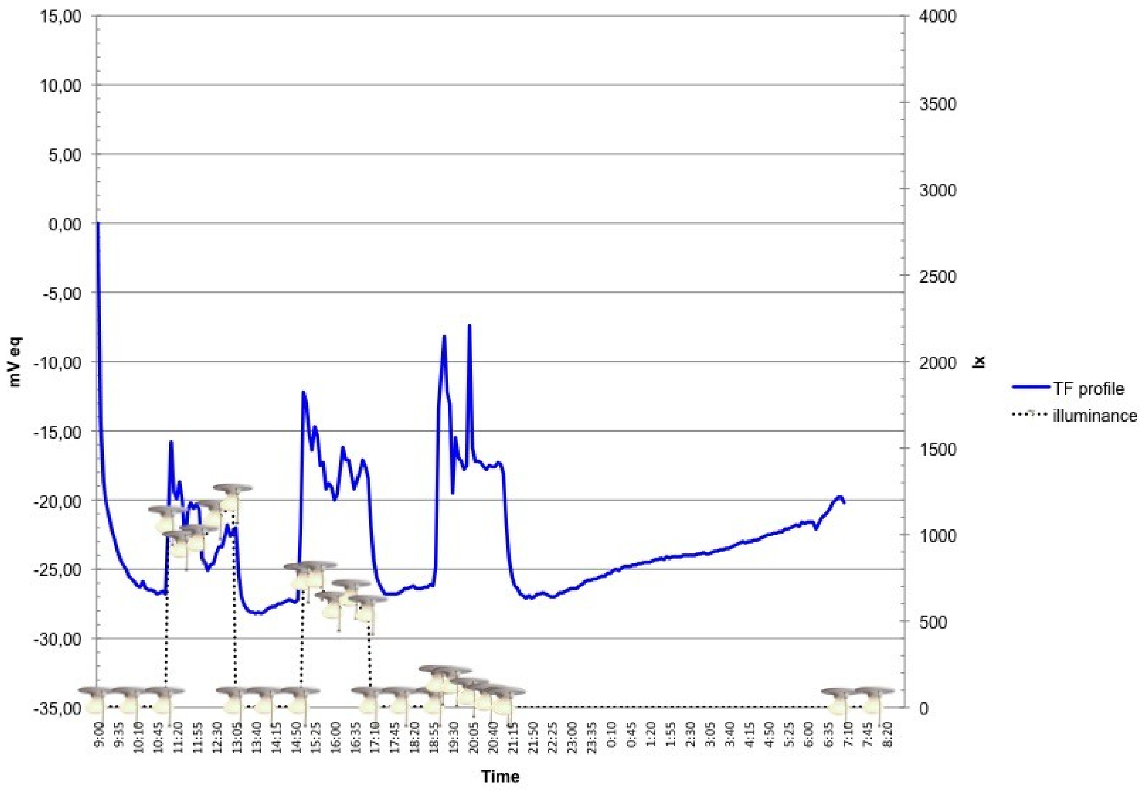


Figure 31: Test 7 – TF profile vs. illuminance

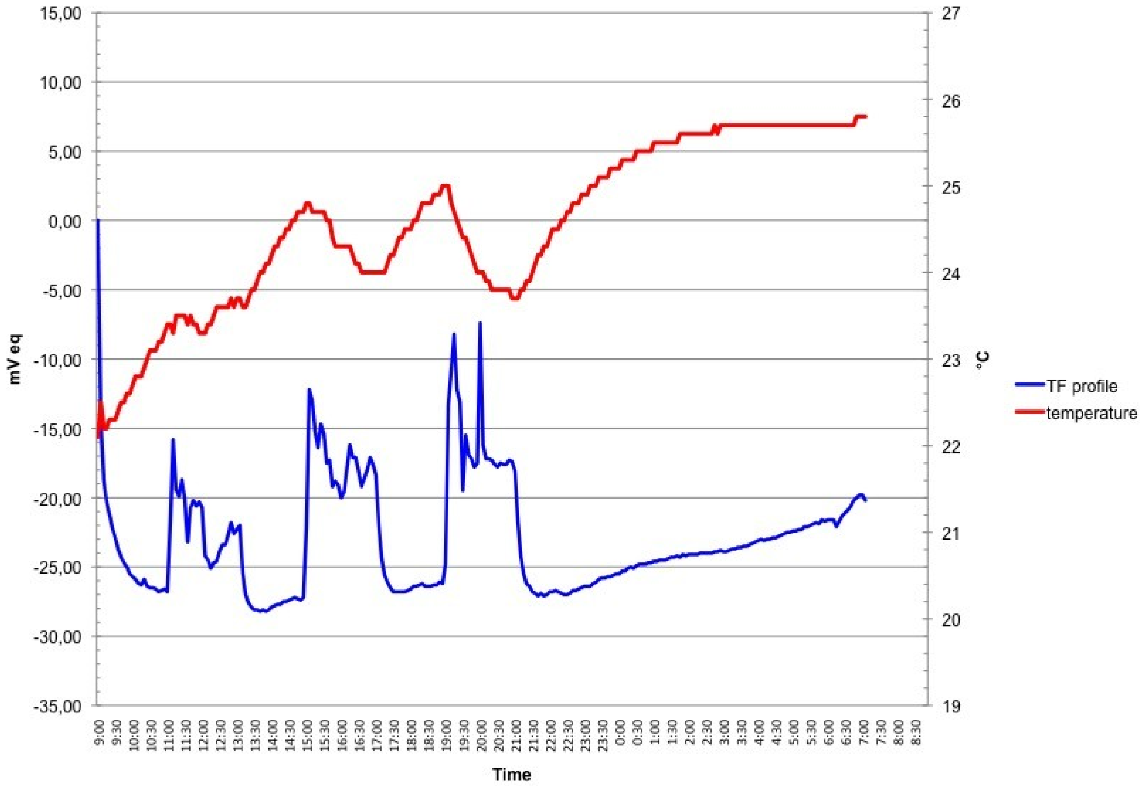


Figure 32: Test 7 – TF profile vs. temperature

3.8 Test 8

The **eigth** and final test was performed with a cold-light light source. CLS profile revealed a mean of 7.48 mV eq (min 0.00 mV eq; max 13.30 mV eq; median 7.50 mV eq; SD: 2.19 mV eq; skewness: -0.010). Illuminance showed a mean of 589 lx (min 0 lx; max 1326 lx; median 14 lx; SD: 611 lx; skewness 0.084). The solutions temperature had a mean of 20.5°C (min 19.9 °C; max 22.8 °C; range 2.9 °C; median 20.5 °C; SD: 0.39 °C; skewness: 1.838).

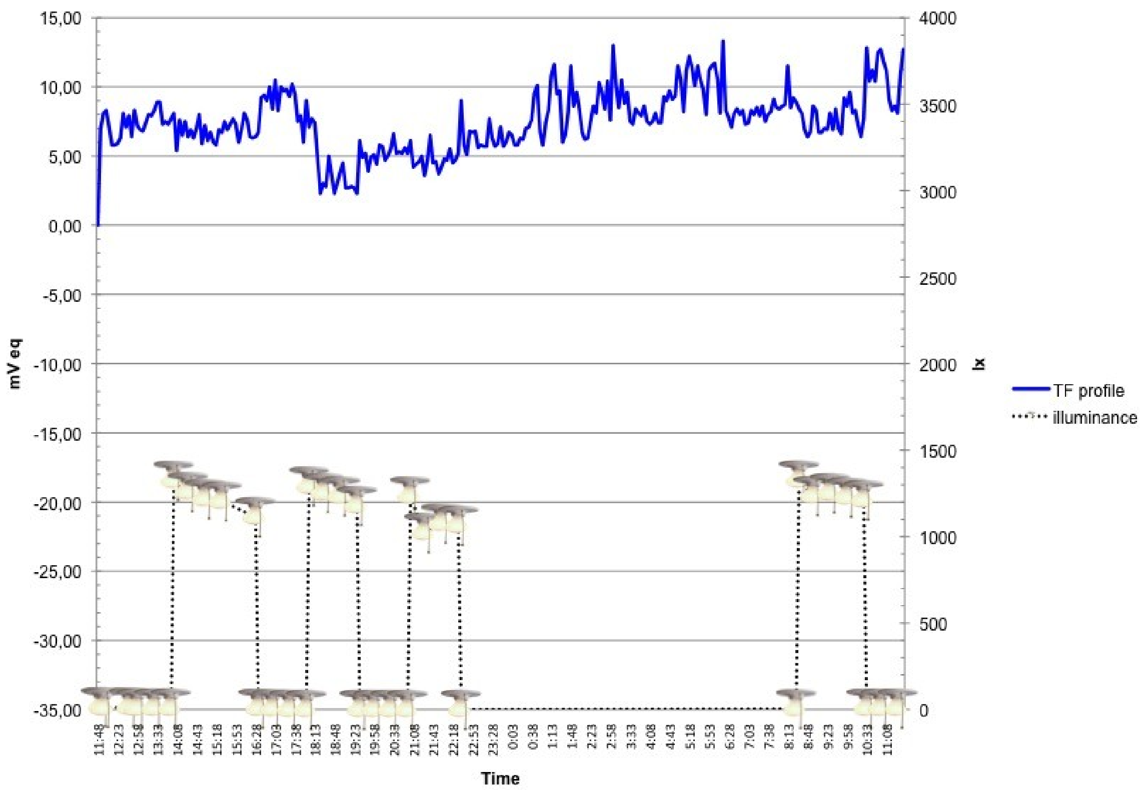


Figure 33: Test 8 – TF profile vs. illuminance

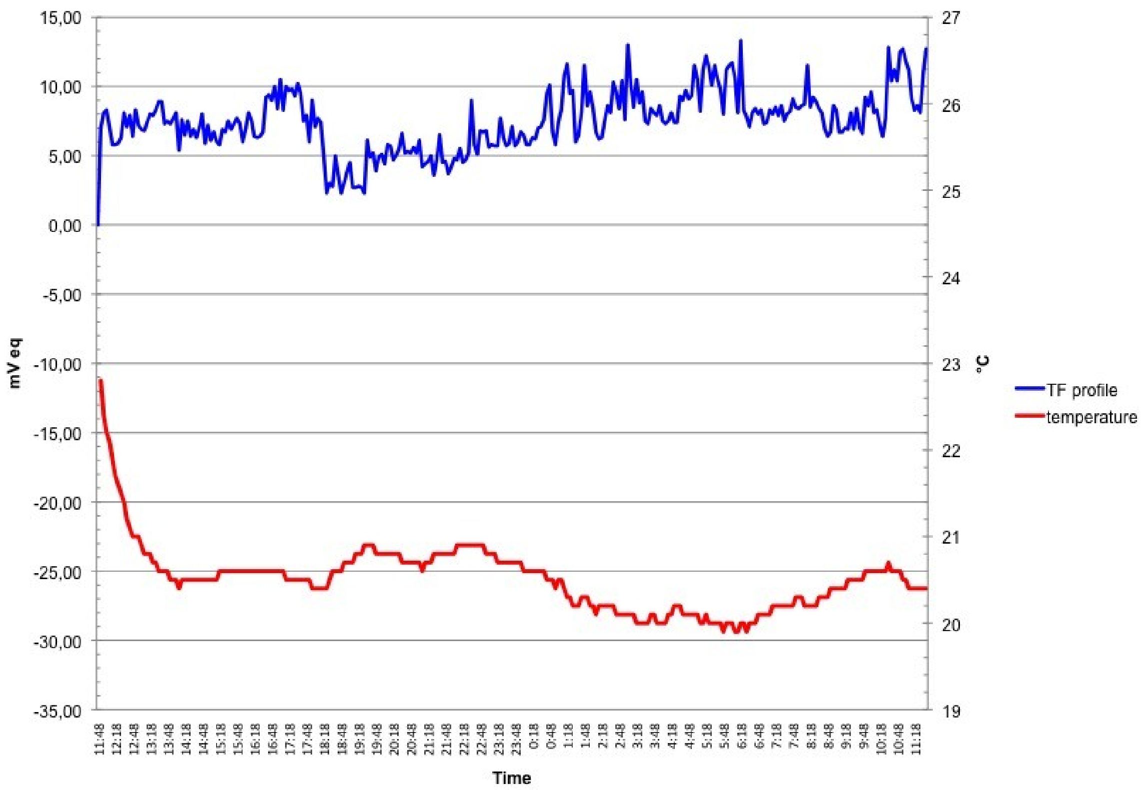


Figure 34: Test 8 – TF profile vs. temperature

3.9 Summary of all test runs

	test 1			test 2			test 3		
	mV eq	lx	°C	mV eq	lx	°C	mV eq	lx	°C
minimum	-14,30	0	20,2	-12,50	0	20,9	-10,50	0	21,6
maximum	4,10	2772	22,8	4,80	3380	23,5	2,50	438	23,8
range	18,40	2772	2,6	17,30	3380	2,6	13,00	438	2,2
mean	-3,78	870	21,6	-2,34	1058	22,3	-6,97	211	22,4
median	-3,60	472	21,5	-1,75	676	22,4	-7,00	31	22,5
SD	2,91	871	0,56	3,58	865	0,74	1,70	202	0,50
skewness	-0,622	0,994	0,098	-0,772	1,136	-0,039	1,069	0,084	0,142
Q1	-5,10	230	-3,6	-4,50	554	21,6	-8,30	21	22,0
Q2	-3,60	472	12,2	-1,75	676	22,4	-7,00	31	22,5
Q3	-2,00	1670	21,5	0,70	1510	23,0	-6,20	413	22,9
	test 4			test 5			test 6		
	mV eq	lx	°C	mV eq	lx	°C	mV eq	lx	°C
minimum	-9,95	0	20,8	-33,60	0	24,3	-8,60	0	24,6
maximum	9,85	430	23,1	0,00	447	25,5	5,80	799	26,9
range	19,80	430	2,3	33,60	447	1,2	14,40	799	2,3
mean	-3,49	158	21,6	-22,90	189	24,9	-6,39	247	26,2
median	-3,82	20	21,5	-22,30	44	25,0	-7,60	29	26,4
SD	2,83	194	0,50	5,16	187	0,32	2,45	300	0,62
skewness	0,831	0,553	0,446	0,104	0,316	-0,071	1,597	0,745	-0,816
Q1	-4,95	7	21,2	-27,23	28	24,6	-8,10	5	25,9
Q2	-3,82	20	21,5	-22,30	44	25,0	-7,60	29	26,4
Q3	-2,30	395	21,9	-18,88	399	25,1	-5,15	598	26,8
	test 7			test 8			total		
	mV eq	lx	°C	mV eq	lx	°C	mV eq	lx	°C
minimum	-28,20	0	22,1	0,00	0	19,9	-33,60	0	19,9
maximum	0,00	1179	25,8	13,30	1326	22,8	13,30	3380	26,9
range	28,20	1179	3,7	13,30	1326	2,9	46,90	3380	7,0
mean	-22,90	312	24,5	7,48	589	20,5	-7,70	475	23,0
median	-24,00	16	24,6	7,50	14	20,5	-6,20	353	22,5
SD	4,18	419	0,96	2,19	611	0,39	10,32	630	1,95
skewness	1,504	0,933	-0,439	-0,010	0,084	1,838	-0,501	1,902	0,433
Q1	-26,30	5	23,8	6,10	5	20,2	-12,43	14	21,4
Q2	-24,00	16	24,6	7,50	14	20,5	-6,20	353	22,5
Q3	-20,70	649	25,5	8,60	1226	20,7	-1,90	629	24,8

Figure 35: Summary of results of all test runs

4 Discussion

The idea of light influencing the TF profile is based upon empiric findings in already published studies (1, 2, 35). These studies however did not offer any explanation on why and how these findings were observed. It is quite difficult to say if light could interfere with the Contact Lens Sensor and its parts, with the telemetric transmission of data or with the physiology of the human eye. In the first two issues interference of different waves of light could play a factor, although this is quite unlikely due to complete different ranges of wavelengths. The electromagnetic field deriving from artificial light and wiring might be another factor to be taken into account, although wavelengths are highly likely to be still different and nearly all of modern medical devices are build to not be influenced by these known factors or at least filter these artifacts. However, the physical background to these assumptions is rather complex and the attempt of its explanation would go beyond the scope of the discussion within this paper.

The possible influence of light on the physiology of the eye is either caused by light playing a role in the maintenance of a normal circadian rhythm or light being a stand-alone factor itself as proposed by McLaren et al (46) among others in a study featuring a rabbit model. These theories however might have played a role in the above-mentioned studies on the TF CLS, but did not influence our experiment.

We soughed to fill the gap in literature regarding the evaluation of light as a possible factor for artifacts in the TF profile. Therefore we wanted to conduct an experimental study, which supports or disproves those previous empirical findings in a technological in-vitro experiment and by empirical methods itself.

4.1 Discussion of our results

It is interesting to see that our results of the experiments with the CLS and light did show a wide range in signals by reaching from a minimum of -33.6 mV eq to a maximum of 13,3 mV eq. The start point is always a value of 0 mV eq since it is used as a baseline to dimensional changes in the strain gauges. Although we always used the same basic principle in administering the CLS the results of the profile were very diverse. It is not explainable why test five shows a negative mean of mV eq, whereas test eight shows a positive mean of mV eq.

The cause for the disruptions of measurement in test runs **four** and **six** could be that the antenna got in contact with the NaCL-solution. This assumption is supported by the fact that the problems resolved by exchanging the antenna. Maybe this problem could be avoided by making minor adjustments in the set-up of the experiment.

As stated before it is specified by the company that the level of hydration will not affect the lens in its measurements, since it is made out of silicone and is therefore not absorbing water. In our setting there was no component, which would put any strain on the lens. Theoretically the CLS should therefore not be sending signals without any active changes in the strain gauges. Therefore the assumption can be made that at least major variations from the baseline have to be artifacts of some kind triggered by another, yet unknown factor.

When further evaluating these artifacts it does seem that light has a direct influence on the TF profile. Complete darkness seems to trigger a rather flat line or at least a profile with less major aberrations when compared to the time when light was turned on, which seems to cause various spikes in the profile. This can be seen in every single test run, beside test **eight**.
This would mean that the CLS sends up to none signals during complete darkness (zero lux), whereas light periods led to signals within a wider range of mV eq.

These phenomena cannot be ascribed to temperature alone, which was thought to be the main competing factor on influence on the profile. Temperature alterations were limited quite well within an average range of 2.5 °C (1.2 °C min; -3.7 °C max).
The use of polystrene boxes did not show any superiority since the range of temperature variations even increased.
During daytime it is quite hard to analyze the profiles on any correlation since the light periods are quite always accompanied with an increase in temperature. Therefore night periods are most informative when wanting to describe the influence of temperature on the profile.

Tests **one** and **two** showed a partly similar situation as described by Faschinger et al (30). A decrease in temperature caused a slight increase in the TF profile. Differing from that, test runs **three** and **four** showed a quite flat TF profile during the nighttime, although temperature continuously decreased. In test run **six** the polystrene box was used, which led to a nightly increase of temperature. Increasing temperature did not influence the profile in test **six**, however in test **seven** a rising TF profile can be seen in addition to the rising temperature. Faschinger et al (30) already described this ambiguous influence of temperature on the TF profile. Our results also support such a multidimensional influence of temperature on the profile.
However, the relative limitation of the temperature variations allows the interpretation of the influence of light, although an exact differentiation between those two factors cannot be made.

Although complete darkness seems to cause a quiet profile, a correlation between light and mV eq cannot be made during the daytime. Test **seven** seems to show a correlation between those two factors since changes of up to 20 mV eq are to be seen during every light period. These spikes seem to be inversely proportional to the illuminance, since the differences in mV eq increase with lower lux.
Taken into account that every other experimental set up did not show any correlation between light and the profile during daytime it is difficult to verify the potential correlation found in test run **seven**.
In summary it also has to be stated that even if there would be a correlation, it would not be correlating to the amount of lux. Some test runs featured maxima of over 3000 lx, whereas some just had a peak of below 500 lx. The TF profile did not show any notable alterations when test runs with different lux maxima are compared.

We conclude that we could not find a definite correlation between the degree of illuminance and the TF profile. However, the fact that the fewest noise was recorderd during nighttime (zero lux) suggests that there could be an influence, which has to be evaluated in further studies.
Furthermore we summarize that temperature seems to trigger changes in the profile as already published (30). These changes are not vectored in one direction,

but are rather ambiguous. This would further mean that the compensating gauges featured inside the Wheatstone bridge of the CLS are not able to fully compensate temperature changes even within a very close range.

We cannot define the value of the device in clinical situations solely on our results. Therefore we have summarized the most important publications made on the clinical use of the device within the next section to provide an overview about pros and cons of this device.

4.2 Implementation of the TF CLS into practical clinical work

4.2.1 In-vivo studies using TF

It was already mentioned before, that the device received its CE-mark in 2009. Since then there are several in vivo studies to be found, which focus on reliability, validity, reproducibility, safety and tolerance of the TF device in a clinical setting. Since the conclusions of these different studies were quite diverse, we will try and summarize the most important clinical trials in the following section.

The first results derived from the in vivo use of the TF sensor, were actually obtained at the Department of Ophthalmology at the Medical University of Graz by Faschinger et al (29) in 2010. Faschinger et al applied the TF lens in eleven patients and a 24-hour measurement was completed. The tolerability of the device was described as rather good in all patients. Two of the eleven patients were already diagnosed with open angle glaucoma, and those patients showed some changes in their profile, compared to healthy patients. Especially in the nighttime an elevation of the IOP was noticeable. Furthermore Faschinger et al described some intermittent spikes in the profile, which could not be completely explained by blinking of the eyelid, nor ocular pulsation. It was concluded that those spikes may be true, intermittent raises of IOP, or may simply be artifacts.
To that point not enough studies had been conducted to validate the results, nor to evaluate the reproducibility of the device.

Mansouri and Shaarawy (2) conducted a study in 2011 at the Department of Opthalmology in Geneva, which examined 15 consecutive patients suffering from primary open angle glaucoma (POAG). They focused especially on tolerability of the device. In two patients the measurement had to be interrupted, due to technical difficulties in one and due to intolerance in the other. One patient, who suffered from dry eye disease, showed corneal erosion (1x1mm) and four patients showed superficial punctate keratitis. All mentioned complications resolved within 24-hours. Eighty percent of patients showed prolonged periods of high IOP, with 75% of those detected outside of normal office hours. After the monitoring, glaucoma therapy was changed in 11 out of 15 patients.

Mansouri and Shaarawy concluded, that the device yielded good safety and tolerability results, with its complications being similar to corneal changes described in the use of normal contact lenses. Furthermore they stated that the obtained data was highly relevant, also because a large amount of changes in IOP were obtained outside of normal office hours, and led to changes in the therapeutic scheme of the majority of patients.

It is remarkable that Mansouri et al changed their therapeutic pathway due to the results obtained by the TF lens at a rather early point in time. Until then there were no studies confirming the validity of the TF profile. There were no other studies to be found which stated that therapeutic schemes were changed on the basis of the CLS profile.

The first study with a rather large study population was also taken by Mansouri et al (28) in 2012. Forty patients, suspected of having glaucoma after suspect perimetry, masked stereophotography or simply an IOP more than 22 mmHg, were studied at two points within a one-week interval. Adverse events, visual analogue scale score (VAS) were also assessed. The main adverse events were blurred vision in 82%, conjunctival hyperemia in 80% and superficial punctate keratitis in 15% of patients, whereas the mean VAS score was 27,2 with 0 meaning no discomfort and 100 meaning most severe discomfort. The Pearson correlation for 36 patients and between the two study points was determined as fair to good (r = 0,59).

The conclusion was that tolerability had once again been shown to be rather good with no major adverse effects, but reproducibility was classified as fair to good with a correlation coefficient of 0,59. However, it has to be stated that due to the physiological fluctuations and the different behavior, it is not mandatory or even possible to achieve the exactly same results when comparing measurements of the same subject (47). However, the *pattern* of the results is supposed to show a correlation, just as it did in the above-mentioned study by Mansouri et al.

Another study solely focusing on the tolerability and functionality of the TF device was conducted by De Smedt et al (1). The contact lens was applied in 10 healthy volunteers and comfort level was scored as well as the inquiry of objective parameters like best corrected visual acuity, position and mobility of the lens and its surface wetting ability. After the removal a full eye examination was performed. The comfort level stayed high in all 10 volunteers, furthermore there was no evidence of changes in corneal thickness, which may be caused by corneal edema or metabolic suffering. This finding will be addressed in the following with different other publications showing contrary results.
Three of ten participants developed a corneal epithelial micro-defect, which resolved rather quickly. Furthermore a temporary shift towards myopia was found, which was explained by the corneal astigmatism induced by the lens impression on the corneo-scleral junction. Reduction of vertical corneal radius was seen after 24-hour application of the TF sensor, to which also other factors like viscoelasticity and biomechanics of the cornea may contribute. It was not stated if these changes influenced the output signal of the TF CLS.
Best-corrected visual acuity was reduced while wearing the lens and also stayed significantly reduced immediately after removal of the device. This was explained by temporary irregularities in corneal surface caused by the lens. In conclusion the authors stated that the device showed rather good tolerability and functionality.

Another very interesting study was conducted by Hubanova et al (48) in 2014. There have already been questions about the influence of the TF lens on the human eye. Hubanova et al wanted to investigate if the longtime wear of the lens could influence central corneal thickness (CCT). The hypothesis was that this may influence the data output of the device. Since corneal swelling is known to happen in individuals wearing soft contact lenses, the TF lens may also cause alterations in the cornea and maybe even in corneal curvature and corneoscleral angle, which would influence the acquired profile. Twenty-four eyes of twelve healthy subjects were therefore extensively examined before and after the use of the CLS, whereas one eye was used as the CLS group and the other as the control group.

The CCT changed significantly in both eyes after the sleeping period, but the CCT in the CLS group changed significantly more than in the control group. Throughout the study CCT increased significantly more (p= < 0,05) in eyes with CLS applied in every measuring point (every 2 hours), however CCT decreased again after opening eyes, or after the removal of the TF lens. It was also found that there were more corneal curvature irregularities in the CLS eyes, compared to the control eye. These results are very interesting, since the principle of the CLS lays within the alteration in corneal curvature. It was not possible to evaluate if these findings have an influence on the signals recorded in this study and there were no other studies done on this topic until now.

Pajic et al (49) examined 5 patients in 2011 with normal tension glaucoma (NTG). The patients were either not having any IOP-lowering medication, or have gone through a six-week wash out phase prior to the first measurements. Every patient was measured with Goldmann applanation tonometry (GAT) before and after the application of the TF lens. Measurements were repeated after an average of 6 weeks and after the patients received IOP-lowering medication (prostaglandin analogues and/or carboanhydrase inhibitors) for the same amount of time. The GAT as well as the TF profile showed a significant difference in the mean IOP taken at the first and at the second measure point, which implies that the TF profile responded quite well to medical lowered IOP.
Additionally they found that the mean 'IOP' of TF profile did not differ significantly from the IOP curve obtained by GAT.

Mottet et al (13) used the TF CLS in comparison to the 24-hour measurement of IOP with a noncontact tonometry (NCT) while subjects stayed in a sleep laboratory. Twelve healthy subjects underwent four sessions with two sessions of simultaneously use of CLS and NCT, one session with just the use of CLS in on eye and one session with NCT measurements in both eyes. They found a significant nycthemeral IOP pattern, described as acrophase in the late night/early morning in previous studies, in 86% of NCT measured subjects and in all subjects where CLS was used. It was found that acrophases and bathyphases of nightly IOP were significantly earlier detected when using the CLS.

Moreover the authors found that the CLS was more sensitive in detecting and characterizing the 24-hour IOP rhythm, in comparison to the NCT. Both findings are likely to be traced back to the higher frequency of data acquisition.

Reproducibility of CLS patterns in itself was found to be fair to good once again. The study described the main shortcoming of the CLS for the first time in depth, that it is not able to provide absolute values and IOP changes in mmHg, since the output is just the variation in voltage from its baseline. That is, in the opinion of the authors, why the CLS is a good device to model the IOP rhythm and characterize acro- and bathyphases, but not to get absolute IOP values. This is a very interesting statement, which has to taken into account when talking about the possible superiority over other methods.

Another interesting finding of this study was, that the authors stated that hourly awakening during NCT measurements did not significantly change the mean phases and general pattern evaluated using the CLS.

This would mean that the often-stated argument against 24-hour measurements using common tonometry with mandatory hourly awakening, causing fluctuations in the physiological pattern and behavior of IOP (2, 20), is at least partly challenged. However, this finding does not validate if the nightly mean IOP is altered when waking patients during nightly measurements.

After most of the studies being rather optimistic about the impact the newly designed device might have on the clinical approach on glaucoma patients, some studies emerged, which created some questions regarding the usability of the TF sensor lens.

Faschinger et al (31) published a study in 2012 which tried to compare the IOP changes in TF profile after body position was altered to the values measured with GAT. For this the contact lens was applied in the left eye of five healthy subjects and their body position was altered several times from standing upright, to horizontal, to horizontal with reclined head and back to standing or sitting upright. The idea was that the change of the body position alters the IOP physiologically and that these alterations in IOP could be compared between GAT and the TF sensor output. The examination was repeated after 2 to 8 weeks, which showed no statistically significance between the measurement points.

The IOP value taken by GAT showed an increase of IOP from a mean baseline of 14 mmHg in upright position. In horizontal and horizontal with reclined head position the IOP increased up to the highest mean peak of 22,4 mmHg while reclining the head in a horizontal position. This finding can be explained by physiological orthostatic regulations such as the Bayliss-effect, which is described as a contraction of vascular muscles due to increasing intravasal blood pressure (50), and by obstruction of the aqueous fluid outflow caused by increased venous pressure in episcleral veins (41).
However, the TF profile did not show the expected findings. There was no increase in the TF profile due to changes of body position, but there was a statistical significant decrease of this profile when going from upright position into horizontal with reclined head body position. This finding in TF profile was the exact opposite of the values surveyed by the GAT. Additionally the reproducibility was shown to be good, with no significant difference in the first and the second measurement point.
With the reproducibility of both methods being rather good, the question, why the profiles were entirely different remains open.

Furthermore Faschinger et al (33) recreated the studies conducted by Leonardi et al (27, 42) to try and understand the findings described earlier. Instead of juvenile porcine eyes they used human bulbi, which were not suitable for transplantation purposes. The bulbi were cannulated with two needles. One needle was connected to a pressure transducer with the ability to measure and store the gathered data and the other needle was connected to a hydrostatic head filled with 0,9% NaCl-solution. The cornea was kept under moist conditions with the same 0,9% NaCl-solution.
The baseline pressure was set at 10 mmHg and the pressure was raised in 5 mmHg steps, which were maintained for 30 minutes. The data acquired by the pressure transducer was, as expected, a stepwise elevation of IOP levels. The TF profile, however, did not correlate with this.
There was a second experimental set-up arranged, which was supervised by M. Leonardi and two technicians. This set-up differed in the bulbi being kept moist by a nebulizer, the hydrostatic head replaced by a piston pump, another pressure transducer used for measuring and a custom made software, allowing more

frequent measurement points. Additionally the IOP was raised and lowered to its baseline in 50 or 120 seconds lasting periods, similarly to how it was done in previous experiments by Leonardi et al (27, 42), and not in 5 mmHg steps over 30 minutes like in the first experiment. The TF profile showed a good reproduction of this much faster surge in contrast to the findings of the first test.
The conclusion out of this study is that the first experiments done by Leonardi et al (27, 42), on which the whole idea of the TF contact lens is based on, should probably be repeated and validated. The question raised by Faschinger et al (32) is, that the rather short periods of artificial raised pressure, to which the CLS shows good correlation, may not mimic the physiological conditions of IOP in the human eye.

Sunaric-Megevand et al (51) published a pilot investigation in 2014 which caused further irritation. The study used a set-up in which the IOP could be artificially raised in-vivo. In two subjects, both authors of the study, a device was used to raise the IOP while wearing the TF lens. It was stated that a SENSIMED representative had been present during the whole time, to avoid any misunderstandings concerning the principle of function.
The ‘pressure elevation device’ uses a ring consisting out of PMMA (Polymethyl metacrylate, PMMA does not influence the electromagnetic transmission of the CLS), to apply pressure on the eyelids. The applied pressure can be exactly reproduced for future references and its influence on IOP can be verified by GAT.
The starting IOP was measured by GAT and CLS. After that, the IOP was artificially increased and at seven measure-points IOP was detected by GAT and CLS. At the end the physiological IOP was measured again.
The correlation coefficient of the results of both devices was r=-0,28 in one subject and r=-0,19 in the other, with both being not statistical significantly different from zero (p=0,46 and p=0,62). Therefore there was no correlation detected between the measurements taken by GAT and CLS.
The authors reasoned this finding to be caused by a missing correlation between IOP and the corneal curvature. This would be a contradiction with the findings of Leonardi et al. (27, 42) The authors explained that this contradiction has a simple physical explanation, with Leonardi oversimplifying his porcine model. Variations in IOP are not only produced by increasing volume, which is extending the curvature

radius of the cornea, but are also influenced by the eyes' geometry. Deformations to the bulbus, which can even be caused by eye- or lid-movements, will also influence the IOP. Any such movements will also have an influence on the corneal curvature and therefore changing the proportion of relation in IOP and corneal curvature. Furthermore, the rigidity of the cornea and the sclera are not the same in all places, but varies with its location, causing the geometry of the bulbus to react differently to increased IOP in comparison to a perfect model. Concluding that the relationship between IOP and corneal curvature is a complicated function depending on thickness and elasticity of cornea and sclera, anatomical structure influencing the movement of the bulbus and even on corneal hydration level. Therefore, the authors stated that, corneal radius cannot be correlated directly to IOP.

It is quite interesting that Mansouri and Weinreb (38) used similar reasoning when criticizing the GAT as outdated and ready to be overtaken by different methods, specifically meaning the TF CLS.

Leonardi (52) responded to the publication of Sunaric-Megevand et al by stating that: 'In the presented pilot investigation, IOP was raised artificially by a ring pressing against the eye. Under these conditions, the SENSIMED Triggerfish Sensor will not be able to record ocular dimensional changes related to IOP without being significantly influenced by the rings' force exerted against the eye, and hence its output is to be considered as mere noise.' To further explain the mode of operation of the CLS, he added that: 'By principle, to capture ocular dimensional changes in the corneo-scleral area related to IOP, the globe must be able to expand freely and naturally without any external force applied or [sic!] device that pushes against it or against the sensor'.

Additionally he explained that the TF CLS was used 'outside its scope of application' and that therefore the study 'does not reflect clinical reality or on label use of the product'. Furthermore he claimed that there were no company affiliates present at the point of investigation.

There was no further response by the authors of the pilot study, however there are still concerns if the in-vitro model of a porcine eye is a proper analogy for the human eye.

There were more studies, which suggested a rather pessimistic approach towards the new emerged CLS. Hollo et al (53) examined the CLS profile in patients, in which the IOP was reduced by administration of prostaglandins. Nine patients, with either ocular hypertension or primary open angle glaucoma (POAG), were washed out from IOP-lowering medication and underwent two baseline measurements with the CLS and one with GAT. After that, all patients received travoprost for three months as a single-therapy. The measurements were repeated after this period and CLS results were compared to the values obtained by GAT, as well were the CLS profiles correlated to each other to evaluate reproducibility.

Whereas the GAT results showed a significant reduction of IOP after the administration of travoprost, which was more significant during the daytime than during nighttime, the CLS profile did not show any significant reduction of IOP. Additionally there was no difference seen when the CLS profile of the daytime (8am to 8pm; upright/sitting position) and the nighttime (12 midnight to 4am, horizontal position) was compared separately.

The correlation of all three CLS curves (two after wash-out and one after 3 months therapy of travoprost) was high (r=0,726). The authors found that there was always an increasing trend in the CLS profile over time, therefore a significant difference in the mean value of the first 50 minutes of use compared to the last 50 minutes of use was found. When IOP was measured by GAT before and after the use of the TF lens, there was no significant difference in those values however. Therefore they corrected the increasing time trend, which led to a lower correlation coefficient of the three CLS profiles (r=0,434).

It has to be remembered that the CLS profile output is not in an absolute value of mmHg. However, it was expected that other factors like diurnal variation of the curve would correlate with findings obtained by GAT. Standard deviation of GAT IOP values was decreased by 50% after treatment, while standard deviation of CLS IOP values did not change before or after the treatment. The authors were not able to explain the lack of correlation between the profiles obtained by GAT and CLS. As conclusion they stated that the CLS shows great results in laboratory settings, but that, at least according to these study results, the TF lens is not suitable to detect IOP reduction due to medication and therefore is limited in its clinical usefulness.

Recently, speaking of the last two years, there have been some studies involving rather large study populations, not solely focusing on the TF CLS itself, but already using it as an established diagnostic tool.
In the following we will give a short insight into these studies.

There was another study, which aims to show the clinical effectiveness of the CLS, conducted by Mansouri et al (54).
Thirty-three subjects in total, 31 healthy subjects and two glaucoma patients, were included. In one eye the CLS was used and in the other eye the IOP was measured by a pneumatonometer. The IOP curves acquired by the CLS on the one hand and by the pneumatonometer at 2-hourly time points on the other hand showed good correlation (r = 0,914).
Furthermore the authors measured the heartbeat at several occasions to show that the CLS profile records the ocular pulse frequency sufficiently. However, they also stated that the current TF software is not suitable for depicting the ocular pulsation in a suitable fashion. Furthermore it has to be stated that just 60% of the profiles were taken into account for manual evaluation by two independent graders. In the remaining part of the profiles it was not possible to evaluate the relation of heart beat and ocular pulsation in CLS curves, due to large artifacts covering the rather low-amplitude oscillations. These artifacts were specified as artifacts caused by blinking and movement. Eventually the authors found a good representation of ocular pulse frequency in TF profiles.
Another finding was that all subjects but one showed significant elevation in their respective CLS profile during the sleep period. The nocturnal slope of the curve was less prominent, but also positive in all profiles, when measured with the pneumatonometer.
The effect of CLS on CCT was also addressed. Surprisingly the study showed a significant decrease of CCT after CLS use in comparison to the control eye. In contrast, one other study (48) showed a significant increase of CCT after the use of the TF lens and a further one showed no effect at all (1), with both studies being cited in this paper beforehand. In summary, the question whether alterations in CCT would influence the outcome, was yet again not explainable.
In conclusion this study showed a good correlation of CLS profile with values obtained by pneumatonometer. Furthermore the physiological increase in IOP

during sleeping periods was represented well in CLS curves. If the ocular pulsations could be shown sufficiently is open to debate, however the authors stated that ‘the CLS detects short-term changes of IOP related to the cardiac cycle with good accuracy’ (54: p.12)

Agnifili et al (14) examined 10 healthy subjects, 20 patients suffering from primary open angle glaucoma (POAG) and 10 patients diagnosed with normal tension glaucoma (NTG) using the CLS. All patients were treated with prostaglandins for the last 6 months. The main outcome of the study was the 24-hour CLS pattern. The nocturnal acrophase, which was already observed in other studies, was found in all patients, but the patterns differed significantly between the three groups. Highest nocturnal IOP levels were observed in POAG patients, whereas POAG and NTG patients showed prolonged IOP peaks in general when compared to the healthy population. The authors concluded, as with other previous publications, that the CLS is a valuable tool to unmask high ‘IOP’ levels outside of office hours and an additional help in making treatment decisions, rather than just on measuring the IOP value once.

A study group from the USA, De Moares et al (15), evaluated the potential of CLS predicting the progression of disease. Forty patients diagnosed with glaucoma under treatment and therefore stable IOP values were enrolled in the study. All patients received visual field testings prior and throughout the study in a period of at least two years and eight tests before the CLS was used. The patients were divided into two groups, specified by the progression of glaucoma, which was defined by the means of changes in the visual field. Three patients were excluded out of each group, leaving 36 patients in total. The average visual field mean deviation (MD), measured before application of the CLS, was as expected significantly worse in patients of the fast progression group, whereas single-measured GAT IOP was not significantly different between both groups. The number of antiglaucomatous drugs was 2.6 in the slow and 3.4 in the fast progressing group (non significant).
When comparing visual field MD changes over time, it came to notice, that the fast progressing group had significantly more negative slopes in visual field MD changes than the slow progressing group. As this is expectable, it was quite

surprising that this finding resolved after time. The last six visual field examinations, closer to the application of the CLS, did not show any significant difference in slopes between both groups. Seemingly the progression of disease was fastest at the beginning and was equally distributed at the point of CLS assessment. This may be explained by different treatment strategies. Patients with a faster change in visual field MD were treated more aggressively, leading to deceleration of visual field changes. Therefore the previous classification was no longer used, but the change in visual field MD was solely taken as a parameter to assess the progression of disease in synopsis with the CLS pattern. The CLS pattern was similar to the already in previous sections described 24-hour curve, showing a nocturnal acrophase in all patients.

In analysis some parameters in CLS profile showed association with a faster visual field MD change, although just at a p-value set at < 0,25. The most important factor turned out to be the mean peak ratio (mean peak height to time-to-peak) during sleep. Meaning that a higher mean peak ratio during sleep, which suggests that there were more peaks with shorter latency, is in strong correlation with a steeper negative slope of visual field MD over time. Additionally the authors examined the ability of the CLS model to explain faster negative visual field MD changes in comparison to continuous single-IOP measurements over time. The CLS model explained approximately 40,9% of the variance in visual field MD slopes, whereas multiple IOP measurements over time were just able to explain 16,8% of these changes, with fluctuation in between GAT IOP values being the strongest factor in faster negative visual field MD changes.

In conclusion the study showed that CLS parameters explained the variance in visual field progression better than single IOP values measured by GAT over time. Therefore the CLS could be a valuable tool in determination of the progression of disease in treated glaucoma patients, and therefore in adjustments in glaucoma therapy.

Parekh et al (55) examined the 24-hour IOP pattern in patients with thyroid eye disease and found that these patients had the same acrophase in early morning hours while sleeping as already found. Additionally they also showed a second positive slope in the morning after awakening.

This study stands an interesting point, just as another study by Tojo et al (56) examined IOP fluctuation in patients suffering from pseudoexfoliation syndrom, because it is evaluating IOP patterns not only in classic glaucoma patients, but also in other groups of diseases, which may have an influence on and a pathological finding in the IOP.

Tan et al (17) from Hong Kong studied 25 eyes of patients with the CLS and diagnosed with POAG. They suggested that fluctuations of IOP may have a relevant influence on the progression of glaucoma, as it was already considered in previous publications. The patients were classified with stable or progressive POAG, which was based on significant decrease in visual field mean deviation, visual field index and/or retinal nerve fiber layer (RNFL) thickness in serial examinations. Interestingly there was found to be a significant difference in IOP fluctuation between both, stable and progressive, groups. In the progressive group were larger fluctuations to be found, in terms of gradient and curvatures, at the time of going to bed (6pm-1am) and waking up (3am-11am). This could lead to the assumption that larger fluctuations of IOP are a factor in progression of POAG, as it was also found in previous studies (57), although these publications focused on fluctuation assessed by GAT.

In conclusion to the studies cited above, it can be stated that there is no unanimous position in research regarding the clinical usefulness of the TF CLS. There are some studies, which showed very interesting and promising results (14, 15, 17, 28, 49, 54). On the other hand it seems that the basic concept of mechanics behind the TF lens needs to be addressed again (33, 48, 51) and that the CLS shows limited ability to obtain clinically relevant values (13, 31, 53). Some studies were actually conducted, although the reproducibility and validity are still not completely resolved. There were trials using the CLS for monitoring the fluctuations of IOP after trabeculoplasty (58, 59) and after cataract surgery (60) in glaucoma patients. Mansouri et al even changed their therapeutical strategy due to the results obtained by the CLS (2).
After reading and studying all available publications, we want to summarize the positive and negative aspects of the use of the CLS in the following to clarify status quo.

4.2.2 Pros and Cons

After this section of different studies conducted on the TF CLS device, we want to summarize the possible benefits and disadvantages of the device for its clinical use.

4.2.2.1 Pros

- **good tolerability and safety**

  The device has been proven to show good tolerability and safety in various studies. (1, 2, 28, 29) Its adverse effects are comparable to those in subjects wearing regular contact lenses (2), with no study showing complications that did not resolve within 24-hours after removal of the device, besides corneal epithelial micro-defects, which were treated with antibiotics as a precautionary measure in one study (1), but also resolved rather quickly.

  VAS was measured in one study and showed good tolerability with an average VAS of under 3 (if a range of 1 – 10 is used). (28)

  One study (1) showed significant lowered visual acuity while wearing the CLS, but this did not influence patients daily activities to a significant degree.

- **good patient comfort**

  The biggest advantage for patients is that the examination can be done in an ambulatory setting. There is no need to stay inside a sleeping laboratory and therefore the patient can follow his daily routine to nearly full extend. The application of the device is rather easy and there are no main contraindications known to this point.

  Additionally the gadget offers another big advantage in its vividness to the patient. Obtained profiles can be compared to previous measurements and are displayed in an easy and understandable way, which offers the possibility for patients to get an idea of their own status and could eventually improve compliance. Furthermore the device could lead towards a more individualized therapy for patients by creating the possibility of a more meticulous follow-up and validating changes made in medication.

- **fair to good reproducibility**

  Three studies showed that measurements obtained by the CLS at various time points, showed fair to good correlation. (13, 28, 61) Therefore the device shows rather good reproducibility in its observations.

It has to be taken into account that even IOP obtained by GAT shows some fluctuations over time and therefore it is not possible to receive an exact reproduction of results at all times. (47)

- **validity**

Validity cannot be easily evaluated, since the results of studies focusing on the comparability to GAT as the current standard showed mixed results. One study (49) compared the profile obtained by the CLS to the profile derived from multiple measurements by GAT, which still is the widely used standard in IOP evaluation. This comparison showed good correlation between the CLS and GAT.

However, there were also studies showing that the CLS profile did not show good correlation with measurements obtained by applanation tonometry. (31, 62) This was especially evident in patients where IOP was lowered medically. (53)

Furthermore it has to be remembered that the CLS output is not an absolute value of mmHg, but just deviations from an arbitrary set baseline. Therefore it is mandatory to measure the IOP in absolute value, for example by GAT, before and after the use of the TF lens to set its profile into perspective.

- **ability to show IOP profile outside of office hours**

An often-stated argument throughout the publications was, that the CLS offers the possibility of an alternative to GAT measurements within a sleeping laboratory, which is of high effort and rather high financial cost. It has to be said though, that the idea, that awakening of patients might alter the nocturnal IOP (2, 20), had been disproved by a study comparing 24-hour measurements by CLS and pneumatonometer (13). This assumption was often mentioned as one of the benefits of the CLS over conventional diagnostic tools.

The 24-measurement of IOP, regardless by whatever modality, is an important asset to the handling of glaucoma patients. (22) Several studies concluded that the IOP pattern obtained by the CLS shows different morphology outside of normal office hours. (2, 14) Especially important in this aspect is, that most patients show not just a general increase of IOP during nighttime (13-15), but also more fluctuations of IOP (17). Both of these factors are or may be substantial features in progression of glaucoma.

There was even one study suggesting that the CLS may have some benefits regarding the earlier recognition of IOP profile changes, especially in those during nighttime, over conventional devices in long-term measurement of IOP. (13)

- **new tool in prediction of progression of disease**

Two studies (15, 17) showed that some of the parameters obtained by the CLS could predict the progression of glaucoma. Therefore it may have an impact on the ongoing treatment and follow-up procedure. However, these findings will have to be validated again in studies featuring a larger study population. Additionally there should be studies focusing on prevention, meaning the ability of the device to detect early, unfavorable IOP profiles in risk population.

- **diagnostic tool, not only for classic glaucoma patients, but also in other fields of medicine**

Some groups went even further and extended their curiosity from glaucoma patients to different other clinical pictures, where IOP becomes important. One study went on and did its research on patients suffering from pseudoexfoliation syndrom. (56) Another study used the CLS to measure IOP in patients suffering from thyreoid eye disease. (55) So maybe the use of the TF lens could become a valuable asset in diagnosis and prevention of other diseases than glaucoma.

4.2.2.2 Cons

- **no absolute values**

This fact is already known since the introduction of the device and was mentioned in all publications so far.

One may tend to look at the TF profile in mmHg. However, in reality the CLS measures the deviations from an arbitrary baseline, which is set at the beginning of the measurement cycle. The inventor Leonardi mentioned a relation between central corneal radius and the prevalent IOP (42), but still the profile is not to be used in absolute values (2, 13, 29, 33). The strength of the device is in displaying the pattern of IOP over time and not to determine the exact IOP in mmHg value. Therefore conventional tonometry has to be performed before and after the CLS use to put the profile into perspective.

- **scepsis about the basic idea of function**

There have been some findings, which shed a new light onto the basic principle of function behind the TF lens. As already described into detail in the section before, there was a study (33) recreating and expanding the in-vitro trials done by Leonardi (27, 42) with somehow conflicting outcome. Another study (51) caused great controversy with its methods, which even led to a rectification by Leonardi, but its statements still seem to be rather valid. There were trials were IOP was physiologically, artificially increased by obtaining different body positions, which is a proper and accepted way of doing so (41), but to which the CLS did not show any accordance (31).

All of this leads towards a more pessimistic approach regarding the CLS and it should cause verification of the most basic and first studies done on the TF lens.

- **changes induced by the CLS which may alter its output**

There has been rather great controversy about the alterations to the eye, which can be found after the use of the TF lens and if those changes influence the output of the device.

There was a main focus on the central corneal thickness (CCT) in most of the studies dealing with this topic. One study showed that there was no difference in CCT after the use of the lens (1), one found that CCT got higher (48) and one group stated that the CCT got lower after an overnight period wearing the CLS (54).

All of the above-mentioned publications did not find a model, which might explain if the alterations of CCT may or may not influence the outcome values of the lens.

However, one further study showed that CCT increased non-significantly in eyes wearing the CLS over night and also stated that the increase of CCT is not altering the values obtained. (63) Additionally the same study found that the CLS is not affecting central corneal radius (CCR) significantly, and therefore it is quite unlikely that the longtime use of the lens itself is altering its own outcome in terms of CCR.

Still there is a gaping hole in the evaluation of this question, due to the great variety of results obtained by different groups and due to the fact that some areas of changes in biomechanics (rigidity and thickness of the sclera, humidity of the cornea, etc.) have not even be addressed until now.

- **artifacts**

There is not a lot of literature to be found, which deals with the artifacts in the TF profile.

Firstly Leonardi et al (27) described that the lens also captures the ocular pulsation, which was simulated by an amplitude of 3 mmHg in enucleated pig eyes in their study and is also seen in actual patients profiles. To be clear this is actually not to be described as an artifact since it may have a diagnostic value.

Secondly Leonardi wrote that: ‘Perturbations caused by movements of the eye and blinking ... will create very short spikes of large amplitude in the signal ... The movements of the contact lens itself ... may also induce perturbations in the recorded signal, but we expect the contact lens to return to a fixed balanced position after each eyelid blink or eye movement ...’ (27: p.436).

Furthermore it was stated (27, 28) that the impact of other biomechanical aspects, such as CCT, corneal diameter, rigidity of the sclera, etc., should be further investigated, which happened just to a certain degree, especially focusing on CCT (1, 48, 54, 63) and central corneal diameter (63), and was already mentioned above.

Faschinger and his team found some spikes in the profiles, which could not be totally explained and could eventually be artifacts.

These were the findings, which also led to the urge to compose this work.

5 Conclusion

Our study showed that light intensity itself did not influence the TF profile directly, although there are some hints on a potential impact of light especially when comparing complete darkness to light of any illuminance. These findings make further investigation into this topic necessary.

On the contrary temperature may have an influence on the profile, supporting already published data by Faschinger et al (30).

Beside our findings, further studies have to be conducted to detect more of possible causes and factors influencing the artifacts in the TF profile before making a significant statement on the actual utility of the device in clinical use. In the evaluation of the device's usability, studies focusing on the safety and tolerability of the CLS revealed a satisfying outcome. Publications focusing on the validity of the device however showed mixed results, which makes a recommendation for clinical use difficult. Furthermore the uncertainty regarding a standardized output value, missing definition of findings in the profile like fluctuations or artifacts and the rather unclear correlation to IOP remain further issues in the evaluation of the device.

Limitations of our study were the inability to totally rule out temperature. It would therefore be interesting to carry out this experiment within a setting were temperature can be kept on a steady level throughout the test run, without any influence on data acquisition and transmission. Using a thermostat inside the fluid is questionable, since every metal component and especially every electronic device close to the CLS may cause artifacts or even disruptions of the measurements. If possible a new study design could be created to meet these mentioned needs.

Additionally it would be interesting to rule out all other influencing factors such as electromagnetic fields to evaluate the basic noise of the CLS profile we found in our experiments. A Faraday cage could be used, although it remains unclear if data transmission will be influenced by this or not.

Taking all of this into account it has to be stated that, although the TF CLS provides a groundbreaking opportunity in theory, the device can nowadays not be recommended for everyday use in clinic.

6 Appendix

study logbook (Excel-file):

Test X	TT.MM.JJJJ				Light				Air			Weather		
Zeit	Ereignis	Lux	Temperaturlogger (Ch1;Ch3/Ch2)		100% open	100% closed	artificial	artificial*	air	dirSun	clear	partcloudy	cloudy	rain
09:00	Beginn													
09:30														
10:00														
11:00														
11:00														
11:20														
12:00														
12:00														
13:00														
13:00														
13:30														
14:00														
14:30														
15:00														
15:30														
16:00														
16:30														
17:00														
17:30														
18:00														
18:00														
18:30														
19:00														
19:30														
20:00														
20:00														
20:30														
21:00														
21:00														
	Sonnenuntergang:													
Nacht														
	Sonnenaufgang:													
07:00														
07:00														
07:30														
08:00														
08:30														
09:00	Ende													
100% open	*Jalousie 100% offen*													
100% closed	*Jalousie 100% geschlossen*													
artificial	*Neonlicht an (zwei Lampen)*													
*artificial**	*Leselampe an*													
air	*Fenster gekippt*													
dirSun	*direktes Sonnenlicht*													
clear	*wolkenlos*													
partcloudy	*leicht bewölkt*													
cloudy	*bewölkt*													
rain	*Regen*													

file of the data output of the TF CLS (PDF-file):

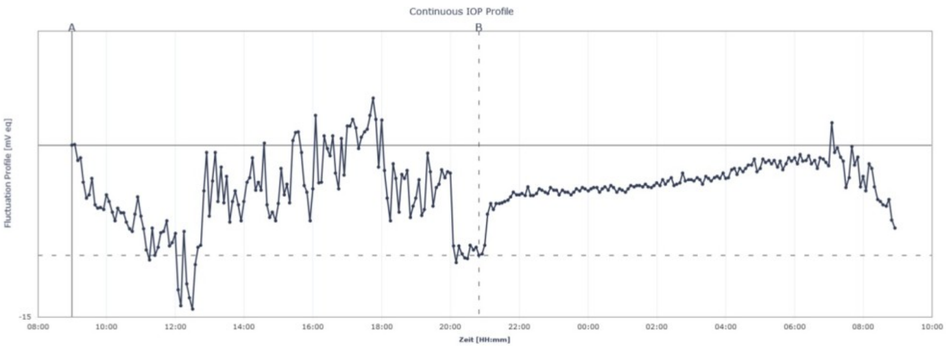
SENSIMED Triggerfish Zusammenfassung

SENSIMED Triggerfish

Patientendaten

Patientendaten		Aufzeichnungsdaten		Keratometrie	
Name des Patienten	Test 23.4.2015,	Beginn der Aufzeichnung	Apr 23, 2015 [08:59]	Radius 1	D (mm)
Geburtsdatum	-	Ende der Aufzeichnung	Apr 24, 2015 [08:59]	Achse	0
Patienten-Code	12345	Anfangs-IOD [mmHg]	0	Radius 2	D (mm)
Ethnische Zugehörigkeit	Sonstige	End-IOD [mmHg]	-	Achse	0
Geschlecht	Nicht definiert	Auge	Links	Empfohlene Sensor	STEEP

Continuous IOP Profile



SENSIMED Triggerfish Ver[Version: 2.4.9.3056] Bericht erstellt am 12.05.2015 @ 10:33

file of the data output of the temperature data logger (PDF-file):

EBI310 Leihlogger 1000 Kal. bis 01/2015

-ebro-

Allgemeine Informationen

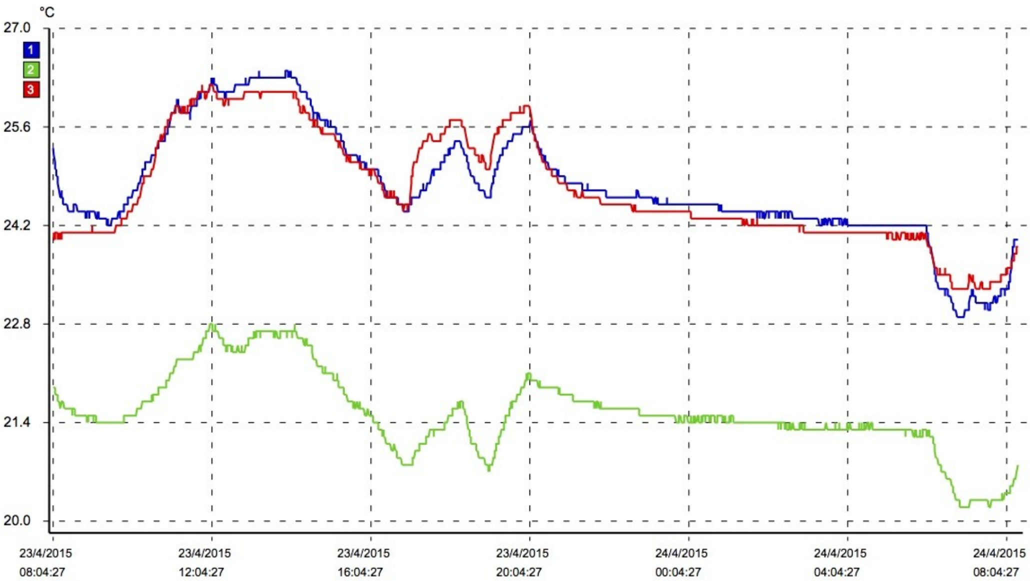
KTK
Kälte Technik Klima
Riedackerweg 1
A-8435 Wagna

Geräteinformation

Loggertyp	EBI 310 V1.32.0	Programmiert durch	Admin
Seriennnummer	15088551	Profil ID	0000
Fühlertyp	TPX 310 (#15158425)		

Aufzeichnungsinformation

Messmodus	Messen bis Speicher voll	Startzeit	23/4/2015 08:04:27
Intervall	1 Min.	Stoppzeit	24/4/2015 08:22:27
Messdauer	1d 00:18:00	Anzahl Messwerte	1459



Kanal	Unterer Grenzwert	Alarmzeitpunkt	Oberer Grenzwert	Alarmzeitpunkt
1 °C	✓ -200.0		✓ 400.0	
2 °C	✓ -100.0		✓ 400.0	
3 °C	✓ -100.0		✓ 400.0	

....
Unterschrift

24/4/2015 08:23:01 UTC+01:00
EBI310.pdf

-ebro-
www.ebro.com

1 / 4

contribution at the 12th EGS-Meeting in Prague, 19-22 June 2016:

P2.27

Is the contact sensor lens triggerfish influenced by light?

Christoph Faschinger, Maximilian Mächler, Georg Mossböck

Univ. Eye Clinic, Medical University Graz, Graz - Austria

References

1. De Smedt S, Mermoud A, Schnyder C. 24-hour intraocular pressure fluctuation monitoring using an ocular telemetry Sensor: tolerability and functionality in healthy subjects. J Glaucoma. 2012;21(8):539-44.

2. Mansouri K, Shaarawy T. Continuous intraocular pressure monitoring with a wireless ocular telemetry sensor: initial clinical experience in patients with open angle glaucoma. Br J Ophthalmol. 2011;95(5):627-9.

3. sensimed.ch. Company - About us: sensimed.ch; 2014 [08.06.2016]. Available from: http://www.sensimed.ch/en/company/about-us.html.

4. Nicolai T, Busse C. Glaukom: Pschyrembel Online; 2014 [08.06.2016]. Available from: https://www-1pschyrembel-1de-1pschyrembel.han.medunigraz.at/#q=glaukom&d=kw_4387612&f=&v=doc.

5. Kanski JJ. Kanski's Clinical Opthalmology - Chapter 10 Glaucoma. 8 ed. Bowling B, editor. Sydney: Elsevier; 2016.

6. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014;121(11):2081-90.

7. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006;90(3):262-7.

8. Cook C, Foster P. Epidemiology of glaucoma: what's new? Can J Ophthalmol. 2012;47(3):223-6.

9. Lang GK. Augenheilkunde - Kapitel 10 Glaukom. 1 ed. Stuttgart, New York: Georg Thieme Verlag; 2008.

10. Lüllmann-Rauch R. Taschenlehrbuch Histologie. 3 ed. Stuttgart: Thieme; 2009.

11. Llobet A, Gasull X, Gual A. Understanding trabecular meshwork physiology: a key to the control of intraocular pressure? News Physiol Sci. 2003;18:205-9.

12. Weinreb RN, Khaw PT. Primary open-angle glaucoma. Lancet. 2004;363(9422):1711-20.

13. Mottet B, Aptel F, Romanet JP, Hubanova R, Pepin JL, Chiquet C. 24-hour intraocular pressure rhythm in young healthy subjects evaluated with continuous monitoring using a contact lens sensor. JAMA Ophthalmol. 2013;131(12):1507-16.

14. Agnifili L, Mastropasqua R, Frezzotti P, Fasanella V, Motolese I, Pedrotti E, et al. Circadian intraocular pressure patterns in healthy subjects, primary open angle and normal tension glaucoma patients with a contact lens sensor. Acta Ophthalmol. 2015;93(1):e14-21.

15. De Moraes CG, Jasien JV, Simon-Zoula S, Liebmann JM, Ritch R. Visual Field Change and 24-Hour IOP-Related Profile with a Contact Lens Sensor in Treated Glaucoma Patients. Ophthalmology. 2015:744-53.

16. Singh K, Shrivastava A. Intraocular pressure fluctuations: how much do they matter? Curr Opin Ophthalmol. 2009;20(2):84-7.

17. Tan S, Yu M, Baig N, Chan PP, Tang FY, Tham CC. Circadian Intraocular Pressure Fluctuation and Disease Progression in Primary Angle Closure Glaucoma. Invest Ophthalmol Vis Sci. 2015;56(8):4994-5005.

18. Excellence NIfHaC. Glaucoma. Diagnosis and management of chronic open angle glaucoma and ocular hypertension London: National Collaborating Centre for Acute Care at The Royal College of Surgeons of England; 2009 [28.06.2016]. Available from: https://www.nice.org.uk/guidance/cg85/evidence/full-guideline-243555949.

19. Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. Surv Ophthalmol. 2000;44(5):367-408.

20. De Smedt S. Noninvasive intraocular pressure monitoring: current insights. Clin Ophthalmol. 2015;9:1385-92.

21. Aref AA. What happens to glaucoma patients during sleep? Curr Opin Ophthalmol. 2013;24(2):162-6.

22. Barkana Y, Anis S, Liebmann J, Tello C, Ritch R. Clinical utility of intraocular pressure monitoring outside of normal office hours in patients with glaucoma. Arch Ophthalmol. 2006;124(6):793-7.

23. Mansouri K. The road ahead to continuous 24-hour intraocular pressure monitoring in glaucoma. J Ophthalmic Vis Res. 2014;9(2):260-8.

24. Morgan WH, Yu DY. Surgical management of glaucoma: a review. Clin Experiment Ophthalmol. 2012;40(4):388-99.

25. Fanghänel J. Descemet-Membran: Pschyrembel Online; 2012 [06.07.2016]. Available from: https://www-1pschyrembel-1de-1pschyrembel.han.medunigraz.at/#/Descemet's%20membrane/K05RJ/doc/.

26. Ang LP, Ang LP. Current understanding of the treatment and outcome of acute primary angle-closure glaucoma: an Asian perspective. Ann Acad Med Singapore. 2008;37(3):210-5.

27. Leonardi M, Pitchon EM, Bertsch A, Renaud P, Mermoud A. Wireless contact lens sensor for intraocular pressure monitoring: assessment on enucleated pig eyes. Acta Ophthalmologica. 2009;87(4):433-7.

28. Mansouri K, Medeiros FA, Tafreshi A, Weinreb RN. Continuous 24-hour monitoring of intraocular pressure patterns with a contact lens sensor: safety, tolerability, and reproducibility in patients with glaucoma. Arch Ophthalmol. 2012;130(12):1534-9.

29. Faschinger C, Mossbock G. [Continuous 24 h monitoring of changes in intraocular pressure with the wireless contact lens sensor Triggerfish. First results in patients]. Ophthalmologe. 2010;107(10):918-22.

30. Faschinger WC, Rabensteiner FD, Mossböck G. How do temperature variations influence the signal in the Triggerfish contact lens sensor? Spektrum der Augenheilkunde. 2014;28(5):197-204.

31. Faschinger C, Mossbock G, Krainz S. [Validity and reproducibility of sensor contact lens profiles in comparison to applanation tonometry in healthy eyes]. Klin Monbl Augenheilkd. 2012;229(12):1209-14.

32. Faschinger C, Faschinger E, Krainz S, Mossböck G. About The Contact Lens Sensor Triggerfish®: Experiences Up Until Now. Acta medico-biotechnica. 2012;2012; 5 (1):39–45.

33. Faschinger C, Mossböck G, Strohmaier C, Reitsamer AH. 24-hour "intraocular pressure" measurement with sensory contact lens Triggerfish: from euphoria to disillusion. Spektrum der Augenheilkunde. 2011;25(4):262-8.

34. Leonardi M. Microfabricated thin film strain gaga sensor with telemetry micrprocessor embedded in a soft contact lens for minimally invasive intraocular pressure monitoring [dissertation]. Lausanne: Swiss Federal Institute of Technology Lausanne; 2007.

35. Sit AJ. Continuous monitoring of intraocular pressure: rationale and progress toward a clinical device. J Glaucoma. 2009;18(4):272-9.

36. sensimed.ch. Technical white paper: Principles and rationale for the SENSIMED Triggerfish® Sensor device. 2013 [19.05.2016]. Available from: http://www.sensimed.ch/images/pdf/sensimed_triggerfish_white_paper_2014.pdf.

37. sensimed.ch. SENSIMED Triggerfish®: sensimed.ch; 2014 [16.12.2015]. Available from: http://www.sensimed.ch/en/sensimed-triggerfish/sensimed-triggerfish.html.

38. Mansouri K, Weinreb R. Continuous 24-hour intraocular pressure monitoring for glaucoma--time for a paradigm change. Swiss Med Wkly. 2012;142:w13545.

39. Administration USFaD. FDA permits marketing of device that senses optimal time to check patient's eye pressure. Increased eye pressure is associated with nerve damage common in glaucoma: U.S. Food and Drug Administration; 2016 [20.06.2016]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm489308.htm.

40. Hjortdal JO, Jensen PK. In vitro measurement of corneal strain, thickness, and curvature using digital image processing. Acta Ophthalmol Scand. 1995;73(1):5-11.

41. Lam AK, Douthwaite WA. The effect of an artificially elevated intraocular pressure on the central corneal curvature. Ophthalmic Physiol Opt. 1997;17(1):18-24.

42. Leonardi M, Leuenberger P, Bertrand D, Bertsch A, Renaud P. First Steps toward Noninvasive Intraocular Pressure Monitoring with a Sensing Contact Lens. Investigative Ophthalmology & Visual Science. 2004;45(9):3113-7.

43. National-Instruments.com. Measuring Strain with Strain Gages 2014 [18.01.2016]. Available from: http://www.ni.com/white-paper/3642/en/.

44. National-Instruments.com. Strain Gauge Configuration Types 2006 [18.01.2016]. Available from: http://www.ni.com/white-paper/4172/en/.

45. Ebro. EBI300/310/330 (manual). Ingolstadt: WTW GmbH; 2014.

46. McLaren JW, Brubaker RF, FitzSimon JS. Continuous measurement of intraocular pressure in rabbits by telemetry. Investigative Ophthalmology & Visual Science. 1996;37(6):966-75.

47. Realini T, Weinreb RN, Wisniewski SR. Diurnal intraocular pressure patterns are not repeatable in the short term in healthy individuals. Ophthalmology. 2010;117(9):1700-4.

48. Hubanova R, Aptel F, Chiquet C, Mottet B, Romanet JP. Effect of overnight wear of the Triggerfish((R)) sensor on corneal thickness measured by Visante((R)) anterior segment optical coherence tomography. Acta Ophthalmol. 2014;92(2):e119-23.

49. Pajic B, Pajic-Eggspuchler B, Haefliger I. Continuous IOP fluctuation recording in normal tension glaucoma patients. Curr Eye Res. 2011;36(12):1129-38.

50. Meyer GP. Bayliss-Effekt: Pschyrembel Online; 2012 [01.06.2016]. Available from: https://www-1pschyrembel-1de-1pschyrembel.han.medunigraz.at/#q=Bayliss-Effekt&d=kw_4379563&f=&v=doc.

51. Sunaric-Megevand G, Leuenberger P, Preussner PR. Assessment of the Triggerfish contact lens sensor for measurement of intraocular pressure variations. Acta Ophthalmol. 2014;92(5):e414-5.

52. Leonardi M. Response to the letter to the editor entitled 'Assessment of the Triggerfish((R)) contact lens sensor for measurement of intra-ocular pressure variations'. Acta Ophthalmol. 2016;94(1):e79.

53. Hollo G, Kothy P, Vargha P. Evaluation of continuous 24-hour intraocular pressure monitoring for assessment of prostaglandin-induced pressure reduction in glaucoma. J Glaucoma. 2014;23(1):e6-12.

54. Mansouri K, Weinreb RN, Liu JH. Efficacy of a contact lens sensor for monitoring 24-h intraocular pressure related patterns. PLoS One. 2015;10(5):e0125530.

55. Parekh AS, Mansouri K, Weinreb RN, Tafreshi A, Korn BS, Kikkawa DO. Twenty-four-hour intraocular pressure patterns in patients with thyroid eye disease. Clin Experiment Ophthalmol. 2015;43(2):108-14.

56. Tojo N, Hayashi A, Otsuka M, Miyakoshi A. Fluctuations of the Intraocular Pressure in Pseudoexfoliation Syndrome and Normal Eyes Measured by a Contact Lens Sensor. J Glaucoma. 2015:e463-8.

57. Sultan MB, Mansberger SL, Lee PP. Understanding the importance of IOP variables in glaucoma: a systematic review. Surv Ophthalmol. 2009;54(6):643-62.

58. Tojo N, Oka M, Miyakoshi A, Ozaki H, Hayashi A. Comparison of fluctuations of intraocular pressure before and after selective laser trabeculoplasty in normal-tension glaucoma patients. J Glaucoma. 2014;23(8):e138-43.

59. Lee JW, Fu L, Chan JC, Lai JS. Twenty-four-hour intraocular pressure related changes following adjuvant selective laser trabeculoplasty for normal tension glaucoma. Medicine (Baltimore). 2014;93(27):e238.

60. Tojo N, Otsuka M, Miyakoshi A, Fujita K, Hayashi A. Improvement of fluctuations of intraocular pressure after cataract surgery in primary angle closure glaucoma patients. Graefes Arch Clin Exp Ophthalmol. 2014;252(9):1463-8.

61. Mansouri K, Liu JH, Weinreb RN, Tafreshi A, Medeiros FA. Analysis of continuous 24-hour intraocular pressure patterns in glaucoma. Invest Ophthalmol Vis Sci. 2012;53(13):8050-6.

62. Faschinger C, Mossbock G. Validity of the results of a contact lens sensor? JAMA Ophthalmol. 2013;131(5):696-7.

63. Freiberg FJ, Lindell J, Thederan LA, Leippi S, Shen Y, Klink T. Corneal thickness after overnight wear of an intraocular pressure fluctuation contact lens sensor. Acta Ophthalmol. 2012;90(7):e534-9.