

O kontaktni leči Sensor Triggerfish®: dosedanje izkušnje

About The Contact Lens Sensor Triggerfish®: Experiences Up Until Now

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Izvleček

Namen prispevka je prikazati novo napravo, senzorsko kontaktno lečo Triggerfish, za stalno merjenje intraokularnega pritiska, dosedanje izkušnje in oceniti možnost njene uporabe. Prikazane so do sedaj objavljene raziskave na to temo. Naprava se dobro prenaša, je varna, preiskava se lahko ponovi. Do sedaj je še premalo podatkov, da bi jo lahko uporabljali že v vsakodnevni praksi pri zdravljenju glavkoma. Potrebne bodo še dodatne raziskave.

Abstract

The purpose is to describe the new device Triggerfish, a sensor contact lens for continuous intraocular pressure measurements, the experiences so far and to judge the possible necessity. Literature search and own publications are presented. Good tolerability and safety, good to fair reproducibility, no validity was observed. Up to now there are too less data to include this new device in every-day practice as a necessary tool for the management of glaucoma. Much more studies testing the validity are warranted.

INTRODUCTION

Glaucomas are a variety of diseases defined by a typical optic atrophy with typical visual field defects. Beyond several risk factors like age, race, positive family history and high myopia, the main and only treatable risk factor is the intraocular pressure (IOP). This pressure increases above an individual, unknown level of tolerance (many decades before, the level was set at 21 mm Hg). Nowadays, the gold standard to measure the IOP is the Goldmann applanation tonometry (GAT). Usually, the IOP is measured in an upright, sitting position during the office hours for a few times (2–3x), rarely more often, in a supine position or during the night time. Well known, but differently judged as a risk factor for glaucoma per se or its progression, are the fluctuations of the IOP (1). According to the results of perfectly performed studies the IOP was higher during the nocturnal period than the diurnal period (2). Two-thirds of glaucoma patients and over 90% of healthy individuals had IOP peaks during the nocturnal period. Night measurements are very costly (infrared goggles etc) and reserved for distinct sleeping laboratories (3).

Therefore it has been a dream for many years to obtain measurements of the IOP over a continuous period, comparable to the 24-hours electrocardiogram or 24-hours blood-pressure measurements. After several attempts of continuous monitoring in rabbits with strain gauges embedded in contact lenses, Leonardi was the first to develop a “pressure sensing” contact lens for use in human. We describe the device and summarize the experiences to answer the question, if it is worth to use this contact lens sensor now as an additional tool in the management of glaucoma (4, 5).

Device Triggerfish®

In 2009 the Swiss company Sensimed received the CE-mark for their product Triggerfish. This is a contact lens made out of silicone with a special, hydrophilic coating for long-term tolerance. The contact lens is available in 3 different radius (steep, medium, flat). Their choice depends on the radius of the cornea. Inside the contact lens are embedded:

- 1 golden circular microantenna of 30 μm width

- 2 active strain gauges, circular, acting as sensors, made out of titanium–platinum, one peripheral of the antenna at about 11 mm, one central of the antenna, each of 7 μm width
- 2 passive strain gauges, short
- 1 microprocessor unit for communication with the antenna, 100 μm thickness, coated.

A second antenna has to be worn around the margins of the orbita. This antenna takes and brings impulses from and to the microchip (radio transmission) and is connected with a thin wire to a storage box (recorder), which is hold in a small basket and fixed around the belly. (Fig 1., Fig 2.). The output signals are milliVolt. Measurements take place after each 5 minutes for 30 seconds for 24 hours, in total 244 times. After 24 hours it stops automatically.

The result is a graph where the x-axis is the time and the y-axis is an arbitrary unit, not mm Hg (mercury). Each point of the measurements can be analysed in



Figure 1. Sensor contact lens in the left eye, the square microprocessor and the golden antenna are easily visible. Around the orbita a second antenna for data transfer is placed.

detail, in which high spikes of the lid movements may be recognized. During sleep those spikes are missing, only the small amplitudes resulting from the heart beats are visible (Fig 3). This graph is easy to understand and might improve the patients understanding and compliance of the disease.

The 24-hour monitoring is an outpatient procedure. The patients should do anything they like, as they behave all days, should use their eye drops as usual (against glaucoma or/and against dry eyes). They are asked to write a diary about the kind and time of their activities. Glasses with metallic frames are not permitted because of probable interferences.



Figure 2. The second antenna around the orbit is connected to a recorder, which is worn in a small basket around the belly.

The principle of the measurement is a detectable change of the corneal curvature near the limbal region due to changes of the IOP. One mm Hg changes the curvature in $3 \mu\text{m}$ and this change alters the resistance of the strain gauge.

The costs for the hardware and software including 3 sensor contact lenses are about 10.000.- Euro. Additional lenses cost 500 Euro each. They are one-way-products and cannot be used a second time without hazards.

Leonardi's experiments

Leonardi et al were the first to continue past experiments with pressure sensors by the first time use of an embedded strain gauge in a soft contact lens (4). They chose six juvenile enucleated porcine eyes, cannulated them and changed the IOP by pump sets of injections and ejections of fluid. Five cycles between 17 and 29 mm Hg within 200 seconds were performed. The contact lens graph followed the IOP graph well. But do those rapid changes of the IOP (each 50 seconds \pm 12 mmHg) resemble human every-day fluctuations?

Five years later Leonardi et al published their results of a wireless data transmission set (5). They again used enucleated pig eyes (10) and changed the IOP by cannulation, but this time from 11 to 14 mm Hg and vice

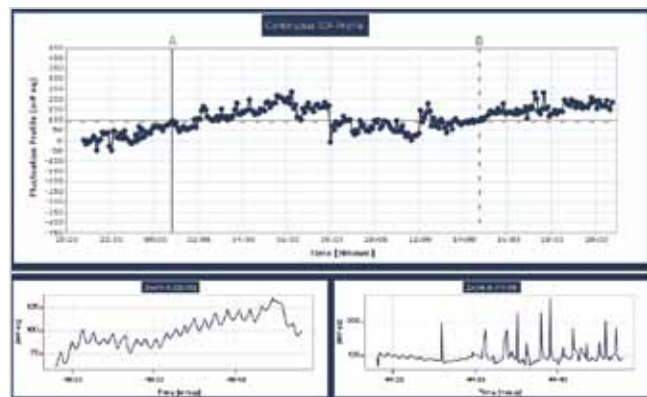


Figure 3. Result of a 24-hour monitoring. Each black dot symbolizes a period of 30 seconds with measurement, between are 5 minutes interval. Each point may be analyzed in detail. The left inferior graph shows one point during the sleeping period: only the heart beats are detected. The right inferior graph shoes one point during at 14:44 o'clock with high spikes due to movements of the lids. The y-axis is in an arbitrary unit, not in mm Hg.

versa within 5 seconds. In all cases, the CLS signal correlated well with the IOP measurements. Again, do those even more rapid changes (each 5 seconds \pm 3 mm Hg) resemble human every-day fluctuations? A second experiment was done with a setting of a step-wise increase in IOP of 1 mm Hg between 20 and 30 mm Hg. Again, the CLS showed high linearity and reproducibility.

The first in-vivo human measurements were done in 5 healthy volunteers (6). The filtrated CLS signals correlated well with the Goldmann tonometer. In a scuba mask manoeuvre to increase and decrease the IOP, the CLS signals correlated well again.

In 2009, the Swiss start-up company Sensimed obtained the CE mark for safety and tolerability and started to contact universities for first clinical trials.

First results: Safety and tolerability

The enthusiasm to have such a “convincing” device led to phenomenon, that most of the patients, who participated in these clinical trials, had an ocular hypertension or glaucoma. They were easily convinced to try the Triggerfish to “get more insight in the behaviour of your IOP, especially during activities and night time”.

Our first results in 11 patients with glaucoma or ocular hypertension were good. None of them discontinued the 24-hour measurements. All patients showed typical limbal impressions of the conjunctiva due to the steepness of the contact lens. All corneas remained clear, no infections occurred. I myself tried it for 24 hours. The CLS was tolerated well, I could do all my activities (even mountain biking), but was glad to remove it next morning (not used to wear contacts) (7). Mansouri and Shaarawy were the next to publish their results of 15 patients with glaucoma. Thirteen finished the 24-hours monitoring, 1 patient with severe dry eye discontinued after 13 hours, and monitoring was interrupted in a second patient after 17 hours. No serious adverse events were recorded, 4 patients showed a superficial punctate keratitis. The average comfort score was 7 (10 = best) (8).

Ten healthy volunteers were examined by de Smedt et al and showed good tolerability and functionality. Visual acuity was reduced during the wear of the CLS.

After the removal of the CLS a transient myopisation was recognized. The comfort score was between 7.5 and 9 (best comfort = 10). In all recordings, the highest values were reached at night time (9).

Mean adverse events in 40 patients suspected of having glaucoma or with established glaucoma were blurred vision (82%), conjunctival hyperemia (80%) and superficial punctate keratitis (15%). The investigators qualified the adverse events as mild and the tolerability as moderate to good (10).

Finally, Schweiger et al reported on pain and foreign body sensation in all of her 4 patients with glaucoma. All showed a superficial punctate keratitis after removal of the CLS (11).

In summary, the safety is good and the tolerability moderate to good, but both are not excellent.

Next results: Reproducibility

Reproducibility of the results is an important factor in any device. Due to long-term fluctuations and different behaviour, for intraocular pressure phasing it is not mandatory to obtain exactly the same results when repeating the measurements within several days (12). But at least the pattern of the measured results should show a high correlation.

Pajic et al examined 5 patients with normal tension glaucoma with the CLS after a washout period of local treatment and repeated the monitoring on a second occasion at least 6 weeks later with treatment. All patients showed a similar pattern of the 2 monitoring sessions, with profiles significantly lower in the treated session (13).

Mansouri et al repeated the complete 24-hours recordings in 37 patients after a 1 week interval. They found a fair to good agreement in patients with untreated glaucoma, but a weaker correlation (especially the day-to-night slope) in the treated patients (10).

Still missing were examinations of the reproducibility in healthy, young and elderly subjects.

Therefore our group examined 5 healthy young students for 2 hours with the CLS in different body positions and repeated the experiment 2–8 weeks later. Only after a certain period of “accustoming” of the CLS to the eye (45 minutes after the start) the profiles were comparable (14).

Further results: Validity

Validity means comparison of the results with the gold standard method, the Goldmann applanation tonometry in healthy as well as in diseased persons. In the presence of Leonardi we repeated his experiments, but with an enucleated human globe. After positioning of the CLS and cannulation we increased the IOP stepwise in 5 mm Hg, but remained at this level for a longer time (30 minutes). The pressure transducer showed a perfect stepwise profile, the Triggerfish did not show any increase of the profile. We had no explanations for these results (15). This experiment with human globes should be repeated.

Additionally, we performed an experiment in 5 young, healthy students, who received a CLS in one eye and got standard IOP-measurements by Goldmann applanation tonometry in their second eye (assuming, that there is no difference in the behaviour of both eyes). After a certain period of getting used to the CLS (45 minutes in upright position) we changed the position of the head and body in a supine (for 30 minutes) and head-body-down position (for 20 minutes), followed by 30 minutes in upright position. The Goldmann measurements were done at the slitlamp when upright and by a Clement-Clarke applanation tonometer in supine or head-body-down position by the same and experienced person (CF). All experi-

ments were done in strictly identical conditions (same time, same location) (14).

Due to physiology (16, 17), the applanation tonometries showed an increase of the IOP in supine position and a further increase in head-body-down position, decreasing when upright again (Fig 3.). In all of our 5 students no CLS profile showed this slope-like profile. In contrast, the profile was flat or went downwards when the IOP increased, and went upwards at the end of the experiment, when the IOP decreased (Fig 4.).

The reason(s) for this missing validity is (are) unclear. The CLS fitted perfectly, there were no disturbing conditions (too hot temperature, too humid, computers or cellular phones, goggles with metallic frames, etc).

Summary

The CLS is a new device for measuring changes of the corneal curvature due to changes of the IOP, as stated by the inventors and their experiments on enucleated porcine eyes.

Up until now we do not have enough data to know exactly what the CLS Triggerfish measures. It perfectly demonstrates the regular curves generated by the heart beats as short pulses with high amplitudes, transmitted by the blood pressure via the vessel walls to the vitreous, thus deforming the shape of the cor-

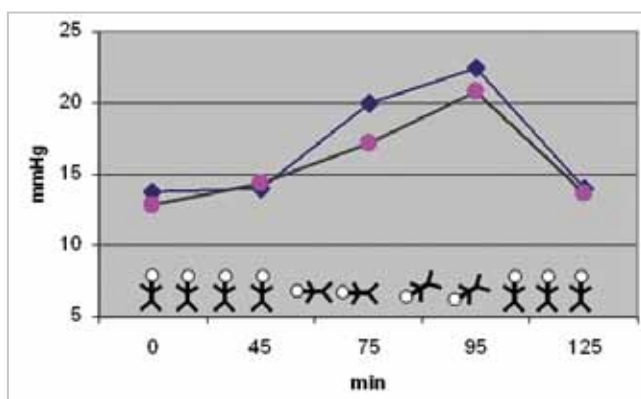


Figure 4. Graph of 5 subjects, who changed their body positions (symbols) and got their intraocular pressure measured by applanation tonometry (right eye). The graph shows the expected increase in supine and head-body down position. The experiment was repeated after 2-8 weeks and showed a good correlation.

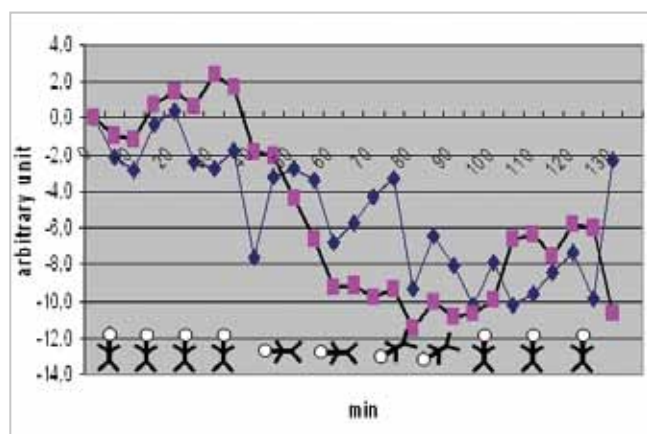


Figure 5. Graph of the same 5 subjects, who got a sensor contact lens in their left eye simultaneously to the applanation tonometry. The graph shows no increasing slope when supine or head-body down. The reproducibility 2-8 weeks later was fair to good.

nea. The IOP and its fluctuations, which are usually slowly changing parameters (except active Valsava maneuvers), change the curvature of the cornea (18). But whether or not the Triggerfish can measure these subtle changes cannot be answered with (scientific) certainty. Maybe different locations of the active strain gauges may lead to more valid results. Several further qualities of the cornea and the sclera, like thickness, stromal hydration, elasticity or viscosity, are not taken into consideration so far.

It would be fair, not to describe the result as “continuous” measurements as advertisements (and publications) did. There are always periodical interruptions in measurements.

Up to now the CLS Triggerfish is no necessary tool in the management of glaucoma. Nevertheless, fur-

ther studies should be encouraged (19), especially in normal and healthy people of different ages. Maybe the implantation of a strain gauge (in the ciliary sulcus), together with an intraocular lens (in the bag) in phacoemulsification would be a superior solution.

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