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# Implantation and testing of a novel episcleral pressure transducer: A new approach to telemetric intraocular pressure monitoring

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## ABSTRACT

Measurement of intraocular pressure (IOP) is an essential tool in monitoring glaucoma. Single IOP assessments during clinical routine examinations represent punctual values and are not able to identify IOP fluctuations and spikes. Telemetric IOP measurements are able to monitor IOP during the day and night, and are location-independent. Six telemetric episcleral IOP sensors were investigated after minimally invasive subconjunctival implantation in 6 eyes of 6 New-Zealand-White rabbits. Three of the 4 edges of the implant were fixated intrasclerally with non-absorbable sutures. The sutures were stitched into the edges of the implants' silicone rubber encasements. Telemetric IOP measurements were validated 1 week, 4 weeks, 8 weeks, 12 weeks and 30 weeks after implantation. For each validation the anterior chamber was cannulated and connected to a height-adjustable water column. Different intracameral pressure levels (10–45 mmHg) were generated by height adjustment of the water column. Measurement reliability and concordance between telemetric and intracameral IOP was validated using Bland-Altman analysis. Overall comparison (10–45 mmHg) between telemetric and intracameral pressure revealed a standard deviation of ± 1.0 mmHg. A comparison of pressure values in the range between 10 and 30 mmHg revealed a standard deviation of ± 0.8 mmHg. Device deficiency was related to follow-up length: 4 weeks after implantation, 3 of the 6 sensors showed malfunction, with all sensors having failed 30 weeks after implantation. The most likely reason for the sensor malfunction is the loss of hermeticity as a result of penetration of the encasement during the episcleral fixation, resulting from the lack of preformed suture holes at the implants encasement. However, no clinical signs of injury or inflammation of the conjunctiva, sclera, implantation site or any other involved structures were observed, except for an expected mild short-term irritation postoperatively. The episcleral pressure transducer for telemetric IOP monitoring is able to assess IOP without the need for invasive intraocular surgery. Episcleral implantation is an easy and safe procedure and can be undone very easily, so even temporary implantation and IOP measurements could be possible in the future. Sensor malfunction over time is a problem that needs to be addressed. Improvements in sensor encapsulation and especially preformed suture holes could significantly decrease the failure rate and increase durability.

## 1. Introduction

Intraocular pressure (IOP) is the most important risk factor for the progression of glaucomatous optic neuropathy and glaucoma-associated visual field defects (Bengtsson et al., 2007; Heijl et al., 2002; Tan et al., 2015). IOP can only be assessed as punctual measurements in clinical routine examinations. Progression of glaucomatous optic neuropathy was observed in some cases, despite IOP measurements being within the desired range during single measurements. Undetected IOP fluctuations and spikes during those routine measurements were identified as a possible reason for glaucoma progression in those cases (Asrani et al., 2000; Nouri-Mahdavi et al., 2004; Walland et al., 2009).

Telemetric IOP measurements enable glaucoma monitoring via a new way of assessing IOP, even outside the clinical setting in the patient's familiar surrounding without the need for Goldmann applanation tonometry (GAT; Mansouri and Weinreb, 2012; Yung et al., 2014). Different approaches have been adopted to establish telemetric IOP measurements. Removable contact lens-based sensors were developed for 24 h measurements (Agnifili et al., 2015; De Moraes et al., 2015; Lorenz et al., 2013). Implantable IOP sensors for long-term measurements based on capacitor plates showed promising results. In particular, telemetric pressure transducers for implantation in the ciliary

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sulcus (Koutsonas et al., 2015; Melki et al., 2014) and pressure transducers for implantation in the suprachoroidal space (Mariacher et al., 2016) based on capacitive sensing were investigated. For implantation of the sulcus-based sensor, the natural lens needs to be replaced sometime (but not necessary directly) before implantation. However, implantation of the sulcus-based sensor in the recently published study from Koutsonas et al. was conducted directly following previous cataract surgery with IOL (intraocular lens) implantation in the same procedure for ethical reasons (Koutsonas et al., 2015). However, the sulcus-based sensor does not require cataract surgery in the same procedure. The sulcus-based sensor is designed for implantation between the iris and the IOL and is therefore potentially affected by pigment dispersion, pupillary distortion and iris atrophy caused by possible iris chafing (Paschalis et al., 2014). The implantation of the suprachoroidal sensor requires a scleral incision with separation of the sclera and choroid (Mariacher et al., 2016). The suprachoroidal implantation requires a scleral incision of approximately 4–5 mm. Therefore, choroidal damage is theoretically possible during this procedure. Ocular viscoelastic devices can be used to separate the sclera and choroid during implantation and therefore reduce the risk of possible complications (Mariacher et al., 2016).

A novel episcleral pressure sensor was developed to address these problems. The telemetric IOP sensor for subconjunctival implantation should minimize several risks associated with invasive intraocular surgery (e.g. intracameral or suprachoroidal surgery). It was the aim of this study to evaluate the reliability and measurement accuracy of the novel episcleral pressure sensor after implantation between the conjunctiva and the sclera in an *in vivo* setup over a follow-up period of 30 weeks.

For better comparison of the measurement accuracy, we stated SD from conventional and telemetric IOP measurement principles. Tondani et al. investigated repeated measurements of different measurement principles, which resulted in SDs of 3.4 mmHg, 2.7 mmHg and 0.8 mmHg for applanation tonometry with Tono-Pen, pneumatotonometry and sulcus-based telemetric IOP sensors using the principle of capacitive measurements, respectively (Todani et al., 2011). In addition, suprachoroidal implanted telemetric IOP sensors based on the same capacitive measurement principle revealed a SD of 1.5 mmHg (Mariacher et al., 2016). Therefore, we defined the target accuracy range as an SD of 0.8 mmHg.

## 2. Material and methods

Six novel episcleral pressure transducers (Fig. 1) were implanted in 6 eyes of 6 New-Zealand-White rabbits under xylazine and ketamine anesthesia. The episcleral pressure transducers were provided by Implandata Ophthalmic Products GmbH (Germany). Mean age was 13.7 ± 4.1 months with a minimum age of 11 months and a maximum of 19 months. The minimum age of 11 months was chosen to avoid any residual growth of the eyeball during the follow-up measurements. The mean weight was 5.5 ± 0.9 kg (minimum 5.0 kg; maximum 7.1 kg).

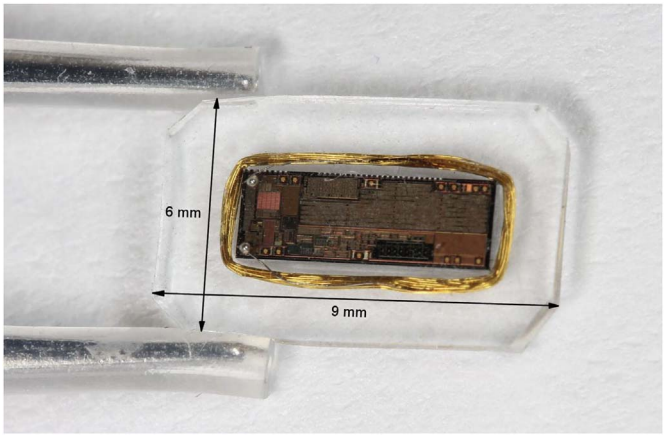


**Fig. 1. Novel implantable episcleral pressure transducer.** The ASIC (application-specific integrated circuit) itself is surrounded by a wire coil and embedded in a biocompatible silicone rubber encasement.

The episcleral pressure transducer is based on 6 capacitive pressure-sensing units located on an application-specific integrated circuit (ASIC). A wire coil surrounded the ASIC and enabled telemetric data exchange with a hand-held reading device. Telemetric IOP measurements were powered via induction from a hand-held reading device by placing the device in front of the eye and pressing the measuring button. The maximum distance between the outer surface of the eye and the reading device was approximately 4 cm for telemetric communication without interruption. Hence, no battery or other power source was required inside the implant. The episcleral pressure transducer was encapsulated in a biocompatible silicone rubber encasement. The outside of the episcleral implant was 9 mm long, 6 mm wide, and 0.9 mm thick. There were no predefined suture holes at the silicone rubber encasement, so the silicone rubber was penetrated with the needle for fixation during implantation. Therefore, the external dimensions of the episcleral sensor encasement was larger than technically required, in order to provide enough silicon rubber material for suture fixation of the implant's edges via penetrating sutures through the silicone encasement during episcleral fixation of the implant in the subconjunctival space (Fig. 1).

For episcleral implantation, the conjunctiva was excised over 2 clock hours at the temporal corneoscleral limbus. Subconjunctival implantation was performed very carefully using a prototype of a silicon rubber coated forceps (Implandata Ophthalmic Products GmbH, Germany) to protect the episcleral pressure transducers from damage through mechanical irritation (Fig. 1). Afterwards, each implant was fixed to the sclera via intrascleral sutures. Three of the 4 edges of the implant were fixed with non-absorbable sutures (Prolene 10-0, Ethicon Inc., Johnson & Johnson, US) to the sclera above the pars plana. For safety reasons, a distance of at least 1 mm was left between the suture needle penetration sites of the silicon rubber encasement and the ASIC sensors. At the end of the implantation procedure, the conjunctiva was repositioned to the corneoscleral limbus and fixed with 1 or 2 absorbable sutures (Vicryl 8-0, Ethicon Inc., Johnson & Johnson, US; Fig. 2).

Concordance between telemetric IOP measurements and intracameral manometry were investigated 1, 4, 8, 12 and 30 weeks after implantation. IOP was assessed 5 times for each intracameral applied pressure level. After placing the hand-held reading device in front of the eye, the measurement procedure started by pressing the measurement button on the reading device and 5 consecutive measurements were recorded. At the end of each measurement process, the average of these 5 measurements was displayed on the hand-held reading device in the form of a mean pressure value with one decimal place. This procedure was repeated 5 times for each intracameral pressure level. The intracameral manometry was recorded simultaneously for comparison with the telemetric IOP values.

Measurement function and reliability of the episcleral sensors were assessed using a height adjustable water column (Balanced Salt Solution infusion bag, Bausch & Lomb GmbH, Germany). Different intracameral IOP levels were applied between 10 and 45 mmHg in 5 mmHg steps (10 mmHg, 15 mmHg, 20 mmHg, 25 mmHg, 30 mmHg, 35 mmHg, 40 mmHg and 45 mmHg). The water column and a portable manometer (Delta-Cal, Utah medical products Inc., US) were connected to an anterior chamber maintainer (Lewicky Anterior Chamber Maintainer, Rumex International Co., US) using a 3-way valve (Discofix-3, B. Braun Melsungen AG, Germany). The anterior chamber maintainer consisted of a luer-lock connector and a self-retaining threaded tip for a stable fixation within the corneal stroma with a flexible tube in-between. The anterior chamber maintainer was inserted in a previously preformed temporal 3-plan clear cornea incision using a 20-gauge knife (MVR

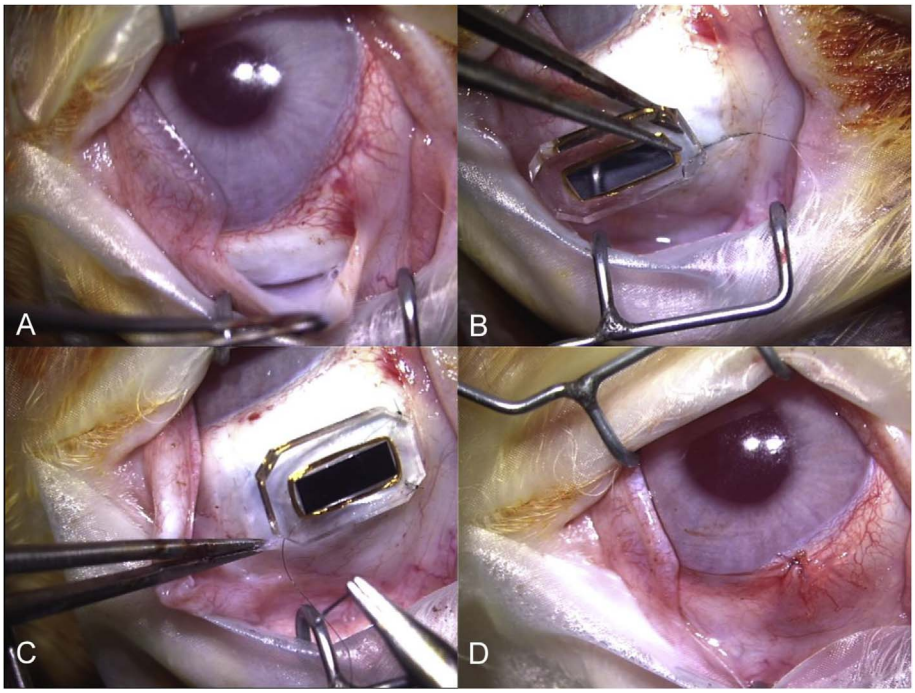


**Fig. 2. Episcleral implantation procedure of the telemetric pressure transducer.** After excision of the conjunctiva (A), the implant was inserted in the subconjunctival space (B) and fixed by sutures on 3 of the 4 edges (C). At the end of the implantation procedure, the conjunctiva was repositioned to the corneoscleral limbus (D).

knife 20 gauge, Mani Inc., Japan). After stabilization of the required intraocular pressure, the infusion was switched off so that the anterior chamber was directly connected to the manometer via the 3-way valve.

At the beginning of each measurement, the manometer was equalized to the intracameral incision by height adjustment of the manometer's lifting platform (Digimatic Height Gage, Mitutoyo Corp., Japan). After changing between different intracameral pressure levels, an adjustment time of 2 min was chosen. To avoid any measurement error according to leakage caused by cannulation of the anterior chamber using the anterior chamber maintainer, 2 methods to identify possible leakage were used. We cannulated the anterior chamber using a 3-plan clear cornea incision and observed the setup regarding any kind of leakage after switching off the infusion for at least 2 min before starting the measurements. Furthermore, we observed the connected real-time manometer during this time to detect any possible pressure decrease as a secondary sign of leakage. If any visual leakage or decreasing pressure was observed after the anterior chamber maintainer was already inserted, we used one suture (Ethilon nylon suture 10-0, Johnson & Johnson Medical GmbH, Germany) to seal the clear cornea incision. If this procedure did not stop the leakage, we performed a second suture on the other side of the clear cornea incision. There were no signs of persisting leakage, at least after the second suture.

The investigation focused on functionality of the implant and reproducibility of data. The wireless episcleral pressure sensor can be calibrated to any handheld IOP measurement device by simultaneously holding a specially equipped reading device in front of the sensor while the comparative measurement is performed. This can be done at any time point after the implantation. In addition, the calibration procedure can be repeated as often as necessary if any measurement drift occurs during long-term use. To ensure the comparability of IOP values across all sensors, each sensor was calibrated to its own linear function by a linear calibration curve at each follow-up measurement. To ensure the comparability of IOP values across all sensors, each sensor was calibrated using a sensor-specific linear calibration at each follow-up measurement. Having determined the slope and intercept of the best-fit line (calibration curve), we corrected each entire measurement series accordingly.

Clinical examinations of the eyes were performed prior to and after surgery and at the beginning of each intracameral measurement 1, 4, 8, 12 and 30 weeks after implantation. Eyelids, conjunctiva, cornea, anterior chamber, lens and the implantation site in particular were examined using a portable handheld slit lamp unit (Keeler PSL, Keeler Ltd., UK). Assessment of the posterior eye segment (vitreous body, retina and choroid) was performed by indirect binocular ophthalmoscopy (Heine Omega 500 binocular ophthalmoscope, Heine Optotechnik, Germany) with a 20 Diopter Lens (20D Lens, Volk Optical Inc., US).

This study was carried out in strict accordance with the EU Directive 2010/63/EU for animal experiments and complies with the ARRIVE guidelines. The protocol was approved by the governmental authority and the Committee on the Ethics of Animal Experiments of the University of Tuebingen. All surgery was performed under ketamine and xylazine anesthesia, and all efforts were made to minimize suffering.

For comparison between telemetric and intracameral IOP values, Bland-Altman analysis was conducted. Limits of agreement were defined as the mean measurement difference (mean bias) ± 1.96 SD (Bland and Altman, 1986). All statistical analyses were performed using SPSS Statistics 22.0 (IBM Corp., US). Graphics were generated using Microsoft Excel 2010 (Microsoft Corp., US).

## 3. Results

The agreement between telemetric IOP values and corresponding intracameral applied pressure levels was investigated using scatter plots and Bland-Altman analysis. Mean differences between those measurements, corresponding SD and limits of agreement (95% CI) are presented in Table A.1 in total and separated for each follow-up measurement. Analogously created Bland-Altman analysis for each follow-up measurement at 1 week, 4 weeks, 8 weeks and 12 weeks after implantation are displayed in Fig. 3. Overall analysis showed a mean measurement difference between telemetric and intracameral measurements of 0.0 ± 1.0 [-2.0, 2.0] mmHg (mean ± SD [95% CI]) ranging from 0.0 ± 1.5 [-2.9, 2.9] mmHg 1 week after implantation to 0.0 ± 0.5 [-0.9, 0.9] mmHg 4 weeks after implantation, 0.0 ± 0.1 [-0.2, 0.2] mmHg 8 weeks after implantation to 0.0 ± 0.0 [-0.0, 0.0] mmHg 12 weeks after implantation (Table A.2).

Furthermore, concordance between telemetric IOP measurements and intracameral applied IOP levels was evaluated for each intracameral IOP level between 10 mmHg and 45 mmHg among all pressure sensors and all follow-up measurements (Table A.1). The mean differences between telemetric assessed IOP values and intraocular manometry increased from −0.5 ± 0.9 [-2.4, 1.3] mmHg and −0.3 ± 0.5 [-1.3, 0.7]

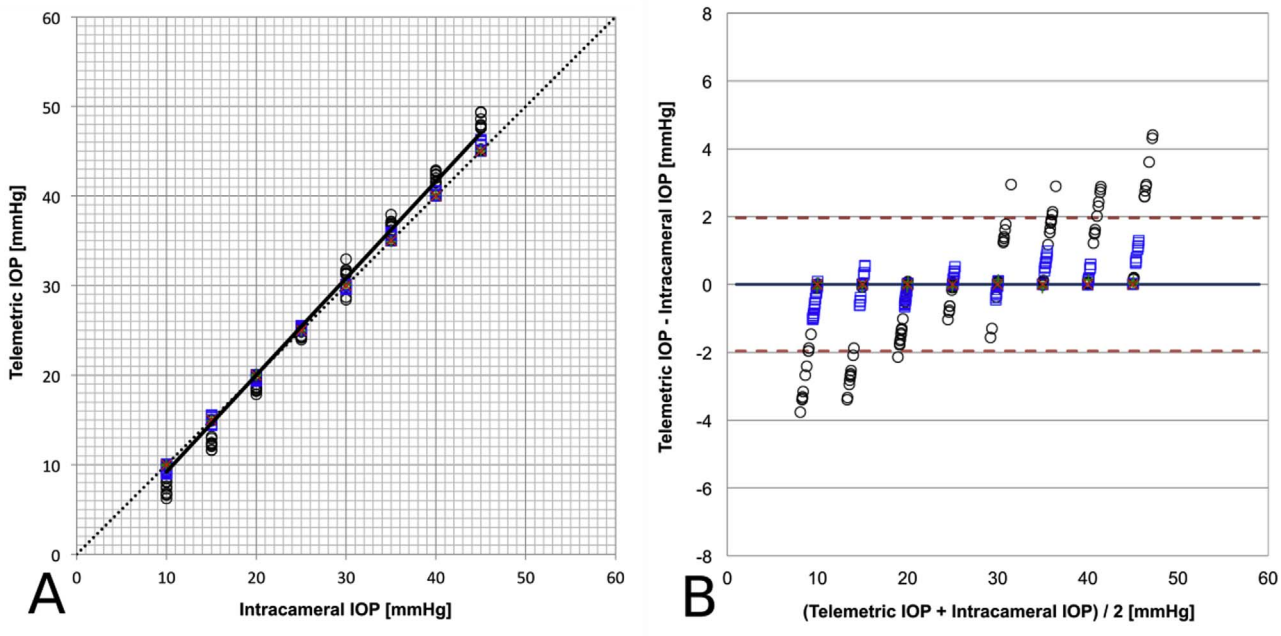


**Fig. 3. Scatter plot (A) and Bland-Altman plot (B) for overall comparison between episcleral pressure transducers and intracameral pressure levels 1 week (circles), 4 weeks (squares), 8 weeks (pluses) and 12 weeks (crosses) after implantation.** Angle bisector (dashed line) is stated in the scatter plot. The Bland-Altman plot shows limits of agreement (dashed lines) and mean bias (solid line). Both plots represent intracameral IOP values between 10 and 45 mmHg.

mmHg for the intracameral 10 and 20 mmHg level, respectively, to values up to 0.6 ± 0.8 [-1.1, 2.2] mmHg and 1.0 ± 1.4 [-1.7, 3.6] mmHg for the intracameral 35 and 45 mmHg level, respectively. In conclusion, overall mean difference was −0.3 ± 0.8 [-2.0, 1.3] mmHg for IOP levels between 10 and 30 mmHg and increased appreciably for IOP values equal to or above 35 mmHg (Table A.1).

Individual analyses of each sensor at each follow-up resulted in standard deviations of 0.02 to 2.2 mmHg and 0.002 to 1.6 mmHg for the 10 to 45 mmHg and 10 to 30 mmHg intracameral applied pressure ranges, respectively. In detail, 7 of 9 (78%) follow-up measurements were within a SD of 0.8 mmHg (95% CI ± 1.6 mmHg) and 5 of 9 (56%) measurement series were within a SD of 0.1 mmHg (95% CI ± 0.2 mmHg) in the intracameral applied pressure range of 10 to 45 mmHg. The other 2 sensors were within a SD of 2.2 mmHg (95% CI ± 4.3 mmHg). However, one of those two sensors with a higher SD at 1 week after implantation (SD ± 2.1 mmHg) showed improved measurement accuracy (SD ± 0.5 mmHg) 4 weeks after implantation.

Scatter plot and Bland-Altman plot (Fig. 3) indicate the tendency to underestimate IOP in the lower IOP range (10 to 15 mmHg) and overestimate IOP in the higher IOP range (30 to 45 mmHg). In Table A.3, mean measurement differences and corresponding SD as well as limits of agreement were separated for the different follow-up measurements (1 to 12 weeks after implantation) analyzing only IOP measurements between 10 and 30 mmHg (Fig. 4).

To assess possible IOP measurement drift over time between calibrations (1, 4, 8 and 12 weeks after implantation), the calibration curve of each sensor at the 1 week follow-up was set as a reference and each following measurement (4, 8 and 12 weeks after implantation) was additionally corrected using this calibration curve. Mean measurement differences between the measurements 1 week after implantation and following measurement series using the initial (1 week) calibration curve for both data sets for each sensor was 0.08 mmHg, 0.04 mmHg, 0.22 mmHg and 5.98 mmHg (overall 1.58 mmHg) 4 weeks after implantation, 0.09 mmHg 8 weeks and 1.95 mmHg 12 weeks after implantation.

Before and after the implantation and during each follow-up measurement, ophthalmic examinations were conducted with special regard to the implantation site. No clinical signs of injuries or inflammation of the conjunctiva, the sclera or any other involved structure were observed, except mild postoperative short-term irritation, as expected (Fig. 5). IOP measurements *in vivo* without anesthesia were possible, but revealed no satisfying results due to contraction of the eyelids with consecutive narrowing of the eyes to a slit. These measurements resulted in altered IOP values which are not suitable for a meaningful analysis.

During the first intracameral measurement (1 week after implantation), 1 episcleral sensor showed malfunction and was excluded from IOP analysis; this was true for another episcleral sensor during the 4 week assessment and 4 episcleral sensors at the 8 and 12 week assessments. One rabbit died of pneumonia 4 weeks after implantation. During autopsy, no link to the episcleral implant was found.

## 4. Discussion

We investigated the capability of a novel episcleral pressure sensor in rabbit eyes *in vivo*. Although our results indicated at least similar measurement accuracy compared to sulcus-based or suprachoroidal telemetric IOP sensors, the promising findings at the beginning of the study were limited by an increasing failure rate of the transducers.

The most likely explanation therefore is an impairment of the hermetically sealed encasement after the needle of the suture penetrated the implants' silicone rubber embedding during implantation. There were no predefined or preformed holes in the implant's silicone rubber encasement for fixation, so the silicone rubber embedding was inevitably damaged during fixation, resulting in a loss of hermeticity. As a consequence, malfunction of the pressure transducer after a couple of days or weeks was very likely due to water infiltration inside the implant. The most likely explanation therefore is that the suture material cut through the soft silicone encasement over time. In order to overcome this impediment, improved fixation facilities such as predefined holes at the edges of the implants encasement in combination with a grommet to strengthen the edges of the preformed holes, which strengthen the edges of the preformed holes, could prevent/resolve this issue. Having modified the fixation in this way, we expect that episcleral IOP sensors will provide lasting and reliable measurements.

Since the device relies on the measurement of IOP through the sclera, it is unclear if the episcleral approach would work in a human eye, as the sclera in rabbits is thinner than the sclera in humans. In addition,

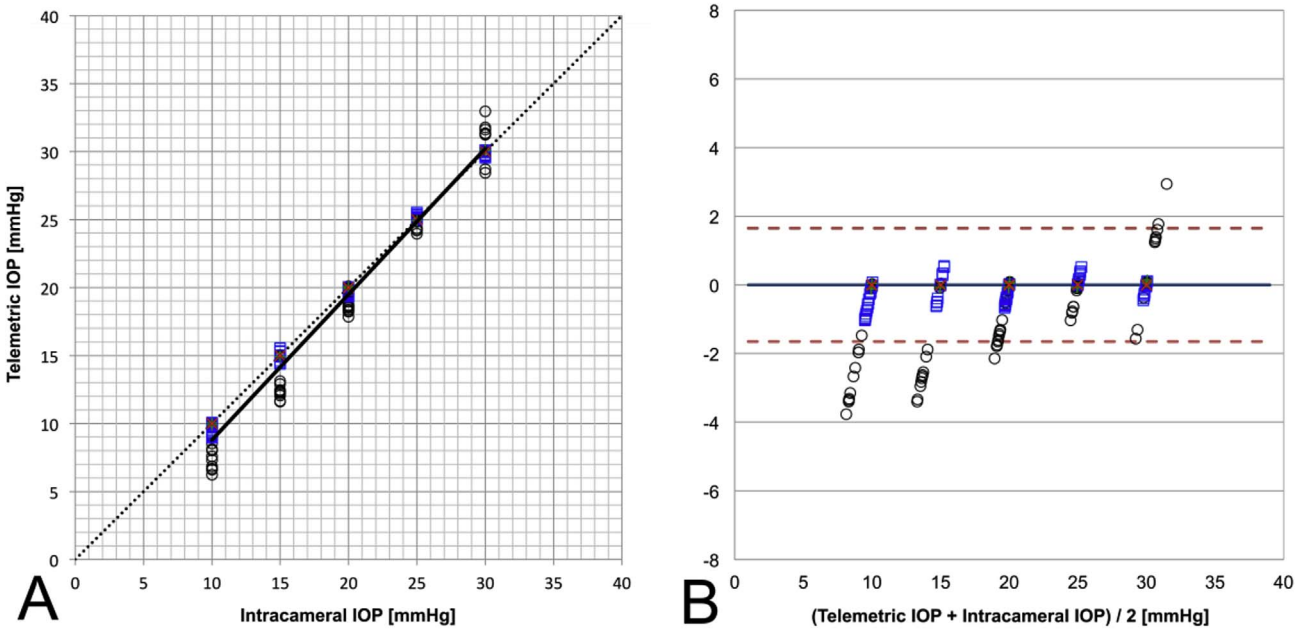


**Fig. 4. Scatter plot (A) and Bland-Altman plot (B) for comparison between episcleral pressure transducers and intracameral IOP levels measured/created through water column 1 week (circles), 4 weeks (squares), 8 weeks (pluses) and 12 weeks (crosses) after implantation.** Angle bisector (dashed line) is stated in the scatter plot. The Bland-Altman plot shows limits of agreement (dashed lines) and mean bias (solid line). Both plots represent intracameral IOP values between 10 and 30 mmHg.

dimensions of the human and rabbit's eyeball alter distinctly. However, results can only be translated carefully into the human situation. Human sclera was 0.53 mm ( ± 0.14 mm) thick at the corneoscleral limbus and 0.39 mm ( ± 0.17 mm) thick at the equator in an investigation from Olsen et al. (Olsen et al., 1998). On the contrary, the sclera of rabbits' eyes is 0.40 to 0.50 mm thick at the corneoscleral limbus and 0.19 to 0.25 mm at the equator (Davis, 1929; Downs et al., 2003). Smaller anatomical conditions with steeper curvatures of the rabbit eyeball in comparison to the human eyeball in combination with the rigid ASIC and therefore more or less rigid implant with a nearly cuboid form could serve as an explanatory model for mechanical stress in the form of bending forces with possible consecutive measurement variations. This can be illustrated by comparison of the axial length. The mean axial length is 23.67 mm ( ± 0.9 mm) in human eyes (Oliveira et al., 2007) and 16.24 mm ( ± 0.01 mm) in rabbit eyes (Barathi et al., 2002). Additionally, the rabbit's anteroposterior proportion is compressed in comparison with human eyes, so the posterior segment in rabbit eyes is proportionally smaller than in human eyes (Davis, 1929). However, early follow-up data suggest comparable measurement accuracy between the episcleral capacitive sensors and previously investigated suprachoroidal and sulcus-based capacitive sensors according to the SD of mean measurement differences. Furthermore, function of the measurement principle was proven in previous studies investigating telemetric pressure transducers using capacitive IOP measurement sensors based on a similar measurement principle (Koutsonas et al., 2015; Mariacher et al., 2016; Todani et al., 2011).

The hand-held reading device allowed only punctual measurements by pressing the measurement button. However, an additional device consisting of a coated coil with a diameter of 5 cm could be placed or stuck for a predefined time (e.g. 24 h) on the periorbital skin of the patient to monitor IOP in a constant manner with several measurements per second. The pressure sensor can measure/record IOP even at night when attaching the additional wire coil for automated IOP measurements to the periorbital skin (e.g. in form of a sleeping mask). The wire coil needs to be connected to the hand-held reading device, which has to be switched to the automated measurement mode. However, IOP can only been measured as fast as the integrated algorithm is working, so detection of fluctuations with high frequencies in the millisecond range are limited using these technique and has to be noted as a limitation of the capacitive microsensor.

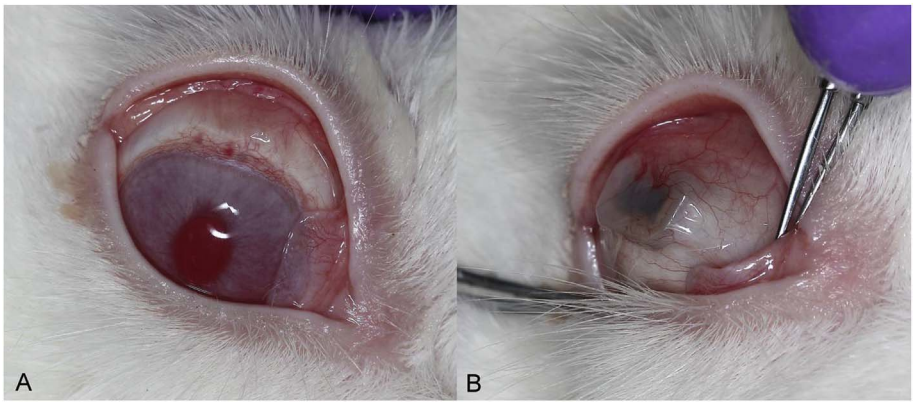


**Fig. 5.** Rabbit eye 30 weeks after implantation. Picture from anterior (A) - the implant is covered by the rabbit's nictitating membrane and eyelid and is not visible. After lifting the nictitating membrane and rotating the eyeball, the implantation site and the episcleral pressure sensor are visible (B).

Episcleral telemetric IOP measurements showed the tendency to overestimate intracameral pressure in the range between 30 and 45 mmHg. Analysis of the limits of agreement and mean measurement differences between telemetric and intracameral pressure values revealed higher measurement accuracy in IOP levels lower than or equal to 30 mmHg (Fig. 3 and Table A.2 and A.3). This phenomena was also described in a previous study investigating suprachoroidal IOP sensors (Mariacher et al., 2016) and could be related to mechanical forces due to smaller proportions in the rabbit eye described in the previous paragraph. The SD of the overall mean measurement difference reflecting the measurement accuracy was lower than the corresponding SD of the capacitive sulcus-based sensor and the capacitive suprachoroidal sensor (Mariacher et al., 1016; Todani et al., 2011). This range can serve as a proof of measurement principle of episcleral implants using capacitive sensors. Every sensor was analyzed separately at each follow-up measurement. The individual analysis for each sensor at each follow-up measurement resulted in 5 of 9 measurement series with a 95% CI of ± 0.2 mmHg and in 7 of 9 series with a 95% CI of ± 1.6 mmHg. Therefore, episcleral telemetric IOP sensors seem to provide acceptable measurement accuracy compared to sulcus-based and suprachoroidal capacitive pressure sensors.

However, leakage was a possible source of bias during the intracameral pressure measurement using the Lewicky anterior chamber maintainer. Even though we placed great effort in ruling out leakage, undetected leakage could have influenced our measurement results and is a limitation of the measurement set-up.

A major limitation of this study is that the telemetry device is designed to measure IOP through the sclera and doesn't measure IOP directly over the vitreous body or inside the anterior chamber. In contrast to the Triggerfish contact lens that measures corneal stretch, the scleral approach has the advantage that it doesn't block access to the cornea, and can therefore be calibrated against tonometers that use corneal applanation like GAT. The pressure sensor has been calibrated during the manufacturing process and function of the IOP measurement function is available without further *in vivo* calibration. However, in-vivo calibration after the implantation can improve the measurement accuracy. The most accurate method to calibrate would be with anterior chamber manometry; it seems that ophthalmodynamometry could be done in humans but it could be difficult to maintain steady elevated IOP long enough to register IOP with both standard tonometry and the telemetry device. However, in this study we calibrated the pressure sensor with intracameral manometry but in humans the calibration procedure would possibly rely on GAT.

The capacitive pressure-sensing units detect the pressure on the silicon encasement located directly above the ASIC. The sensing units are located at the bottom of the implant facing the sclera. Therefore the pressure sensor detected IOP through the sclera, the choroid and the retina. The transducer does not measure any kind of sclera stretch akin to the Triggerfish, it measures pressure directly through the sclera. However, this approach is more susceptible to any kind of alterations of the underlying structures (like remodeling) of the sclera or choroid compared to intraocular placed sensors. In addition, any kind of alterations of the conjunctiva or sclera could influence the viability of the telemetry system in a patient eye, that must be weighed against the risks of surgical implantation.

Transient IOP fluctuations can be seen in humans during volitional activity. IOP increments for squeezing of lids, blinking or even accommodation have been recorded in a human volunteer prior to enucleation for ocular tumor (Coleman and Trokel, 1969). In non-human primates fluctuations were recorded in a ten-minute time-window from 7 to 14 mmHg during the day. High-frequency IOP fluctuations highly probable due to saccades and blinks were identified while measuring pressure 500 times per second (Downs et al., 2011). While it is unknown if transient IOP fluctuations are an important factor in glaucoma onset or progression, it is a limitation of the episcleral pressure sensing device that it doesn't capture transient IOP fluctuation in the millisecond range.

Major advantages of the episcleral telemetric IOP sensing principle are the easy calibration of the episcleral sensor to conventional tonometry (e.g. GAT) during clinical examinations, possible home measurements in a pain free manner and the easy implantation without the need for invasive intraocular surgery. As a potential development in the future, IOP readings could be transmitted encrypted via mobile communication to cloud-based storage for access by the attending physician.

This allows the episcleral pressure sensor to operate like an implantable home tonometer and enables the detection of circadian IOP fluctuations by assessing IOP several times during the day and night in the form of self-measurements by the patient himself without special technical knowledge in a pain-free manner. The simple way of implanting sensors under the conjunctiva and episcleral fixation is a further major advantage.

In conclusion, the investigated episcleral telemetric pressure transducer showed promising results and is therefore a potential tool for sufficient pressure monitoring in glaucoma patients in the future without the need for intracameral or suprachoroidal surgery. There are still some issues, like the high failure rate and the size of the encasement, which need to be addressed. Design improvements and enhancement of the fixation procedure of the implant could resolve these issues.

## Conflict of interest

The authors received financial support for the experiments and travel support by Implandata Ophthalmic Products GmbH, Hannover, Germany.

## Appendix

Table A.1
Overall mean differences, standard deviations (SD) and limits of agreement (95% CI) between intracameral and telemetric IOP measurements separated for each intracameral applied IOP level between 10 mmHg and 45 mmHg.

| Follow-up measurement | Mean difference [mmHg] | SD [mmHg] | Lower limit of agreement [mmHg] | Upper limit of agreement [mmHg] |
|---|---|---|---|---|
| 10 mmHg | −0.5 | 0.9 | −2.4 | 1.3 |
| 15 mmHg | −0.6 | 1.2 | −3.0 | 1.7 |
| 20 mmHg | −0.3 | 0.5 | −1.4 | 0.7 |
| 25 mmHg | −0.1 | 0.3 | −0.6 | 0.5 |
| 30 mmHg | 0.2 | 0.8 | −1.3 | 1.7 |
| 35 mmHg | 0.6 | 0.8 | −1.1 | 2.2 |
| 40 mmHg | 0.6 | 0.9 | −1.2 | 2.4 |
| 45 mmHg | 1.0 | 1.4 | −1.7 | 3.6 |

Table A.2
Overall mean differences, standard deviations (SD) and limits of agreement (95% CI) between intracameral and telemetric IOP measurements 1 week, 4 weeks, 8 weeks, and 12 weeks after implantation and in total. Values represent all intracameral pressure levels between 10 and 45 mmHg.

| Follow-up measurement | Mean difference [mmHg] | SD [mmHg] | Lower limit of agreement [mmHg] | Upper limit of agreement [mmHg] |
|---|---|---|---|---|
| 1 week | 0.0 | 1.5 | −2.9 | 2.9 |
| 4 weeks | 0.0 | 0.5 | −0.9 | 0.9 |
| 8 weeks | 0.0 | 0.1 | −0.2 | 0.2 |
| 12 weeks | 0.0 | 0.0 | −0.0 | 0.0 |
| Total | 0.0 | 1.0 | −2.0 | 2.0 |

Table A.3
Mean differences, standard deviations (SD) and limits of agreement (95% CI) between intracameral and telemetric IOP measurements 1 week, 4 weeks, 8 weeks, and 12 weeks after implantation and in total. Values represent intracameral pressure levels between 10 and 30 mmHg.

| Follow-up measurement | Mean difference [mmHg] | SD [mmHg] | Lower limit of agreement [mmHg] | Upper limit of agreement [mmHg] |
|---|---|---|---|---|
| 1 week | 0.0 | 1.2 | −2.3 | 2.3 |
| 4 weeks | 0.0 | 0.4 | −0.7 | 0.7 |
| 8 weeks | 0.0 | 0.1 | −0.2 | 0.2 |
| 12 weeks | 0.0 | 0.0 | −0.0 | 0.0 |
| Total | 0.0 | 0.8 | −1.7 | 1.7 |

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