Graefes Arch Clin Exp Ophthalmol (2014) 252:1179–1188
DOI 10.1007/s00417-014-2668-5

REVIEW ARTICLE

An overview of home tonometry and telemetry for intraocular pressure monitoring in humans

Edward Yung · Valerie Trubnik · L. Jay Katz

Received: 16 November 2013 / Revised: 29 April 2014 / Accepted: 6 May 2014 / Published online: 29 May 2014

Abstract
Purpose To review the existing technology for self-tonometry and evaluate methods for continuous monitoring of IOP currently undergoing development and clinical trials in humans.
Background Glaucoma is one of the leading causes of blindness worldwide. Current glaucoma therapy is focused primarily on lowering intraocular pressures (IOP). Decisions to modify treatment regiments are primarily based on office IOP. Since IOP fluctuates throughout the day, values obtained in the office may be a poor representation of the patient's disease. IOP measurements outside of the physician's office environment would provide better knowledge of the disease state and allow for better-informed medical decision making.
Methods and results We performed a literature search using Medline and IEEE database for studies investigating technologies that have been developed for continuous 24-hour IOP monitoring.
Conclusion There is currently no technology that has been approved for use to allow for continuous monitoring of IOP fluctuations. New experimental technology being developed and currently undergoing clinical trials has demonstrated potential for changing the diagnosis and management of glaucoma.

Presentation at a Conference: This article is not planned for presentation at a conference.

E. Yung (✉)
Department of Ophthalmology, SUNY Stony Brook, 33 Research Way, East Setauket, NY 11733, USA
e-mail: edward.yung@stonybrookmedicine.edu

E. Yung · V. Trubnik · L. J. Katz
Glaucoma Service, Wills Eye Institute, 840 Walnut Street, Philadelphia, PA 19107, USA

V. Trubnik
e-mail: vtrubnik@ocli.net

L. J. Katz
e-mail: ljkatz@willseye.org

Keywords Glaucoma · Telemetry · Implant · Tonometry · Intraocular · Pressure

Introduction

Glaucoma is one of the leading causes of blindness in the world. In 2002, it was estimated that 37 million people were blind worldwide. Amongst this group, the second most common cause of blindness was glaucoma, accounting for 12.3 % of the cases of blindness, second only to cataracts [1]. It was estimated that in 2010, 60.5 million people suffer from glaucoma worldwide [2]. Glaucoma is characterized by progressive loss of neurons in the retinal nerve fiber layer. This often results in the loss of the peripheral visual fields, which can be monitored using visual field testing.

Primary open angle glaucoma is the most common form of glaucoma, constituting an estimated 74.0 % of cases in 2010 [2]. Risk factors for the development of open angle glaucoma (OAG) include increasing age, family history, African American race, myopia, thin central corneal thickness, and intraocular pressures (IOP). Currently, the only modifiable risk factor is elevated IOP. The mainstay of therapy today is targeted at reduction of IOP through the use of topical and systemic medications, lasers, and surgical procedures. Modification of glaucoma treatment regiments is currently guided primarily by IOP measurements. The gold standard for measurement of IOP is by Goldmann Applanation Tonometry (GAT) in the office. Unlike hand-held devices and pneumotonometry, GAT makes direct contact with the cornea and is mounted on a slit lamp, yielding accurate measurements while eliminating errors caused by improper positioning. The device acts on the principle of applanation, where the force required to flatten a defined corneal area of 3.06 mm2 is measured and correlated to the IOP using the formula Force=Pressure/Area [3–5].

The disadvantage of office GAT is that it only measures pressures at specific time points while the patient is in the office during daytime hours. It has been established that IOP shifts throughout the day in both healthy people and in patients with glaucoma. These diurnal shifts are particularly significant in glaucoma patients, as large pressure shifts have been associated with increased progression of glaucoma [6, 7]. The Advanced Glaucoma Intervention Study found these pressure fluctuations to be particularly important in eyes with low mean IOP, yielding greater visual field progression amongst this population [8]. Thus, IOP measurements during patient office visits may not accurately reflect the patient's disease state. With certain patients, one may measure IOP at multiple times throughout the day in order to create diurnal curves that would record shifts in IOP values. This technique, however, is time-consuming, expensive, and impractical for widespread use [9]. Measurements with GAT are also not possible while the patient is asleep. This is especially problematic, as it has been found that postural changes from sitting to supine elevates IOP due to an increase in episcleral venous pressure and redistribution of body fluid [10–12]. Studies have also found an elevation in IOP during the nocturnal period, regardless of sitting or standing positions [9, 13–16]. A sleep laboratory study by Brown et al., revealed that increases in IOP were detected within 30 minutes after onset of sleep, with further elevations after four hours of sleep. Pressures amongst the subjects returned to baseline within an average of 404 seconds after awakening [17, 18]. The impact of different topical medications for treatment of glaucoma on this phenomenon has also been studied, with latanoprost yielding the most uniform circadian reduction in IOP. Timolol, dorzolamide, and brimonidine, on the other hand, yielded variable results on this circadian fluctuation [19, 20].

Monitoring IOP values at time points outside of the patient's office visit would provide ophthalmologists with additional information about the patient's disease and the effectiveness of current treatment regiments. Home monitoring of other chronic diseases, such as diabetes mellitus by means of blood glucose monitoring, alerts patients when treatment is not effective and allows for improved disease control. Thus, it is a cost-effective tool for improving the quality of life and prognosis of these patients [21]. This concept is applicable to glaucoma, as self monitoring of IOP allows patients and physicians to detect failure of treatment earlier and adjust management protocols accordingly. One study demonstrated that 24 hour inpatient monitoring of IOP changed clinical management in over 75 % of glaucoma patients [22]. Unlike the self-monitoring of blood glucose levels of diabetes, however, no universally accepted method of self-tonometry currently exists. This article will review the existing technology for self-tonometry, and evaluate methods for continuous monitoring of IOP currently undergoing development and clinical trials in humans.

Methods

We performed a literature search using Medline and the IEEE database of articles published from the years 1967 to 2013. Search terms used were glaucoma telemetry, intraocular pressure continuous, intraocular pressure telemetry, triggerfish, home tonometry glaucoma, parylene intraocular pressure, and intraocular lens IOP.

Technology for non-continuous tonometry

In 1997, Draeger et al., published results of a study on intraocular pressure measurements done by astronauts on themselves during the Spacelab D2 mission using an automated version of the Goldmann Applanation Tonometry (GAT). During this mission, the flight crew successfully measured their IOP by positioning the device in front of their eye, and allowing it to automatically applanate the cornea. This was the first reported case of people performing self-tonometry [23]. Since then, multiple attempts have been made to produce a device, which patients can use to measure their own intraocular pressure at home. The result of these include the Proview pressure phosphene tonometer, the Ocuton S, and the Tiolat iCare. Extensive studies have been performed comparing the self-tonometry IOP measurements using these devices with those obtained by the physician via Goldmann Applanation tonometer. Results of these studies have been mixed.

The Ocuton S, an automatic tonometer based on the device created by Draeger during the Spacelab D2 mission, allows self-measurement of IOP by patients. By instructing patients to place the device in front of their eyes, the device automatically contacts the cornea and determines IOP using the principle of applanation. Studies on its accuracy yielded significantly different IOP measurements as compared to GAT despite long periods of training for use in self tonometry. Mean pressure measurements by self tonometry with the Ocuton S were up to 6 mmHg higher than those obtained by GAT, and only 67 % of patients could yield median values within 3 mmHg of GAT even after six repeated measurements [24–28]. In addition, because this device required direct contact with the cornea during applanation, patients using this device for long-term self monitoring of IOP would require chronic use of a topical anesthetic. Patients using the Ocuton S were, therefore, susceptible to adverse sequelae associated with topical anesthesia abuse such as toxic keratopathy, corneal ulceration, and perforation [29–31].

The Proview pressure phosphene tonometer is a small, unpowered spring-compression device that uses the principle of pressure phosphene, the induction of light sensation by application of pressure to the eyes. Patients are instructed to place the tip of the device to the superonasal orbit over the upper eyelid and apply increasing pressure until a visual

sensation resembling a halo is produced. The measured reading is then taken from the device. Most studies done to evaluate self-tonometry with this device have demonstrated significant differences in the IOP values obtained by this device compared to GAT [32–36]. The device tended to overestimate IOP at measurements under 10 mmHg and underestimate at measurements over 20 mmHg, with one study finding only 37.4 % of measurements using the pressure phosphene tonometer falling within +/- 2 mmHg and 67 % within +/- 4 mmHg of measurements with GAT. Patients with IOPs less than 10 mmHg or over 20 mmHg in this study yielded measurements with an absolute mean difference of 6.6 mmHg compared to GAT. Despite these shortcomings, however, use of the pressure phosphene monitor yielded a significant reduction in anxiety (from 1.86 to 1.37 on a 5-point anxiety scale questionnaire) after four weeks to six weeks of use, demonstrating the psychological benefits of self-tonometry [35].

The Tiolat iCare acts on the principle of rebound tonometry, where a moving object colliding with the cornea without the need for topical anesthetic will decelerate more rapidly at higher IOPs. This allows the measurement of IOP values by monitoring the motion parameters of the colliding object against the cornea. Studies on self-tonometry with the iCare rebound tonometer yielded reasonable correlation of IOP measurements with the device compared to GAT, with some studies reporting correlation coefficients between 0.79 to 0.95 [37, 38]. Proper positioning with this device, however, is difficult in a home environment and can greatly affect the results obtained with the device. Muttuvelu demonstrated a mean difference of 3-4 mmHg between central and peripheral corneal measurements [39, 40]

Other portable technologies for monitoring IOP have been developed for use in the office. In theory, many of these devices can be adapted for patient use in monitoring their own IOP at home. These include the Tono-Pen, the Diaton ballistic tonometer, and non-contact tonometers such as the Pulsair Keeler, Reichert AT550, and the Ocular Response Analyzer. The Tono-Pen is the most commonly used portable device. Only one study currently exists reporting a single patient that was taught to use the Tono-Pen to measure his own IOP over the course of four years, with 93 % of his measurements falling within 2 mmHg of the GAT measurements [41]. No large scale studies have been done to determine whether patients can use this device to accurately measure their own IOP. The dexterity required to correctly position the device, as well as the need to keep one's eyelids open during readings makes the device technically challenging for use in self-tonometry. Use of this device also requires the use of topical anesthetics [42–44]. Optimal use of these devices would involve family members performing the tonometry, rather than the patient taking self-measurements.

The Diaton tonometer uses the ballistic principle of tonometry transpalpebrally through the eyelid. This device is designed with a tip that rests on the patient's eyelids and allows for measurement of IOP by monitoring the interaction of a free falling rod with the elastic surface of the eye through the upper eyelid. While this device does not require the use of topical anesthesia, the Diaton tonometer is very technically challenging to be used on oneself. Accurate measurements require for patients to fixate their gaze at a 45^{o} angle and the ciliary line of their upper eyelid positioned to coincide with the upper border of the limbus [42, 45, 46]. No studies on self-tonometry have been done with the Diaton tonometer to determine if it is a feasible option for self-tonometry.

Non-contact tonometers act primarily on the principle of cornea applanation using air released from the device's pneumatic system. The Pulsair Keeler non-contact tonometer has been tested for use in self-tonometry in a single study, which yielded IOP measurements to within 1 mmHg of GAT in 73 % of cases. Only 75 % of patients in the study, however, were able to use the device on themselves successfully [43]. Multiple other non-contact tonometers have also been considered for self-tonometry. The accuracy of these devices in measuring IOP at home has not been evaluated in large scale studies. A major disadvantage to these devices is their inability to obtain IOP measurements while the subject is asleep. The greatest disadvantages of the non-contact tonometers, however, is their cost, with some devices priced at up to $15,000.

Cook et al., published the results of a meta-analysis pooling data from articles that evaluated the agreement of various tonometers with GAT. Although non-contact tonometers produced the most accurate results, only 66 % of measurements were within 2 mmHg of those obtained by GAT. The Ocuton S was the least accurate, with only 33 % of IOP values within 2 mmHg of GAT measurements. Thus, a major disadvantage is the poor overall accuracy of these devices in obtaining IOP values even when operated by trained professionals [47].

Contact lens telemetry

A disadvantage common to all of the portable tonometers is their inability to obtain continuous IOP measurements. This is especially problematic during the nocturnal period, as studies have shown that the highest IOP values tend to occur during the hours of sleep and in the early morning [22, 27]. Hence, we continue to search for devices that allow for continuous 24-hour monitoring of IOP that will be easy and convenient for patient use, as well as reasonably priced.

Recording of ocular dimensional changes related to IOP with the use of a contact lens is an attractive option; it is noninvasive and allows for continuous wear, thus making 24 hour measurements possible. An in vitro study by Hjortdal et al., in 1995 with enucleated human eyes found a human

corneal curvature change of 3 μm in response to an artificial change in the IOP of 1 mmHg [44]. Lam et al., later found similar results with an in vivo study looking at corneal curvature changes associated with postural changes [48]. Since then, this concept has been applied to the creation of contact lenses capable of sensing IOP-related changes in vivo. Leonardi was the first to publish on the creation of a soft contact lens with an embedded microfabricated strain gauge capable of detecting changes in the corneal curvature in response to IOP changes. This design was initially created with a 3 cm microflex connection cable that connected the lens to an external electronic device for recording of these corneal changes. This device was tested in enucleated porcine eyes that were cannulated and connected to an external fluid source allowing for artificial IOP changes. IOP was monitored using manometry, where an electronic sensor directly measures the pressure of the anterior chamber through the tubing connected to the cannulating needle. The contact lens yielded measurements with very good correlation to actual internal IOP values measured by manometry [49]. Leonardi later also produced a wireless version of this strain gauge contact lens. This device contained a built-in gold antenna and telemetric microprocessor allowing for wireless power and transmission of measurement data. The results of in vitro studies with this wireless sensing contact lens on cannulated porcine eyes were published in 2009. The results demonstrated measurements that correlated well with actual IOP values measured by internal manometry with a reproducibility of 0.2 mmHg [50].

The wireless contact lens design has been adapted for commercial manufacturing by Sensimed. This product, called SENSIMED Triggerfish, is a soft silicone contact lens with a 14.1 mm diameter sensor, a built-in circular microantenna, a circular strain gauge acting as sensors, and a microprocessor to communicate with an external antenna (Fig. 1). The external antenna is placed around the eye and allows for transmission of energy from a recorder to the contact lens, and data from the contact lens microprocessor to the recorder through a cable connected to the antenna. The recorder is worn by the patient and allows for transfer of data to a computer using Bluetooth technology after completion of the recording. This lens is designed to capture ocular dimensional changes at the corneoscleral area for 30 seconds every 5 minutes, allowing for the collection of a total of 86,688 data points over a 24-hour period. A clinical trial using SENSIMED Triggerfish demonstrated good tolerability by healthy volunteers without significant discomfort for an average consecutive period of 23.23 hours with only mild visual complaints that resolved within 24 hours of removal [13]. Additional clinical trials with this device in patients with primary open angle and pseudoexfoliative glaucoma yielded 24-hour individual profiles that demonstrated variations related to the circadian rhythm, with the highest value occurring during the nocturnal period [51, 52]. Further study on the safety and tolerability in POAG or POAG suspect patients wearing the device during multiple 24-hour periods revealed good tolerability when measured using a visual analog scale score. A study by Mansouri revealed no persistent serious adverse effects, as the only serious adverse effect observed was conjunctival hyperemia [53]. A second study by Lorenz demonstrated good tolerability, with only one patient in a cohort of 40 participants experiencing intolerance and nonpersistent epithelial defects [54]. The SENSIMED Triggerfish offers a non-invasive method for capturing ocular dimensional changes related to IOP without the use of topical anesthetics. Moreover, recording such changes with a contact lens allows for continuous 24-hour use, including nocturnal recording while the patient is asleep. Self application of this device is also possible for home use in the future, as the only skill required for use of the device is the ability to put in a soft contact lens. Currently, however, the product is only available with a medical prescription, and requires healthcare professionals to set up the system. Efficacy of this device for widespread use, however, is limited by the small possibility of device malfunction. Monitoring was interrupted because of technical problems in a small percentage of subjects. Another possible limitation of the SENSIMED Triggerfish is intolerance in patients with preexisting severe dry eye syndrome. One case of a corneal ulcer was found in a patient with severe dry eye disease after use of the contact lens [52]. Currently, the device is contraindicated in subjects with severe dry eye syndrome. Finally, the current generation of this contact lens sensor displays data for ocular dimensional changes in arbitrary units proportional to the electrical signal generated by the sensor rather than millimeters of mercury. This limitation makes it difficult to translate measured values into clinically useful values, as no conversion to mmHg currently exists [55]. Further human studies with the sensing contact lens will determine the accuracy of the device when used in vivo in comparison to measurements obtained by more established methods of IOP measurement such as GAT.

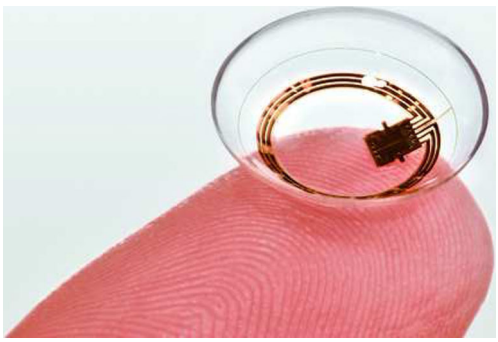

Fig. 1 Triggerfish wireless intraocular pressure sensing contact lens ©Sensimed AG

Another contact lens sensor design was recently tested both in vitro and in vivo conditions, and was reported by Sanchez et al. This device, a rigid, gas-permeable contact lens, is

designed in the shape of a doughnut with a 3.0 mm central hole covered by a round membrane. Two wires are attached to the sensing layer of the membrane and connected with both a reading and recording unit. Data from these units can be transferred onto a computer via a Bluetooth connection. The flexible membrane acts as the sensing component capable of detecting corneal deformations that result in electrical resistance changes.(Fig. 2) Deformation of the cornea, caused by pressure changes of as little as 1 mmHg can be detected by the round membrane. In vitro studies with cannulated porcine eyes demonstrated excellent linear correlation between IOP and contact lens sensor resistance response, with a sensitivity of 0.04 Ω/mmHg. In vivo testing on a single human subject that wore the sensing contact lens for two hours found that use of the sensor caused no signs of relevant clinical complications. Changes in the resistance of the bilayer film were detected in response to physiological changes in IOP that occur during ocular massage, strong blinking, and eye movements. Currently, this device is designed to work with a wired connection to the contact lens, which does not allow continuous wear for more than a few hours [56]. Further work is necessary in order to reconfigure this device for wireless energy and data transmission, thus allowing for better tolerability and longer continuous wear. In addition, transparency of the bilayer film must be improved, as the current design of the device causes significant visual disturbances to the patient while worn. While this design provides an alternative approach to measuring IOP with a contact lens, it remains to be seen whether this finished design will provide any advantage over the Triggerfish lens.

Early implant telemetry

In 1967, Collins reported the development of the first implantable device that could be used to continually monitor IOP. This device relies on the introduction of a gas bubble encapsulated in a rigidly suspended flexible film. Changes in the volume of the gas bubble due to IOP changes are detected using a strain gauge sensor comprised of a pair of parallel spiral coils, which create a circuit whose frequency changes with relative coil spacing (Fig.3). Increased pressure from the intraocular environment acting on the device forces the coils together and lowers their resonant frequency. Repeated sweeping using an external detector, and monitoring of the energy absorbed by the implanted device allows continuous recordings of IOP results. Implantation of the device into rabbits demonstrated significant transient changes in the IOP during blinking, and continued functioning in 90 % of cases after six months of implantation. Further development for clinical trials in humans with this implantable sensor was never done because of reported difficulties with stability and proper positioning after implantation [57, 58].

Wolbarsht et al., reported the design and results of an experimental elastic band implanted at the equator of the globe, similar in design to the scleral buckle used for repair of retinal detachments. Experimentation with cadaveric human and animal eyes found reproducible correlations between changes in the diameter of the eye and changes in the IOP. In this device, a sensor, which is a pressure transducer, is connected to leads composed of thin wire (Fig.4). The transducer is implanted onto the eye in a scleral buckling procedure. Increases in the IOP lead to stretching of the transducer and increased electrical resistance. In vitro studies showed almost linear relationships between the electrical resistance of the device and the IOP of cannulated eyes measured by manometry. A significant advantage of this method of implantation telemetry is the fact that there is no need for entry into the globe, and the rate of endophthalmitis associated with intraocular interventions is minimized. In vivo studies, however, there were several problems arising after implantation of this device, including leakage of current, a high frequency of ocular infection despite the extraocular location of the device, and inflammation at the site of the band [59]. In addition, scleral expansion associated with changes in the IOP is not the same for all parts of the eye. Changes in IOP cause uneven changes in the length of the strain gauge depending on its location, making the relationship between its length and IOP

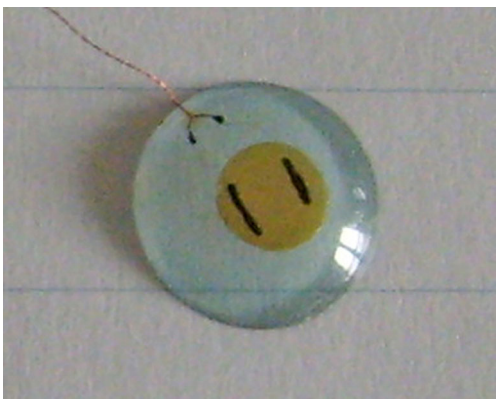

Fig. 2 Sanchez's IOP sensing contact lens using a piezoresistive bilayer membrane. Image provided courtesy of author [56]

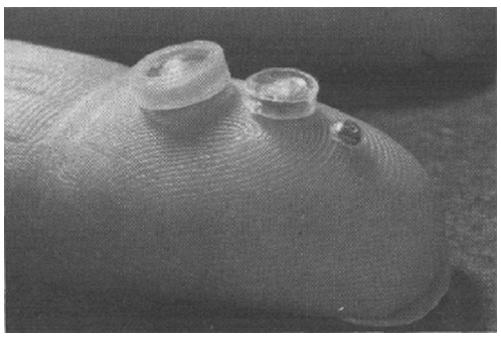

Fig. 3 Passive bubble tonometers developed by Collins for implantation into the eye. © 1967 I.E. [57]

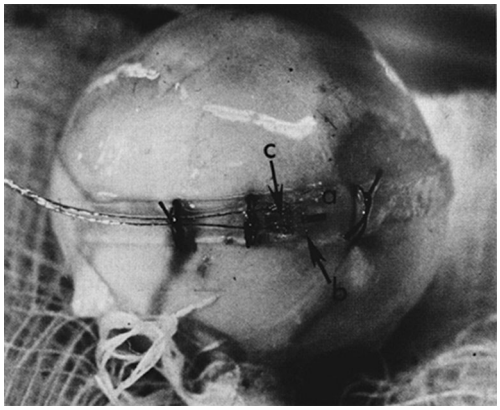

Fig. 4 Elastic band strain gauge applied in vitro to an enucleated human eye, similar to that of a sclera buckle [59]

nonlinear. This problem causes difficulty with interpreting the results obtained by the device [59]. Moreover, scleral expansion will push the band against surrounding tissue, changing strain gauge length depending on the individual orbit anatomy. This makes the device difficult for practical use because it will require in vivo calibration in each individual. No further studies have yet been published on the use of this device.

A choroid surface implant design was proposed by Rizq et al., for continuous monitoring of IOP. This device is designed to be implanted by trephination of a 2.5 mm diameter disc from the sclera with a depth of 0 to 2 mm below the surface of the sclera. The implant is then glued to a plate, which is sutured to the sclera for stabilization. The built-in sensor is in intimate contact with the choroid and detects IOP values (Fig. 5). Signal from the implant is amplified and filtered using an external preamplifier and subsequently logged using a data logger. In vitro testing of the device in cannulated cadaveric eyes revealed measurements that differed from anterior chamber IOP values measured by manometry by 1.9 to 3.3 mmHg. No comparison of measured values with this implant to GAT was done during this study. Similar to the scleral buckle designs previously described, this device has the advantage of being implanted in a nonpenetrating procedure. In vivo studies of this device in humans have not been done [60].

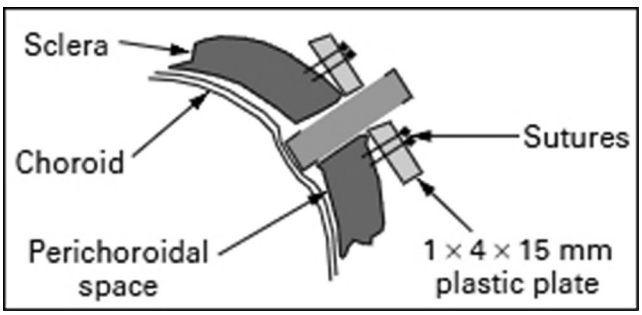

Fig. 5 Schematic of the choroid surface intraocular pressure monitor described by Rizq [60]

Modern telemetry research

While early attempts at developing implantable sensors were met with limited success, the availability of modern technology has paved the way for the development of devices with improved accuracy and biocompatibility. The incorporation of an IOP sensor into an artificial intraocular lens (IOL) that can be implanted into the eye during cataract extraction was first reported in 1992 by Svedbergh. Their device utilizes the bubble spiral circuit proposed by Collins in 1967. The size of this sensor is decreased in order to fit it into the haptics of an IOL. IOP values are obtained by an external detector, which can be integrated into devices such as spectacles. This detector scans resonant frequencies of the circuit, which changes based on effects of IOP acting on the implanted sensor, similar to the design reported by Collins. Only in vitro studies in a non-biological setup have been reported, and though intentions for animal testing with the device had been mentioned, in vivo studies have thus far not been published [61].

Since then, multiple attempts have been made to create an IOL capable of monitoring IOP using modern microchip technology. Walter reported the construction of an encapsulated miniaturized electronic capacitive pressure sensor that is integrated with electronics on a single chip. The device is completely encapsulated in biocompatible silicone similar to that found in traditional IOLs. This sensor is coupled to an external readout device that can be integrated into spectacles using magnetic high-frequency transmission. The sensor has been integrated into the haptics of an IOL and implanted into cannulated enucleated porcine eyes and cannulated rabbit eyes in vivo. Implanted sensors yielded the same IOP data as pneumotonometry both in vitro and in vivo. No long-term in vivo animal studies could be obtained, as this device was too large for long-term implantation in rabbits and would not fit within the capsular bag [62].

Hille reported another design of a sensor integrated into an IOL. This design is a silicone chip with a 1 μm thick membrane that is comprised of two components: a sensor that has no energy source or transmission capability, and an implanted telemetry component that is responsible for signal processing and Alternating Current (A/C) power transmission. In vitro studies with this IOL yielded transmissions accurate to within 1 mmHg of each other at a rate of three measurements per seconds. No in vivo studies have been performed with this IOL design [63].

Despite the fact that these earlier designs have not yet translated into human studies, the integration of an IOP sensor into an implantable IOL offers the advantage of continuous IOP monitoring in glaucoma patients who will undergo cataract extraction and IOL implantation, without the need for an additional procedure. Reducing the number of procedures will reduce the risk of endophthalmitis associated with multiple intraocular surgeries.

An alternative method of continuous IOP monitoring was reported by Chen, which involved the use of a completely unpowered parylene pressure tube sensor. The original device is a spiral tube formed by a biocompatible long, thin-walled channel that is deformed by the difference between the pressure encapsulated in the tube and the ambient pressure around it. This results in the free end of the spiral tube undergoing angular deformation in response to IOP changes when the device is implanted into the anterior chamber. These sensors are then packaged onto platforms with feet that allow for sutureless anchoring onto the human iris. Deformation of the parylene tube IOP sensor can be visually detected by physicians or the patient using magnifying equipment or stereoscopes. Newer long-armed and serpentine-tube designs offer the advantage of being able to be implanted onto the iris using a 19-gauge needle (Fig. 6). This device is currently undergoing in vivo testing to determine its tolerability and efficacy in the intraocular environment. The advantage to this device is good biocompatibility of the device and low cost of production, as no electronic transmission system is required to collect IOP measurements. The main disadvantage to the use of this implant, however, is that because values are not electronically recorded, measurements at home rely on patient's self-visualization of the implant using a stereoscope. Nocturnal IOP values cannot be obtained while the patient is asleep using this implant, as it requires visualization of the device in the anterior chamber. In addition, patients with advanced glaucoma may have difficulty visualizing the deformations of the implant, as many of them possess loss of peripheral visual fields [64, 65].

Clinical trials in humans are currently taking place to evaluate the use of a modern capacitive pressure sensor for continuous IOP monitoring in humans. An implantable sensor utilizing micro plate capacitors, with thin diaphragms that deflect under pressure, has been developed by Implandata GmbH. Similar to the previous designs by Collins, this device detects the distance between two silicone electrodes, which varies depending on applied ambient pressure. It is designed with a link between the reader and the implant that supplies the implanted lens with power and data transmission from the lens to an external reader. This implantable system is encapsulated in a biocompatible silicone rubber material suitable for long-term implantation. The external reader device can allow for up to 3,000 measurements, which equals to about one month of measurements with a 15 minute interval in between each measurement.

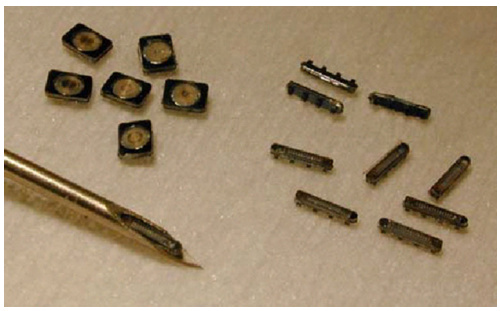

Fig. 6 Different conformations of implantable unpowered parylene MEMS intraocular pressure sensors. Size is compared to a 19 gauge needle (left) [65]

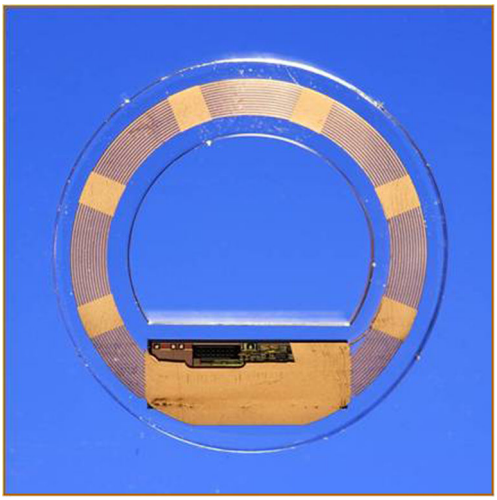

Fig. 7 Implandata GmbH's permanent intraocular pressure sensor implant placed in conjunction with IOL placement during cataract extraction. Figure provided courtesy of Implandata Ophthalmic Products GmbH

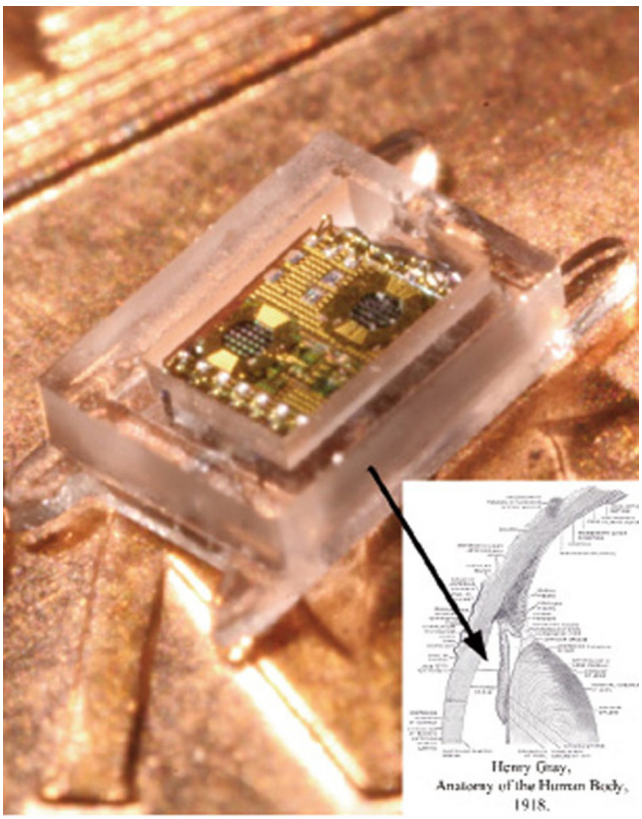

Fig. 8 MEMS capacitative pressure sensor and microprocessor measuring 0.5x1.5x2 mm3 for implantation into anterior chamber [68]

This sensor has been designed as a flexible intraocular implant that can be implanted either into the sulcus between the capsular bag and iris or placed into the capsular bag itself (Fig. 7). This is achieved through a corneoscleral tunnel similar to IOL implantation, and always occurs during cataract extraction (CE-IOL) or keratoprosthesis (Kpro) procedures [66]. Todani et al., reported the results of animal trials in rabbits with the IOL device, yielding good tolerability of the sensor and IOP results with good concordance to true values obtained by cannulation manometry [67]. Currently, this device is undergoing a clinical trial in Europe, where it is placed in the sulcus by piggyback implantation during IOL placement in glaucoma patients undergoing cataract surgery. Preliminary data demonstrates excellent correlation and consistency when IOP data from the implant is compared to IOP measurements obtained by GAT [66]. Moreover, this device would be of particular benefit to patients after Kpro, as current methods of measuring IOP in this population with finger tension palpation and transpalpebral devices have poor correlation with values obtained by GAT [39].

This capacitive pressure sensor was also integrated into an episcleral implant that can be implanted into patients not requiring a CE-IOL procedure. The initial design of this device applanated a 7 mm cross section of the sclera and was fixed onto the sclera with two sutures. In vivo studies in living rabbits demonstrated good agreement between measurements by the episcleral IOP sensor and manometry. Some offset from measurements by manometry, however, did exist and were possibly explained by the extrusion of sutures due to high forces acting on them. A modified form of the episcleral implant by Implandata GmbH that conforms to the shape of the sclera and uses four sutures for fixation may lead to improved implant stability, optimizing experimental outcomes. Success of this device in animal studies will allow for an implant that does not require entry into the globe, lowering risks of endophthalmitis associated with intraocular surgery [66].

Recent advancements in microprocessing technology have paved the way for the creation of cubic-millimeter sized energy autonomous microprocessors for implantation. Chen described a 1 mm3 sized wireless IOP monitor that can be inserted into the anterior chamber through a CE-IOL incision and anchored onto the iris (Fig.8). The device measures IOP every 15 minutes using a capacitive sensor and has an internal thin-film lithium battery capable of powering the device for 28 days with no energy harvesting. To extend battery lifetime, a solar cell is integrated into the device to recharge the battery and allow for energy autonomy with 1.5 hours of sunlight or ten hours of indoor light daily. Up to 500-1,000 readings of IOP data are stored into the built in memory for download to an external device placed near the eye. In vivo studies have not yet been performed, but implantation into animal models are planned for the near future [68].

Lee et al., recently described a second 1 mm3 wireless sensor node that can be adapted for use in biological implantation, including IOP monitoring. This general purpose microprocessor has the advantage of allowing for more flexible re-programming and re-synchronizing than previous designs. Integration of a pressure sensor into this device has been done and in vitro benchtop testing revealed no measurement drifts after two weeks. Additional testing and animal model implantation is expected in the near future to evaluate the in vivo efficacy and tolerability of this device [69].

Conclusion

It has been proven that fluctuations in IOP are important in disease prognosis and can greatly affect clinical management. However, no effective method of 24-hour IOP monitoring currently exists outside of office visits. Current portable devices for IOP measurement have not been shown to be reliable for home use by patients, and have not yet yielded accurate results compared to GAT. These devices are also unable to be used to evaluate nocturnal values while patients are asleep. IOP monitoring by telemetry is a favorable option to overcome these issues and help guide clinical care. Current clinical trials on contact lens and implantable sensors are underway to evaluate potential devices for continuous monitoring of IOP in glaucoma patients. Favorable outcomes in these trials could provide an effective way of monitoring IOP changes that occur throughout the day and night, and provide improved clinical data to guide treatment decisions.

Conflicts of interest There are no conflicts of interest.

References

1. Resnikoff S, Pascolini D, Etya'ale D et al. (2004) Global data on visual impairment in the year 2002. Bull World Health Organ 82(11): 844–851
2. Quigley HA, Broman AT (2006) The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 90(3):262–267
3. Goldmann H, Schmidt T (1957) Applanation Tonometry. Ophthalmologica 134(4):221–242
4. Wessels IF, Oh Y (1990) Tonometer utilization, accuracy, and calibration under field conditions. Arch Ophthalmol 108(12):1709–112
5. Tonnu PA, Ho T, Newson T et al. (2005) The influence of central corneal thickness and age on intraocular pressure measured by pneumotonometry, non-contact tonometry, the Tono-Pen XL, and Goldmann applanation tonometry. Br J Ophthalmol 89(7):851–854
6. Collaer N, Zeyen T, Caprioli J (2005) Sequential office pressure measurements in the management of glaucoma. J Glaucoma 14(3): 196–200
7. Asrani S, Zeimer R, Wilensky J et al. (2000) Large diurnal fluctuations in intraocular pressures are an independent risk factor in patients with glaucoma. J Glaucoma 9:134–142

8. Caprioli J, Coleman AL (2008) Intraocular Pressure Fluctuation: A risk factor for visual field progression at low intraocular pressures in the Advanced Glaucoma Intervention Study. Ophthalmology 115(7): 1123–1129
9. McLaren JW, Brubaker RF, FitzSimon JS (1996) Continuous measurement of intraocular pressure in rabbits by telemetry. Investig Ophthalmol Vis Sci 37(6):966–975
10. Carlson KH, McLaren JW, Topper JE et al. (1987) Effect of body position on intraocular pressure and aqueous flow. Invest Ophthalmol Vis Sci 28(8):1346–1352
11. Yamabayashi S, Aguilar RN, Hosoda M et al. (1991) Postural change of intraocular and blood pressures in ocular hypertension and low tension glaucoma. Br J Ophthalmol 75(11):652–655
12. Kothe AC (1994) The effect of posture on intraocular pressure and pulsatile ocular blood flow in normal and glaucomatous eyes. Surv Ophthalmol 38:S191–S197
13. Smedt SD, Mermound A, Schnyder C (2012) 24-Hour intraocular pressure fluctuation monitoring using an ocular telemetry sensor: Tolerability and functionality in healthy subjects. J Glaucoma 21(8):539–544
14. Hara T, Hara T, Tsuru T (2006) Increase of peak intraocular pressure during sleep in reproduced diurnal changes by posture. Arch Ophthalmol 124(2):165–168
15. Liu JKH, Kripke DF, Hoffman RE et al. (1998) Nocturnal elevation of intraocular pressure in young adults. Invest Ophthalmol Vis Sci 39: 2707–2712
16. Liu JKH, Bouligny RP, Kripke DF et al. (2003) Nocturnal elevation of intraocular pressure is detectable in the sitting position. Invest Ophthalmol Vis Sci 44(10):4439–4442
17. Brown B, Morris P, Muller C et al. (1988) Fluctuations in intra-ocular pressure with sleep: I. Time course of IOP increase after the onset of sleep. Ophthalmic Physiol Opt 8(3):246–248
18. Brown B, Burton P, Mann S et al. (1988) Fluctuations in intra-ocular pressure with sleep: II. Time course of IOP decrease after waking from sleep. Ophthalmic Physiol Opt 8(3):249–252
19. Orzalesi N, Rossetti L, Invernizzi T et al. (2000) Effect of timolol, latanoprost, and dorzolamide on circadian IOP in glaucoma or ocular hypertension. Invest Ophthal VisSci 41(9):2566–2573
20. Orzalesi N, Rossetti L, Bottoli A et al. (2003) The effect of latanoprost, brimonidine, and a fixed combination of timolol and dorzolamide on circadian intraocular pressure in patients with glaucoma or ocular hypertension. Arch Ophthalmol 121(4):453–457
21. De Alva M, Jervell J (1997) Self monitoring improves quality of life and prognosis of people with diabetes. Br Med J 315:184–185
22. Hughes E, Spry P, Diamond J (2003) 24-Hour monitoring of intraocular pressure in glaucoma management: a retrospective review. J Glaucoma 12:232–236
23. Draeger J, Schwartz R, Groenhoff et al. (1993) Self-tonometry under microgravity conditions. Clin Investigator 71:700–703
24. Theofylaktopoulos I, Diestelhorst M, Krieglstein GK (1999) Self-tonometry with the Ocuton S versus Goldmann tonometry. Graefes Arch Clin Exp Ophthalmol 237:720–724
25. Sacu S, Vass C, Schemper M et al. (2004) Self-tonometry with the Ocuton S: evaluation of accuracy in glaucoma patients. Acta Ophthalmol Scand 82:405–409
26. Marchini G, Babighian S, Specchia L et al. (2002) Evaluation of the new Ocuton S tonometer. Acta Ophthalmol Scand 80:167–171
27. Kothy P, Vargha P, Hollo G (2001) Ocuton S self-tonometry vs Goldmann tonometry; a diurnal comparison study. Acta Ophthalmologica Scandanavica 79:294–297
28. Lanfermann E, Jurgens C, Grossjohann R et al. (2009) Intraocular pressure measurements with the newly Ocuton S*TT-MV self-tonometer in comparison to Goldmann applanation tonometry in glaucoma patients. Med Sci Monit 15(11):CR556–CR562
29. Rosenwasser GO, Holland S, Pflugfelder SC et al. (1990) Topical anesthetic abuse. Ophthalmology 97(8):967–972
30. McGee HT, Fraunfelder FW (2007) Toxicities of topical ophthalmic anesthetics. Expert Opin Drug Saf 6(6):637–640
31. Yeniad B, Canturk S, Esin Ozdemir F et al. (2010) Toxic keratopathy due to abuse of topical anesthetic drugs. Cutan Ocul Toxicol 29(2): 105–109
32. Lam DSC, Leung DYL, Chiu TYH et al. (2004) Pressure phosphene self-tonometry: A comparison with Goldmann Tonometry in Glaucoma Patients. Investig Ophthalmol Vis Sci 45(9):3131–3136
33. Tai MC, Chen PL, Wu JN et al. (2005) Clinical evaluation of the intraocular pressure in patients with glaucoma or ocular hypertension by a self-assessable tonometer. J Ocul Pharmacol Ther 21(1):55–61
34. Danesh-Meyer HV, Niederer R, Gaskin BJ, Gamble (2004) Comparison of the Proview pressure phosphene tonometer performed by the patient and examiner with the Goldmann applanation tonometer. Clin Exp Ophthalmol 32(1):29–32
35. Rai S, Moster MR, Kesen M et al. (2005) Level of disagreement between Proview Phosphene Tonometer and Goldmann Applanation Tonometer Intraocular Pressure Readings. J Glaucoma 14:120–123
36. Li J, Herndon LW, Asrani SG et al. (2004) Clinical comparison of the Proview Eye Pressure Monitor with Goldmann Applanation Tonometer and the TonoPen. Arch Ophthalmol 122:1117–1121
37. Rosentreter A, Jablonski KS, Mellein AC et al. (2011) A new rebound tonometer for home monitoring of intraocular pressure. Graefes Arch Clin Exp Ophthalmol 249(11):1713–1719
38. Asrani S, Chatterjee A, Wallace DK et al. (2011) Evaluation of the ICare rebound tonometer as a home intraocular pressure monitoring device. J Glaucoma 20:74–79
39. Muttuvelu DV, Baggesen K, Ehlers N (2012) Precision and accuracy of the ICare tonometer – Peripheral and central IOP measurements by rebound tonometry. Acta Ophthalmol (Copenh) 90(4):322–326
40. Chiu W, Lam A, Chen D et al. (2008) The influence of corneal properties on rebound tonometry. Ophthalmology 115:80–84
41. Kupin TH, Shin DH, Juzych MS et al. (1993) Use of a Tono-Pen for long-term home tonometry. Am J Ophthalmol 116(5):643–644
42. Ruokonen PC, Schwenteck T, Draeger J (2007) Evaluation of the impedance tonometer TGDc-01 and iCare according to international ocular tonometer standards ISO 8612. Graefes Arch Clin Exp Ophthalmol 245:1259–1265
43. Boles Carenini B, Brogliatti B, Tonetto C et al. (1992) The Pulsair-Keeler non-contact tonometer in self-tonometry: preliminary results. Int Ophthalmol 16:295–297
44. Hjortdal J, Jensen PK (1995) In vitro measurement of corneal strain, thickness, and curvature using digital image processing. Acta Ophthalmol Scand 73:5–11
45. Van der Jagt LH, Jansonius NM (2005) Three portable tonometers, the TGDc-01, the ICARE, and the Tonopen XL, compared with each other and with Goldmann applanation tonometry. Ophthalmic Physiol Opt 25:429–435
46. Resua CG, Fernandez MJG, Exposito AC et al. (2005) Clinical evaluation of the new TGDc-01 "PRA" palpebral tonometer: comparison with contact and non-contact tonometry. Optom Vis Sci 82(2):143–150
47. Cook JA, Botello AP, Elders A et al. (2012) Systematic review of the agreement of tonometers with Goldmann Applanation Tonometry. Ophthalmology 119:1552–1557
48. Lam AKC, Douthwaite WA (1997) The effect of an artificially elevated intraocular pressure on the central corneal curvature. Ophthalmic Physiol Opt 17:18–24
49. Leonardi M, Leuenberger P, Bertrand D et al. (2004) First steps towards noninvasive intraocular pressure monitoring with a sensing contact lens. Invest Ophthalmol Vis Sci 45(9):3113–3117
50. Leonardi M, Pitchon EM, Bertsch A et al. (2009) Wireless contact lens sensor for intraocular pressure monitoring: assessment on enucleated pig eyes. Acta Ophthalmol (Copenh) 87(4):433–437
51. Faschinger C, Mossbock G (2010) Kontinuierliche 24-h-Aufzeichnung von Augendruckschwankungen mittels drahtlosem Kontaktlensensor Triggerfish. Ophthalmologe 107(10):918–922

52. Mansouri K, Shaarawy T (2011) Continuous intraocular pressure monitoring with a wireless ocular telemetry sensor: initial clinical experience in patients with open angle glaucoma. Br J Ophthalmol 95:627–629
53. Mansouri K, Medeiros FA, Tafresh et al. (2012) Continuous 24-hour monitoring of intraocular pressure patterns with a contact lens sensor: Safety, tolerability, and reproducibility in patients with glaucoma. Arch Ophthalmol 130(12):1534–1539
54. Lorenz K, Korb C, Herzog N et al. (2013) Tolerability of 24-hour intraocular pressure monitoring of a pressure-sensitive contact lens. J Glaucoma 22(4):311–316
55. Matsumoto T, Nagata TR, Slashin M et al. (1978) Measurement by holographic interferometry of the deformation of the eye accompanying changes in intraocular pressure. Appl Opt 17(22):3538–3539
56. Sanchez I, Laukhin V, Moya A et al. (2011) Prototype of a nanostructured sensing contact lens for noninvasive intraocular pressure monitoring. Investig Ophthalmol Vis Sci 52(11):8310–8315
57. Collins CC (1967) Miniature passive pressure transensor for implanting in the eye. IEEE Trans Biomed Eng 14:74–83
58. Collins CC (1967) Passive telemetry with glass transensors. Proc Nat Telemetring Conf 146–151
59. Wolbarsht ML, Wortman J, Schwartz B et al. (1980) A sclera buckle pressure gauge for continuous monitoring of intraocular pressure. Int Ophthalmol 3:11–17
60. Rizq RN, Choi WH, Eilers D et al. (2001) Intraocular pressure measurement at choroid surface: a feasibility study with implications for implantable microsystems. Br J Ophthalmol 85:868–871
61. Svedbergh B, Backlund Y, Hok B, Rosengren L (1992) The IOP-IOL. A prob into the eye. Acta Ophthalmol (Copenhagen) 70(2): 266–268
62. Walter P, Schnakenberg U, vom Bogel G et al. (2000) Development of a completely encapsulated intraocular pressure sensor. Ophthalmic Res 32:278–284
63. Hille K, Draeger J, Eggers T et al. (2001) Technischer aufbau, kalibrierung und ergebnisse mit einem neuen intraokularen drucksensor mit telemetrischer Ubertragung. Klin Monatsbl Augenheilkd 218(5):376–380
64. Chen PJ, Rodger DC, Humayun MS (2006) Unpowered spiral-tube parylene pressure sensor for intraocular pressure sensing. Sensors and Actuators A:Physical 127(2):276–282
65. Chen PJ, Rodger DC, Meng E, et al. (2006) Implantable unpowered parylene MEMS intraocular pressure sensor. Technical Digest, IEEE Engineering in Medicine and Biology Society Special Topic Conference on Microtechnologies in Medicine and Biology. 256-259
66. Data provided courtesy of Implandata Ophthalmic Products GmbH
67. Todani A, Behlau I, Fava MA et al. (2011) Intraocular pressure measurement by radio wave telemetry. Invest Ophthalmol Vis Sci 52(13):9573–9580
68. Chen G, Ghead H, Haque R, et al. (2011) A cubic-millimeter energy-autonomous wireless intraocular pressure monitor. ISSCC Digest of Technical Papers, pp 310-312
69. Lee Y, Kim G, Bang S, et al. (2012) A modular 1 mm3 die-stacked sensing platform with optical communication and multi-modal energy harvesting. ISSCC Digest of Technical Papers, pp 402-404