Intraocular Pressure Measurement by Radio Wave Telemetry

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PURPOSE. To determine the biocompatibility of a new wireless intraocular pressure (IOP) transducer (WIT) in rabbit eyes and to correlate its measurements with other pressure-measuring devices.

METHODS. The WIT is a ring-shaped intraocular device that allows wireless IOP measurements through radiofrequency. It was implanted into six eyes of New Zealand White rabbits after extracapsular lens extraction. A sham rabbit eye with no transducer implanted was used as a control. The animals were observed and examined by microscopy at various intervals up to 25 months after surgery. IOP was measured at various intervals by pneumotonometry, tonometry, WIT, and manometry. The data from the various devices were compared and analyzed for reproducibility. Two eyes were enucleated at 5.5 and 20 months after implantation and analyzed by histology.

RESULTS. The WIT appears to be well tolerated in the rabbit eye, with no evidence of significant inflammation or scar formation by microscopic in vivo examination. Histology did not reveal intraocular inflammation or membrane formation. Repeated IOP measurements with pneumotonometry, tonometry, and the WIT resulted in SDs of 2.70 mm Hg, 3.35 mm Hg, and 0.81 mm Hg, respectively. The concordance between the WIT and direct manometry measurements was high. A downward drift in IOP measured by the WIT was noted in three rabbits, necessitating recalibration.

CONCLUSIONS. The WIT is well tolerated by the rabbit eye. Its measurements are reproducible and in close concordance with pneumotonometry and tonometry, and the WIT measured IOP in SDs of 2.70 mm Hg, 3.35 mm Hg, and 0.81 mm Hg, respectively. The present study aims to test the biocompatibility and the IOP measurement characteristics of a novel IOP transducer, the wireless IOP transducer (WIT; Implandata GmbH, Hannover, Germany). This device would allow the telemetric recording of the “true” IOP rather than the one inferred from changes in corneal curvature. It would also allow frequent measurements without the currently indispensable visit to a doctor’s office.

MATERIALS AND METHODS

Radio Wave Telemetry System

Pressure sensors cells manufactured by surface micromachine techniques have been an enabling technology for miniaturized, highly reliable, and stable pressure sensor systems, as used in automotive and other technical and consumer applications. The wireless sensor system described in this article is based on such technology, adapted to the special requirements of a medical device. It is designed to make possible quasi-continuous measurements of IOP and patient self-monitoring.

The WIT (Wave Telemetry) transducer is a digital, ultra-miniature device that combines pressure-sensor, temperature-sensor, identification encoder, analog-to-digital converter, and telemetry into a monolithically integrated microelectromechanical system-application specific integrated circuit (MEMSASIC) (Figs. 1, 2). The ASIC is based on complementary metal oxide semiconductor technology.

The system is powered by a reader unit (Fig. 3) that can be placed in proximity of the sensor (within 5 cm). The same reader unit picks up the digital data sent by the transponder implant. The implant itself does not require a battery. The telemetry coil (microcoil) is required for power supply by inductive coupling to an external magnetic field generator; the inductive link is also used for digital data transmission. The inductive link is established to the hand-held external reader device. The sensor signal is converted from analog to digital information, making the data transmission link immune to electromagnetic interference or variations in the geometry (e.g., distance) between the implant and the external reader device.

Materials used for the electronic components were selected to be biocompatible or inert. The ASIC is bonded to a circular microcoil antenna made of gold. Both the ASIC and the antenna are hermetically encapsulated in biocompatible, platinum-cured silicone rubber material, which makes up the entire surface of the implant. The implant is designed to remain in vivo indefinitely.
The outside diameter of the transponder disc is only 11.3 mm; the inside diameter is 7 mm, its thickness is 0.9 mm, and the weight is 0.1 g.

IOP is measured by an array of capacitive pressure sensors. These sensors, in a simplistic model, can be visualized as composed of two parallel plates: a thin flexible membrane that is indented by the IOP and a thicker rigid base. The surface-micromachined pressure sensor cells (Fig. 2) exhibit properties very similar to those of basic plate capacitors. When the cell membrane is mechanically deflected by pressure changes, the capacity of the cell changes because of the change in distance between the "plates." This results in an analog signal that is proportional to the absolute pressure within the eye. The cell structures are an integral part of an accurate but low-power analog-to-digital converter circuit, which enables the ASIC to generate a fail-safe and checksum-secure data telegram. To yield highly accurate readings, an array of eight pressure sensor cells is switched in parallel.

The capacitance between two parallel plates is given by the equation $C = \frac{eA}{d}$, where $C$ refers to the capacitance, $e$ refers to the product of the dielectric constant ($\varepsilon_r$) and the electric constant ($\varepsilon_0$) of the medium between the plates, $A$ refers to the area of the plates, and $d$ refers to the distance between the plates. The membrane, which is indented by the IOP, changes the distance ($d$) between itself and the rigid base, resulting in a capacitance change. The capacitive pressure sensor ($C$) is integrated with an inductor ($L$) to form an LC resonant circuit. The magnitude of the capacitance change is measured digitally and transmitted externally by radiofrequency. As stated, the IOP is then tracked by the external reader unit, which is electromagnetically coupled with the sensor by bringing the reader in proximity with the sensor and pressing a button on the reader unit.
All values are in mm Hg. Six WIT devices were soaked in saline for a period of 515 days at a temperature of 36°C and an absolute test pressure of 1000 hPa. The calculated drift refers to the actual drift adjusted for signal noise. The calculated drift rate per year was 2.46 mm Hg (Table 1). The implantation of Transducers

For the purpose of our study, all transducers were sterilized with ethylene oxide. All transducers were implanted under aseptic conditions in a dedicated animal operating room using a surgical microscope (OPMI 700; Carl Zeiss Surgical GmbH, Oberkochen, Germany). Anesthesia was composed of ketamine HCl 35 mg/kg (Ketaject; Vedco Inc., St. Joseph, MD) and xylazine HCl 10 mg/kg (Transquill; Vedco Inc.) administered intramuscularly 15 minutes before surgery. In addition, 2 drops of topical proparacaine hydrochloride 0.5% eye drops (Alcaine; Alcon, Fort Worth, TX) were instilled into the conjunctival sac of the eye before the procedure. The lids were sterilized with 5% povidone-iodine solution. Polymyxin B trimethoprim ophthalmic solution (Polymixin B trimethoprim ophthalmic solution (Polytrim; Allergan, Inc., Irvine CA) was given immediately before surgery. The animals were placed in a laterally recumbent position for surgery and kept warm with a heating pad. Transducers were numbered consecutively from T1 to T6 according to the chronological order of implantation (Table 2). T1 and T2 were implanted through a corneal auto graft (size of corneal button: 5.5 mm in T1 and 7.0 mm in T2), whereas the transducers from T3 through T6 were implanted through a 10- to 12-mm limbal incision. The crystalline lens was extracted manually through an anterior capsulorrhexis either open-sky (T1, T2) or by a manual extracapsular cataract extraction technique (T5-T6). The transducers either were placed in the ciliary sulcus (T1, T2, T4, T5, T6) or were suspended into the vitreous cavity (T3) after suturing to the sclera ab interno with 9–0 polypropylene sutures (Prolene; Ethicon, Somerville, NJ) (Table 2). For transducers T3, T4, and sham, a posterior capsulotomy and a limited core manual vitrectomy were performed.

All the transducers were fully functional and calibrated with the exception of transducer T4, which was a noncalibrated, actively transmitting transducer with the same structure and design as the other transducers (sham transducer). In one rabbit (no transducer, sham surgery), the crystalline lens was removed using an extracapsular cataract extraction technique, but no implant was placed. The surgical wounds (limbal or corneal) were closed with interrupted 10–0 monofilament nylon sutures (Ethicon), which were removed after 2 weeks. A soft contact lens with a 16-mm base curve (Plano; Kontur Contact Lens Co Inc, Hercules, CA) was given immediately before surgery. The lids were sterilized with 5% povidone-iodine solution. Polymyxin B/trimethoprim ophthalmic solution (Polymyxin B trimethoprim ophthalmic solution (Polytrim; Allergan, Inc., Irvine CA) was given immediately before surgery. The animals were placed in a laterally recumbent position for surgery and kept warm with a heating pad. Transducers were numbered consecutively from T1 to T6 according to the chronological order of implantation (Table 2). T1 and T2 were implanted through a corneal auto graft (size of corneal button: 5.5 mm in T1 and 7.0 mm in T2), whereas the transducers from T3 through T6 were implanted through a 10- to 12-mm limbal incision. The crystalline lens was extracted manually through an anterior capsulorrhexis either open-sky (T1, T2) or by a manual extracapsular cataract extraction technique (T5-T6). The transducers either were placed in the ciliary sulcus (T1, T2, T4, T5, T6) or were suspended into the vitreous cavity (T3) after suturing to the sclera ab interno with 9–0 polypropylene sutures (Prolene; Ethicon, Somerville, NJ) (Table 2). For transducers T3, T4, and sham, a posterior capsulotomy and a limited core manual vitrectomy were performed.


data

The implant and the external reader device are inductively coupled through an electromagnetic link (low-power, high-frequency field at 13.56 MHz). Both sides are set up to be in electric resonance at that frequency to maximize energy efficiency. The external reader device is battery powered; the implant is powered by the electric current, which is induced by the inductive link in the microcoil. Data are transmitted by absorption modulation, which means that the ASIC is changes its resistive load to the microcoil in a specific cycle representative of the data telegram, which can be detected and decoded by the external reader device. The power consumption of the implant is in the range of 250 µA at 3V. There is no galvanic battery or the like for intraocular lens manufacturing. The electronic module is fully encapsulated in that material, with the measurement function not constricted by that coverage.

The encapsulation material layer provides a long-term barrier to the electrolytes dissolved in aqueous humor. Implandata GmbH reports that WIT devices have been functional after being soaked in saline for 4 years.

Ex vivo drift studies were performed on six WIT devices by Implandata GmbH. The devices were immersed in saline for 515 days at a temperature of 36°C and an absolute test pressure of 1000 hPa. The calculated drift refers to the actual drift adjusted for signal noise. The calculated drift rate per year was 2.46 mm Hg (Table 1).

### Table 2. Surgical Approach for Placement of the WIT Transducer in Each Rabbit

<table>
<thead>
<tr>
<th>Animal</th>
<th>Wound</th>
<th>Location</th>
<th>Vitrectomy</th>
<th>Posterior Capsulotomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>5.5-mm Corneal autograft</td>
<td>Sulcus</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>T2</td>
<td>7.0-mm Corneal autograft</td>
<td>Sulcus</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>T3</td>
<td>Limbus</td>
<td>Vitreous</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>T4</td>
<td>Limbus</td>
<td>Sulcus</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sham</td>
<td>Limbus</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>T5</td>
<td>Limbus</td>
<td>Sulcus</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>T6</td>
<td>Limbus</td>
<td>Sulcus</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

* T4 had a nonfunctioning transducer.
† "Sham" rabbit had no transducer implanted.
removed (2–4 weeks). Topical antibiotics (polymyxin B/trimethoprim ophthalmic solution USP [Polysporin; Allergan, Inc., Irvine, CA]) and steroid (prednisolone acetate 1% ophthalmic suspension [Pred forte; Allergan, Inc.]) were administered immediately after surgery and then once daily for 4 to 6 months. The eyes were grossly examined daily in the first month; this was followed by portable slit lamp microscopy when IOP measurement sessions were conducted.

**Telemetric, Tonometry, and Pneumotonometer IOP measurements**

The animals were sedated to minimize sympathetic responses affecting the IOP, which has been reported to occur with animal restraining and with contact tonometry.\(^{12}\) Attempts to obtain measurements in unseated animals were not successful. Given that the reader device has to be within 5 cm of the transducer, this led the frightened animals to forcefully squeeze their eyes, leading to erratic IOP readings. With the sedated animals in the lateral recumbent position, the reader was activated as described, and a series of 12 measurements was taken over a 2-minute period. An average IOP value was then displayed on a 3-digit, 7-segment display screen. These values were stored within the device allowing future download to a separate computer for further tabulation and analysis. Tonometry (Tono-Pen; Medtronic Solan, Jack- sonville, FL) and pneumotonometer (model 30-Classic; Mentor O & O, Norwell, MA) measurements were performed at the same session. Each device was used to obtain a series of 12 readings.

**Manometry Comparison**

Direct manometric measurement is considered the gold standard in assessing IOP.\(^{13}\) We compared the readings obtained from the WIT transducer to those obtained by manometry in four rabbits. The rabbits were anesthetized as described, and the procedure was performed under aseptic conditions. A 21-gauge needle was connected to a balanced salt solution (BSS)-filled syringe fitted with a double stopcock Luer-lock. This was connected to a pressure transducer (Harvard Apparatus, South Natick, MA). If needed, the transducer was calibrated to zero before the procedure. The needle was then introduced through the cornea until it reached the mid-anterior chamber.

Measurements were then recorded simultaneously with the manometer and with the WIT transducer. BSS was slowly injected intraocularly to raise the IOP to a maximum value of 60 mm Hg. The injection was paused for approximately 10 seconds while manometric and WIT measurements were recorded simultaneously. This was necessary because it takes approximately 10 seconds for the WIT to display the IOP reading from the moment the trigger for measurement is activated. The pressure was then allowed to fall passively while data were being collected from the two devices in a similar fashion. This was repeated until the desired number of measurements was obtained.

**Histology**

Eyes of two rabbits, T5 and T2, were enucleated at 5.5 and 20 months after implantation, respectively. Globe integrity was preserved, and the specimens were placed in 4% formaldehyde in phosphate-buffered solution. Dissection was subsequently performed by a transversal cut at the equator, allowing a posterior view of the transducer. Photographs were taken. A transversal cut above the iris was performed when needed to visualize the anterior aspect of the transducer. The transducer was removed and the part of the eye enclosing it was processed and embedded in paraffin. Histologic sections were examined using hematoxylin and cosin, periodic acid-Schiff, and trichrome stains.

**Statistical Analysis**

Reproducibility of WIT was ascertained through the assessment of its measurement variability relative to the Tono-Pen (Medtronic Solan) and the pneumotonometer within each animal as well as across all animals (Table 3). Low variability, quantified by the SD of individual measures from their overall mean, is indicative of high reproducibility. Pooled SD estimates were calculated for all three instruments for individual rabbits. Additionally, an overall pooled SD estimate was computed. Using the Brown-Forsythe test of equality of variances,\(^{14}\) the probability of WIT SD exceeding that of the Tono-Pen and the pneumotonometer was computed for each animal and for all animals simultaneously. Small \(P\) values corresponded to significantly higher reproducibility of WIT values compared with those of the Tono-Pen and the pneumotonometer.

The accuracy of WIT was determined with respect to the gold standard of manometry. Accuracy is a composite measure of bias and precision.\(^{15}\) Pearson’s correlation coefficient \(r\), which quantifies the variance of WIT values around the line of best fit, derived from linear regression of manometry pressures on those obtained with WIT, was used as a measure of precision. Bias was evaluated using the bias correction factor \(C_{b}\),\(^{16}\) which reflects the proximity of the line of best fit to the reference line with an intercept of 0 and slope of 1. The reference line represents the situation in which WIT values are identical with those of manometry at all pressures. Accuracy was determined with Lin’s concordance correlation coefficient \(r_{c}\),\(^{17}\) which quantifies the variance of the observed data from the reference line. Values of \(r_{c}\) close to 1 indicate high precision, low bias, and high accuracy, respectively.

**RESULTS**

The main goal of the study was to examine the safety and biocompatibility of the WIT transducer in the rabbit eye. In the immediate postoperative period, both the transducer and the surgical sham groups demonstrated transient mild anterior chamber inflammation consistent with the procedure performed. Examinations with a portable slit lamp revealed no evidence of fibrinous reaction, membrane formation, or chronic uveitis in any eye at several intervals during the follow-up period. There was mild perilimbal congestion in all the operated eyes that was similar in intensity between the sham

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**Table 3. Reproducibility of the WIT Pressure Transducer Measurements Compared with the Pneumotonometer and the Tono-Pen**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Pneumotonometer</th>
<th>Tono-Pen</th>
<th>WIT</th>
<th>( P ) (WIT &gt; pneumotonometer)</th>
<th>( P ) (WIT &gt; Tono-Pen)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>4.65</td>
<td>4.85</td>
<td>1.09</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T2</td>
<td>2.58</td>
<td>4.52</td>
<td>0.81</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T3</td>
<td>1.27</td>
<td>1.76</td>
<td>0.64</td>
<td>0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T5</td>
<td>0.59</td>
<td>1.71</td>
<td>0.69</td>
<td>0.086</td>
<td>0.011</td>
</tr>
<tr>
<td>T6</td>
<td>1.92</td>
<td>0.94</td>
<td>0.74</td>
<td>0.011</td>
<td>0.286</td>
</tr>
<tr>
<td>Pooled</td>
<td>2.70</td>
<td>3.35</td>
<td>0.81</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Each value represents the IOP standard deviation derived from multiple sessions each consisting of 12 consecutive readings. Rightmost columns denote the probability of WIT standard deviation exceeding that of the corresponding instruments.
A drift in IOP measurements was noted by the WIT compared with pneumotonometer and tonometry. The drift was suspected when lower measurements were recorded compared with the two other devices without an apparent change in the clinical conditions. When drift was noted, calibration was performed as an offset calibration through reprogramming of the external reader device using pneumotonometer and Tono-Pen (Medtronic Solan) readings in sedated animals as a reference value unless manometry data were available.

After the initial calibration, all WIT sensors but one (T1) remained relatively stable compared with the pneumotonometer and Tono-Pen (Medtronic Solan). Although the IOP measurements from the two devices are not accurate in rabbits, they were the best available reference until manometry was performed.

After relative measurement stability for about 1 year of implantation, T1 suddenly markedly drifted downward at a rate of approximately 2 mm Hg/month. This trend was stopped when manometry was performed in this eye, with the sensor remaining stable afterward. T2 was the second rabbit in which drift was noted. T2 remained stable compared with pneumotonometer but showed a sudden drop in readings after approximately 1.5 years (at 608 days). Calibration was performed at the beginning of the manometry experiment.

From a clinical perspective, the manometry value must be considered the true value of IOP. Figure 6 illustrates the comparison between IOP measurements collected by the transducer versus manometry in rabbits T1, T2, T3, and T5. The WIT recordings exhibited high concordance with those simultaneously gathered by manometry over a wide range of IOP values. As noted, recalibration of the WIT was performed at the beginning of the experiment when needed. Pearson’s correlation coefficient values ranged from 0.984 to 0.999; values of the bias correction factor varied between 0.985 and 0.998, whereas those of Lin’s concordance correlation coefficient were found to lie between 0.984 and 0.996 for the four rabbits (Fig. 6).

**DISCUSSION**

Telemetric IOP measurement offers several advantages compared with standard applanation tonometry. It allows monitoring of IOP in patients who cannot be measured by current methods. This primarily pertains to the patient who does not have a healthy cornea or who has received an implanted artificial cornea (keratoprosthesis).

Telemetric IOP measurement may also allow reduction in patient visits and permit better monitoring of response to therapy. Diurnal IOP curves obtained by applanation tonometry also appear to vary in the same rabbit on different days.17,18 Hughes et al.19 showed that peak 24-hour IOP measurements were on average 5 to 12 mm Hg higher than IOP at office visits.
Implanted devices to measure IOP in animals have been reported in the literature from as early as the late 1960s. The first report of an intraocular radio wave pressure-sensor transducer designed for possible human use was Almen et al. 21. They used a miniaturized capacitive pressure sensor that was manufactured using micro machinery techniques. The energy supply of the transponder was realized using electromagnetic coupling between the transponder and an external readout device. Their transponder disc, however, was still fairly large (18-mm diameter, 2.5-mm thick) and not suitable for human implantation. To the best of our knowledge, ours is the first report of an intraocular radio wave pressure-sensor transducer designed for possible human use.

The present study established that there is a high degree of biocompatibility between the rabbit eye and the implanted transducer. Sequential clinical evaluations of the animals determined that the rapid healing after ocular surgery led to an accompanying subsidence of external signs of inflammation, particularly conjunctival hyperemia and circumciliary flush that did not recrudesce. Histopathologically, not even trace evidence of a persistent polymorphonuclear leukocytic reaction was detected. Instead, in the two eyes examined microscopically, the transducer had been securely placed within the lens capsule (“in the bag”). In the first eye, a very light diaspore of mononuclear inflammatory cells was discovered near the lens capsule and in the nearby vitreous, where small clusters or cords of proliferating subcapsular lens epithelial cells emerged from a focal rupture in the capsule. In the second eye examined microscopically, despite the absence of significant anterior segment inflammation, suboptimal surgery had been performed in terms of leaving an excess of lens epithelium left behind. These cells underwent robust fibrous metaplasia that created a thicker, uninflamed fibrous membrane that invested the transducer.

The WIT sensor and antenna are made of potential irritants such as gold, silicone, polyimide, and traces of other materials. Potential leakage through the silicone sleeve is possible if the hermeticity of the device is disrupted. Studies by Donaldson27 show that silicone rubber encapsulations can be functional for more than 20 years. There is no evidence that the hermeticity of the device was invaded throughout the 25 months of our study. This is consistent with the ex vivo studies communicated by Implandata GmbH.

The WIT measurements were tested for reproducibility by taking 12 readings at every data point. The data collected showed excellent reproducibility. The WIT consistently demonstrated smaller variation in IOP measurements at and be-
tween any experimental data point than the pneumotonometer and the Tono-Pen (Medtronic Solan). Unfortunately, the IOP measurements with the Tono-Pen and the pneumotonometer resulted in scattered values for unknown biological reasons and had to be deemed noncontributory. This is consistent with other studies in which the pneumotonometer and the Tono-Pen were found to have low reliability in rabbits.²⁸,²⁹

Manometry readings proved to be of much greater value. Manometer concordance should give the “true value” of the IOP and is considered the most reliable method to validate the IOP measurements.³⁰ Experiments designed to evaluate the concordance of the WIT with manometry showed excellent association between the two devices as late as 20 months after implantation.

One limitation of the device is a drift in IOP measurement noted over time. A downward trend in IOP measurements was noted in two rabbits. Concordance with manometry was still significant despite the need for recalibration in these rabbits. It is unclear why some of the implanted devices exhibited drift while others were stable. The drift observed in our study was not consistent with that in the ex vivo study performed by Implantdata GmbH. We speculate that this could be related to sensor disruption by the fibrous metaplasia of the lens epithelial cells observed by histology or to external pressure forces due to the smaller rabbit eye. The ultimate plan is to monitor implanted devices in humans for accuracy, precision, and drift through direct comparison with Goldman applanation tonometry. This will allow a more detailed characterization of the IOP-measuring properties of the WIT. This may necessitate periodic comparison and calibration until stability is achieved.

In summary, we have demonstrated that the WIT IOP transducer is biocompatible in rabbit eyes without signs of toxicity for up to 25 months. Concordance with manometry data demonstrated transducer drift over time, necessitating recalibration. Once recalibrated, the device showed strong concordance with intraocular manometry over a wide range of pressures. Considering the ease of recalibration, the device should be ready for human testing.

References


