Evaluation of efficacy and biocompatibility of indirect intraocular pressure monitoring using a telemetric scleral sensor

Thesis

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By

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ABSTRACT

Intraocular pressure (IOP) monitoring traditionally requires direct contact with the cornea and special instrumentation which limits the ability of a patient to monitor IOPs outside of the clinical setting. The purpose of this study was to obtain an IOP measurement without the need for topical anesthesia, patient compliance or corneal contact as is necessary with conventional tonometry. This report assesses the efficacy, biocompatibility and stability of a surgically implanted telemetric scleral sensor (TSS) implanted subconjunctivally and sutured to the sclera of rabbits. IOP was monitored using the TSS and a Tono-Vet® over a period of 16 weeks. Manometric IOP values were also recorded in 5mmHg intervals up to 70mmHg and compared to TSS. Eyes were submitted for histopathology for assessment. Although initial readings showed good correlation between the TSS and Tono-Vet®, the overall size and design of the TSS contributed to fibrosis and premature dislocation of the sensor.
Dedicated to my parents, Charlie and Debra Robinson, my sister Carey Richards
and my fiancé Max Corbett
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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Glaucoma is an optic neuropathy in which most, but not all cases are associated with an increased intraocular pressure (IOP). Structural damage to retinal ganglion cells, optic nerve head and nerve fiber layer may ultimately lead to decrease or loss of vision. Glaucoma can be divided into congenital, primary or secondary causes. Congenital glaucoma is most often present at birth, but clinical signs may begin shortly after birth in the neonatal period. This type of glaucoma is characterized by developmental abnormalities of the iridocorneal angle or anterior segment. Primary glaucoma can be further divided into primary open angle glaucoma (POAG), which is the most common form in humans, or angle closure glaucoma (ACG), which is the most common form in dogs. Secondary glaucoma can occur when primary intraocular disease results in obstruction of aqueous humor outflow and subsequently an increase in intraocular pressure. Secondary glaucoma is more common than primary glaucoma in cats and horses.
Incidence in veterinary patients

Glaucoma in veterinary medicine has been an evolving disease over the past 60 years. The incidence in veterinary patients has increased in recent decades, which may be a true increase in prevalence, but may also be a result of more widespread knowledge and detection of disease. Development of portable methods for tonometry has allowed for more convenient evaluation of intraocular pressure, and advances in veterinary literature and research have prompted better screening for glaucoma.

Canine glaucoma was traditionally recognized as an unknown series of diseases with an elevation in IOP as the common component. As the field of veterinary ophthalmology has continued to evolve, a better understanding of these disease processes has contributed to classifications similar to human ophthalmology including primary open angle glaucoma (POAG) and narrow or closed angle glaucoma. Approximately 27 breeds have been represented in recent studies of primary glaucoma. The most common breeds include the following: American Cocker Spaniel, Basset hound, Chow Chow, Shar-pei and Boston terrier. The prevalence of breed-related primary glaucoma has been increasing throughout the recent decades, from 0.29% in a study from 1963-1973 to 0.89% between 1994-2002. The increase in prevalence may be a result of greater awareness of the disease in recent years causing owners to seek veterinary care, veterinarians to screen for glaucoma more often or possibly more animals being bred with a genetic predisposition for this inherited disease.

Secondary glaucoma has recently been shown to be nearly as prevalent as primary glaucoma in dogs, 0.80% and 0.89%, respectively. Another study showed of all
ophthalmic cases presenting during a 5 year period, 6.9% of dogs presented for secondary glaucoma. The most common causes of secondary glaucoma in canine patients listed in descending order include: lens induced uveitis, lens luxation, complication after cataract surgery, uveitis, hyphema, and intraocular neoplasia. The Johnsen study grouped the secondary glaucomas into three categories, non-surgical anterior uveitis (44.9%), post-surgical uveitis (15.8%), and glaucoma secondary to lens dislocation (15.2%).

Congenital glaucoma is rare in dogs with very few references in the literature. A review of 590 dogs presenting to a group of ophthalmologists for congenital ocular problems revealed that only 1% of canine congenital cases were diagnosed with congenital glaucoma. There is some debate or confusion regarding the diagnosis of goniodysgenesis and classifying this as a congenital form of glaucoma vs. a primary inherited form which may limit the assessment of large population studies.

Glaucoma in feline patients is less common than in dogs, with a reported incidence in one study of 0.197% in cats and 0.675% in dogs. Secondary glaucoma is the most frequent type in feline patients, one study reporting 87% of feline glaucoma to be secondary in nature. The two leading causes of secondary glaucoma are undisputed in the literature: uveitis (usually lymphoplasmacytic) or intraocular neoplasia (diffuse iris melanoma, lymphoma, or intraocular sarcoma, and rarely metastatic disease). Congenital feline glaucoma is very rare, but has been described in Siamese cats and is characterized by a narrow iridocorneal angle and pectinate ligament dysplasia. Primary glaucoma in cats is uncommon, but case reports identify narrow and closed angle glaucoma in Burmese, open angle glaucoma in Siamese, and goniodysgenesis in European Shorthair cats.
Glaucoma in horses has an incidence lower than that reported in other species: 0.07% in the United States. Secondary glaucoma is most common in horses, with 85% of all glaucoma cases occurring secondary to equine recurrent uveitis (ERU). The Appaloosa is at risk for developing ERU, and therefore is over-represented as a breed for developing glaucoma, though some also believe the breed to have a genetic risk independent of presence of uveitis.

Congenital glaucoma in horses is uncommon, with only occasional case reports in the literature. Three cases in thoroughbred foals have been documented, one with findings consistent with unilateral Reiger’s anomaly (abnormal development of the mesodermal structures of the eye), one with bilateral lens luxation and one with true anterior segment dysgenesis. One standardbred filly has also been described with bilateral anterior segment dysgenesis. Primary equine glaucoma is exceedingly rare, and in one study was diagnosed not by changes to the iridocorneal angle as in other species, but rather by lack of clinical signs associated with uveitis. No histopathologic evaluation was performed to confirm the diagnosis. However, gonioscopic examination in a small number of horses in another study showed horses with narrow (1/5) and closed (1/5) iridocorneal angles, which may be evidence of a primary cause.

**Incidence in human patients**

Glaucoma is the second most common cause of blindness in the world. There are approximately 60 types of glaucoma established in humans, including the previously mentioned categories of POAG, ACG, congenital and secondary. A statistical model from 1996 states that an estimated 66.8 million people worldwide have
been diagnosed with primary glaucoma and 6 million with secondary glaucoma.\textsuperscript{27} Of the population with primary glaucoma, approximately 10\% of cases (6.7 million people) result in blindness.\textsuperscript{27} In the United States alone, estimates show that roughly 2.5 million people are affected with glaucoma, resulting in legal blindness in approximately 130,000 people.\textsuperscript{25} People of African descent have a higher prevalence of glaucoma, as demonstrated in several population studies.\textsuperscript{1, 25, 27, 28} Age is also a risk factor for POAG regardless of race. Patients over 75-80 years of age show a 2-9 fold increased risk of developing glaucoma compared to patients 40-55 years of age.\textsuperscript{1, 24, 29}

Open angle glaucoma is slowly progressive and is characterized by optic nerve atrophy and retinal ganglion cell atrophy, resulting in vision loss.\textsuperscript{27, 28, 30-32} This is the most common type of glaucoma in humans, and is considered to be the most difficult to detect. Many diagnostic tests have been described in the literature with great debate as to the most reliable. Most ophthalmologists agree a multi-modal diagnostic plan is necessary, and most conclude that the top three diagnostic screening tools include the following: 1) evaluation of the optic nerve to assess the optic cup-disc ratio, 2) visual field screening and 3) intraocular pressure determination.\textsuperscript{27-29}

A more acute, devastating form of glaucoma is angle closure glaucoma (ACG). The true prevalence of this disease is difficult to assess due to the variation in diagnostic criteria of ACG. Diagnosis is usually based on clinical examination, including a decreased axial globe length and a reduced anterior chamber depth, though some studies also take into account IOP and optic nerve damage.\textsuperscript{27, 33} Studies report an overall prevalence of 0.04\%-0.9\% in the general Caucasian population, but certain populations show a much higher rate.\textsuperscript{1, 24, 29, 34} Chinese population studies show an incidence of ACG
three times higher than OAG, which is much higher than the reported Caucasian groups.\textsuperscript{27} Inuit populations in Alaska, Canada and Greenland also show a much higher rate of ACG than Caucasians, ranging from 2.65\% to 4.8\% in patients over 40.\textsuperscript{35} Conversely, the prevalence for ACG in African Americans is equal to or even less than Caucasians.\textsuperscript{1, 27, 34} Despite the relatively low prevalence in the entire population, statistical models report the incidence of OAG and ACG to be relatively equal, though the overall risk of blindness is up to three times greater with ACG when compared to OAG.\textsuperscript{27, 33, 36}

**Standard methods of obtaining IOP**

Diagnosis of glaucoma in humans is complicated by a combination of factors, including subtle progression of the clinical signs and difficulty in accurate testing for the disease in at-risk patients. The limitations include the lack of education regarding early warning signs associated with glaucoma. A retrospective study was evaluated in the early 1980’s, and 750 cases of bilateral blindness were evaluated. Of these patients, 12.4\% were blind from bilateral glaucoma, and 1/3 of these patients didn’t seek treatment until after they were bilaterally blind.\textsuperscript{37} Many patients do not experience ocular discomfort and the onset of blindness is insidious, making it difficult to seek medical help during the initial presentation of disease.\textsuperscript{28} Education about the progression of the disease and early detection is important in control of glaucoma. In veterinary medicine this becomes important as well, as early clinical signs of glaucoma can easily be missed by owners and patients are often not presented to the veterinarian until chronic signs occur such as buphthalmos or blindness.
Over the years, appropriate diagnostic testing for glaucoma has been challenged, making development of a “gold-standard” test to determine an accurate diagnosis of glaucoma difficult. Risk factors have also been analyzed, with some debate. Although some say that IOP is a poor diagnostic test as many patients with OAG can be normotensive, an elevated IOP is a confirmed risk factor, validating the practical use of IOP measurement in clinical practice. A prospective study performed by the Advanced Glaucoma Intervention Study (AGIS) involving 5000 patients demonstrated five significant risk factors to reduced visual field: reduced outflow facility, age, intraocular pressure, cup-disc ratio and IOP increase after drinking water.

Though debate still exists in terms of initial diagnosis of glaucoma, most studies agree that using IOP to monitor the progression and effect of treatment is important. Although other factors exist which contribute to optic nerve and retinal damage, in the absence of other testing and monitoring modalities, many conclude that IOP is the primary marker of glaucoma treatment. In the AGIS, it was determined that a low IOP post-intervention correlated with decreased visual field deficits. The authors concluded that maintaining low normal IOP slows the progression of glaucomatous optic neuropathy.

Methods of obtaining IOP have evolved throughout the years, allowing greater ease and accuracy in IOP measurement by most medical professionals. Three categories of IOP measurement include: transpalpebral, manometry and tonometry. Transpalpebral measurements are less invasive, but as demonstrated in the literature, are the least reliable. Digital palpation is the oldest known method for evaluating IOP, dating back to the 19th century. Though this method is inexpensive and readily available, it is highly
inaccurate. Other transpalpebral devices such as the TGDr-01, IGD-02 and Bausch and Lomb’s Proview were designed with the intent to be used for patients with corneal disease (fibrosis, edema, astigmatism). In addition, the Proview has been marketed for at-home use so patients can measure their own IOP. These devices are not commonly used for routine screening because there is much variation in results, dependant on position of the instrument and the reader’s skill level. In addition, measurements were consistently lower when compared to a standard Goldmann or Tono-pen® tonometer.40

Manometry is a more invasive, yet extremely precise method of measuring IOP, and is the gold standard by which all other tonometers are compared. The principle behind manometry is that the intraocular pressure is higher than atmospheric pressure. If a needle is introduced into the eye, the aqueous fluid will exit the eye through the needle, and the associated fluid pressure can therefore be measured in millimeter of mercury (mmHg).39 Two methods are used, either an open system or a closed system. An open system allows for a constant maintenance of pressure despite contact with the globe.39 A closed system is more realistic to an intact eye, and pressure applied on the globe will cause an immediate rise in pressure, as is commonly encountered with applanation or indentation tonometers.39 Due to its invasive nature, manometry is rarely performed in unanesthetized patients; therefore, this area of study usually occurs with patients under anesthesia or in eyes that have been enucleated.

Tonometry is the most commonly used method of obtaining IOP. This category can be broken down into many subtypes including: applanation, indentation, combination applanation-indentation, contour and rebound. Applanation tonometry uses the principles of the Imbert-Fick law: pressure = force/area.39 Using this formula, the instrument must
have a fixed area of contact with the globe, or a known force applied to the globe. The opposite value is obtained with the instrument, and the pressure is then calculated and displayed. Examples of a fixed-force tonometer include the Maklakoff and the Posner tonometer, both of which proved to be fairly impractical and are not used today.\textsuperscript{39} Fixed-area tonometers are still in use today, the most popular being the Goldmann Applanation Tonometer – the instrument that is most often used in human clinical practice. This tonometer has a fixed diameter surface of 3.06mm, which is located in the center of a plastic cylinder totaling 7mm in diameter. The cylinder is attached to a spring-loaded device that controls the amount of force, which is then read on a scale. The examiner applies pressure to the stained cornea with this device until the patient’s tear meniscus is seen through the plastic cylinder, then adjusts the force until the appropriate area of 3.06 mm is achieved. Forces associated with this process, including corneal rigidity and surface tension of the tears, cancel out, allowing the pressure to be read in 1 mmHg increments.\textsuperscript{39} Limitations of this technique include pre-existing corneal disease such as edema or fibrosis that can alter corneal rigidity. The Goldmann tonometer is not portable, and must be used with a table-mounted slit lamp, which limits its use in veterinary medicine.

The Perkins handheld tonometer is a portable unit that utilizes the Goldmann method\textsuperscript{41}. The portable nature of this unit makes it ideal for use with home-care, nursing homes and in recumbent patients. A recent report compared the Perkins tonometer to manometry in cats and dogs, the first report of potential clinical use in veterinary medicine. The results of IOP measurement with the Perkins in both anesthetized and conscious dogs and cats were lower than previous reports of Tono-Pen\textsuperscript{®} and TonoVet\textsuperscript{®},
but showed excellent correlation when compared to manometry. Similar results were found in a study of anesthetized rabbits, with a direct comparison to manometry, Tono-Pen® and TonoVet®. This study showed very good accuracy of the Perkins tonometer when compared to manometry, and it proved to be even more accurate than the Tono-Pen® and TonoVet®. Other forms of applanation tonometers are not commonly used, and include the Non-contact Air Puff tonometer, applanation and corneal hysteresis, and dynamic observing tonometry.

Indentation tonometry is another method that is still used today in less developed areas, as well as in veterinary medicine. The most common instrument used is the Schiotz tonometer. The principle with indentation tonometry is that a known force will indent a fluid or gas filled object more if the internal pressure is low. The Schiotz tonometer accomplishes this goal by applying weights onto a unit with a footplate, using a known force: gravity. The unit is attached to a pointer, which reads a number on a scale. This number is then converted to mmHg on a conversion table corresponding to the amount of weight applied to the unit. The advantage of the Schiotz is that it is relatively inexpensive and easy to use. The disadvantage is that patients must be in the supine position, which is difficult for some veterinary patients. Less commonly used examples of indentation tonometers include the Bailliart tonometer and the Maurice Electrical tonometer.

The third type of tonometry is the combination applanation-indentation tonometry. These use principles from both designs to evaluate IOP, and these are also commonly used tonometers today. The first is the MacKay-Marg tonometer, which is no longer commercially available. The method behind this instrument is that it uses a
microplunger, which is connected to a sensitive transducer. When corneal contact displaces the plunger, this is converted to an electrical signal that is recorded on tracing paper. This tonometer shows very good correlation when compared to the Goldmann, and may be more accurate in patients with corneal edema or fibrosis.39, 43, 44

The Tono-Pen® is a portable version of the MacKay-Marg, but instead of a tracing of the IOP, a single averaged value appears on a LCD screen. The unit contacts the cornea in the same manner as the MacKay-Marg, and several readings are averaged together to give one final value. The Tono-Pen® shows good correlation with manometric values, but some studies show overestimated readings at low IOPs (less than 9 mmHg), and underestimation at high IOPs (greater than 21 mmHg) with little variation in the 11-20mmHg range.45-47 The Tono-Pen® is a very useful tool due to its portability, and therefore, is commonly used in veterinary medicine.

The last combination tonometer is the Pneumatic tonometer. The benefit of this method is that it offers a continuous reading that can be recorded on paper. A 5mm applanation surface is covered with a silicone membrane attached to a piston. The piston is advanced by a gas flow until the applanation surface is flat against the cornea, where it is held for 5-10 seconds. Erroneous manual pressure from the evaluator is eliminated in this tonometer, as the piston is driven by air flow.39 This is an excellent means of recording pulsatile nature of the IOP, and is shown to correlate well with Goldmann and MacKay-Marg tonometers, but may be less accurate in diseased or grafted corneas.48

Dynamic contour tonometry (DCT) is a means of measuring direct IOP and intraocular pulse amplitude (OPA), which indicates choroidal perfusion and ocular blood flow corresponding to pulse as a function of time.39 This unit has a cylindrical tip with a
surface similar to the contour of the cornea, with a centrally located piezo-resistive pressure sensor. The PASCAL is an example of this type of tonometer that is used on a table-mounted slit lamp. This unit uses a constant force of 1 g applied to the central cornea for 5 seconds, and the piezo-electric sensor generates an electrical signal proportional to IOP. The IOP obtained is defined as a diastolic IOP, and it is an indication of the range of pressure that the optic nerve is exposed to over time.\textsuperscript{39} This tonometer has been evaluated in research settings, but clinical use is not yet described.

Rebound tonometry was first introduced in 1931 and then again in 1967, but wasn’t used often in clinical settings.\textsuperscript{39} In 1997 another version of a rebound tonometer was introduced, the Icare\textsuperscript{®} tonometer, followed by its veterinary counterpart, the TonoVet\textsuperscript{®}. This method of tonometry uses a small hammer-type probe that is spring-released from the unit. The probe impacts the cornea and the tonometer analyzes the deceleration of the probe. A globe with low IOP will have a longer impact and slower deceleration; and a globe with high IOP will have a shorter impact and faster deceleration. The Icare\textsuperscript{®}, when experimentally compared to Goldmann tonometer, slightly overestimated IOP by 0.79-1.94mmHg.\textsuperscript{49-52} A similar study was performed in dogs comparing the Icare\textsuperscript{®} to the Tono-pen\textsuperscript{®}, showing an underestimation of IOP by 1.9mmHg with the Icare\textsuperscript{®}.\textsuperscript{53} Rebound tonometry can be especially useful in patients with changes in corneal pathology due to the limited contact area of 1mm when compared to the standard 3mm footplate of the Goldmann tonometer.\textsuperscript{51} There is some debate as to accuracy of rebound tonometry in relation to central corneal thickness (CCT). Some studies show no effect, while others show that IOP was overestimated in patients with higher CCT using a rebound tonometer.\textsuperscript{50, 54, 55}
Alternate means for obtaining IOP (Telemetry)

Continuous IOP monitors have been used experimentally, though clinical use has not been attempted. Methods of continuous detection include direct manometric monitoring via introduction of a cannula into the globe, and indirect through the use of telemetric devices. Telemetry shows the most promise in terms of clinical relevance, though to date most proposed devices still must be inserted directly into the globe, either into the anterior chamber or vitreous humor.\textsuperscript{56-61} This greatly limits use in clinical patients, as the device elicits a foreign body reaction resulting in uveitis and subsequent decrease in intraocular pressure.\textsuperscript{57} Other invasive methods include an encircling band around the globe, or suprachoroidal implantation devices.\textsuperscript{62-64} Though these can show good correlation and may be useful for research situations, they could not be applied clinically.

In the past 4 decades many attempts have been made at developing a non-invasive method of telemetric IOP evaluation, though few have been repeated due to limited success. Cooper et al. published numerous studies using a modified scleral transensor, which fit into the dorsal or ventral conjunctival fornix measuring IOP by applanation of the scleral surface.\textsuperscript{65-67} The greatest benefit to this research was recording trends of IOP based on different stimuli such as anesthetic drugs, body positions (valsalva maneuver), blinking, and breathing.\textsuperscript{67} These data were not compared to any standard tonometer, limiting the validity for comparison to clinical patients. Further research was performed by the same group, comparing the unit to the MacKay-Marg tonometer in anesthetized dogs and rabbits. This study showed favorable comparison between the two methods,
though factors such as temperature and scleral rigidity were significant variables in the species evaluated.\textsuperscript{66}

Another non-invasive method of IOP monitoring includes a unit incorporated into a soft contact lens. This method has been described as early as 1974, and has been the topic of recent research. In 1974 Greene and Gilman describe a strain monitor mounted in a hydrogel contact lens, which showed good correlation compared with manometry\textsuperscript{68}. Recent reports by Leonardi et al involve in vitro testing of a contact lens sensor with both wired and wireless data transmission.\textsuperscript{69, 70} This method showed good correlation when compared to manometric readings, and shows promise for the future of non-invasive contact lens tonometry. Another recent study compared a contact lens embedded sensor with three configurations of dynamic contour tonometry (DCT), and showed that in a sitting position, IOP and intraocular pulse amplitude were comparable to a hand-held and slit lamp mounted DCT unit.\textsuperscript{71}

**Applications of Telemetric IOP monitoring**

Many studies have discussed the importance of continuous IOP monitoring.\textsuperscript{29, 72-74} Due to limitations of monitoring devices, IOP readings must be taken during visits to the ophthalmologist, making recording of a continuous reading or an IOP curve very difficult. Because current readings are performed at infrequent intervals, IOP elevation between visits may be missed, with each episode of elevated IOP resulting in cumulative and irreversible damage to the retina and optic nerve. In a 24-hour study of 32 patients with OAG, 69\% of patients had a peak IOP in at least one eye outside of regular business hours, which further justifies the need for a 24 hour pressure monitoring system.\textsuperscript{75} As
described previously, current means of continuous IOP monitoring usually involves invasive means, which can cause intraocular complications. The telemetric scleral sensor (TSS) would reduce these complications as it is sutured to the surface of the sclera and will not interrupt normal intraocular fluid mechanics.

Research in the field of telemetric pressure monitoring devices allows repeated measurements without the requirement of topical anesthesia and corneal contact. In the clinical setting, patients/clients with a telemetric device implanted can carry a monitor and obtain IOP readings at home at scheduled intervals prescribed by the ophthalmologist, or when symptoms of glaucoma are detected. Early detection of IOP elevation will allow the individual to contact the ophthalmologist immediately for medical and/or surgical treatment. This also has a practical application in research facilities. Depending on the design of the telemetric sensor, readings can be obtained from a certain distance away from the animal, eliminating handling of the patient, and minimizing the effect of stress on IOP.56

In addition to outpatient clinical use, telemetry has also been validated for use during ophthalmic surgeries for close monitoring of IOP to prevent significant alterations in IOP. Acute elevations in IOP can alter circulation causing ischemic damage to the retina and optic nerve, whereas hypotonous episodes can cause choroidal hemorrhage or retinal detachment.76, 77 One report showed an increased IOP during glaucoma drainage surgery in experimental rabbits. Suturing of the device caused IOP to elevate to 64.3mmHg, and viscoelastic injection caused IOP to elevate to 77.7mmHg.78 Another report of IOP monitoring during vitrectomy of 10 patients showed IOP fluctuation from 0-120mmHg throughout the surgery, with high pressures the result of instrument
Manipulation of the globe. Monitoring of IOP during cataract surgery shows that periods of fluid inactivity such as initial corneal incision, hydrodissection of the nucleus, and insertion of intraocular lens caused transient periods of hypotony of <2-3 mmHg.

An additional application for telemetric IOP monitoring is the potential use during non-ophthalmic surgical procedures that have been associated with a rise in intraocular pressure. A rare but devastating complication after spinal and cardiovascular surgeries is post-operative vision loss (POVL) with a reported incidence rate varying from 0.01-1%. This condition is characterized by uni- or bilateral loss of vision that ranges from temporarily blurred vision to complete irreversible blindness. Different mechanisms have been proposed to cause the vision loss including central retinal artery occlusion, anterior ischemic optic neuropathy, and posterior ischemic optic neuropathy. At this time there is no definitive conclusion as to why this condition occurs, though numerous studies have proposed that elevation of IOP may occur secondary to the position or the systemic physiologic status of the patient during general anesthesia. Continuous monitoring of IOP in patients under anesthesia may be beneficial for early detection of IOP elevation, which may reduce the patient’s risk of POVL.

Biocompatibility of implant materials

When designing a biomedical implant, the design material should satisfy three criteria. Materials should be inert, non-reactive, and non-toxic to the tissue to which it is applied. Knowledge of material biocompatibility is very important to consider during development of novel surgical implants. It is not enough to understand how the material is tolerated by living cells; it is especially important to address the local reaction of the
tissue at the actual site of implantation. Standard regulation for approval of medical
devices and implants requires in vitro toxicity, in vivo sensitization tests and muscle
implantation.\textsuperscript{85} One study attempted to validate in vitro testing for intraocular materials
to assess the response to polymethyl methacrylate (PMMA) and silicone in terms of
fibrinogen adsorption, fibroblast adhesion and proliferation, and macrophage and
granulocyte adhesion.\textsuperscript{85} Though the in vitro and in vivo results were very similar, these
tests were proposed for early stage screening of ocular biomaterials, and can not fully
assess the body’s true inflammatory response, degree of fibrosis and ability to heal
around an implant.\textsuperscript{85, 86} Ocular biocompatibility studies are common in the literature, and
the three major categories of implants include intraocular lenses, keratoprosthesis, and
glaucoma valve/drain implants.

Two of the most common materials used in ocular implants are PMMA and
silicone. PMMA is most commonly used in orthopedics, dentistry, and ophthalmology.
In orthopedics it is used as filler for bone defects, vertebral stabilization, and fixation for
orthopedic implants. In dentistry, PMMA is used for dentures, crowns, orthodontics, and
maxillofacial prostheses. In ophthalmology, PMMA is most commonly used for
intraocular lenses, rigid contact lenses, and is used in various glaucoma drainage
devices.\textsuperscript{87-91} PMMA is generally considered inert, but there have been reports of
infections and tissue necrosis from thermal reactions associated with the implants. These
reports are mostly in cases of orthopedic and dental use where the polymer is mixed just
prior to implantation.\textsuperscript{87} These complications are not reported with ocular use, as the
implants are pre-fabricated.
Silicone can be prepared as a liquid, gel or pliable solid. Common uses of silicone include mammary augmentation, urinary bladder prosthesis, cardiopulmonary bypass, and joint prosthesis. Though the material appears to be inert, metastatic spread of silica gels or foam has been linked to distant inflammatory and autoimmune responses including granuloma, lymphadenopathy and even lymphoma. Ophthalmic use of silicone includes keratoprosthesis, intraocular lens (IOL), soft contact lens, tubes and external surface of glaucoma drainage devices, silicone oil for vitrectomy patients, adnexal implants such as nasolacrimal stents and scleral encircling band for retinal detachment. In general, silicone has proven to be an inert material for both intraocular and adnexal procedures, though there are many conflicting reports on relative biocompatibility of different IOL materials in reference to levels of capsular fibrosis and inflammatory reactions. Two additional materials that have been used for IOL’s include hydrogels and acrylcs.

Previous studies evaluating telemetric IOP monitoring used an array of implants made of various materials. Contact lens tonometry typically used lenses made of PMMA or silicone, while extraocular sensors described as either encircling bands or transscleral sensors were made of silicone, acrylic or PMMA. These reports all appear to be pilot studies that focus on evaluating the device rather than biocompatibility of the device, though no specific comments were made as to any adverse reactions to the materials.
Materials and Methods

Animals studied:

Ten juvenile New Zealand White female rabbits were obtained from Harlon laboratories (Indianapolis IN). The rabbits ranged from 1-3 years of age, and weighed between 1.94 - 2.25kg. All protocols used in this study were approved by the Institutional Animal Care and Use Committee of The Ohio State University. Prior to start of the study, biomicroscopic and indirect ophthalmoscopic examinations were performed with minimal manual restraint following dilation of the pupils with topical 1.0% tropicamide (Bausch & Lomb, Tampa FL). Intraocular pressure was obtained using a TonoVet® without the use of topical anesthetic. Three readings were obtained in each eye, and values were averaged for statistical analysis. Digital photographs were taken of
all eyes prior to implantation using a 1:1 macro lens and a Nikon D1 camera. Rabbits were housed at the veterinary facility for 10 days prior to surgery to allow acclimation to their new environment. The telemetric scleral sensor (TSS) was surgically implanted in the right eye of all rabbits, with the left eye serving as a control. The rabbits were euthanized at time points of 2, 4, 8, 12 and 16 weeks after initial surgical implantation.

Surgical implantation:

No medications were administered to the rabbits prior to the surgical procedure. Rabbits were placed under general anesthesia by administration of intramuscular 50mg/kg ketamine (Fort Dodge, Ft. Dodge, IA) and 10mg/kg xylazine (Tranquived, St. Joseph, MO). Oxygen was administered via a facemask and isoflurane (Butler, Dublin OH) was used as needed to maintain a surgical plane of anesthesia. Each rabbit was placed in left lateral recumbency, and the right eye was clipped and surgically prepared using dilute betadine solution. Topical 0.5% proparacaine (Akorn, Lake Forest, IL) was applied to the right eye for local anesthesia. A barraquer wire eyelid speculum was used and a stay suture of 6-0 silk was placed at the dorsal limbus. The eye was irrigated using 1:10,000 epinephrine to aid in vasoconstriction for hemostasis. The conjunctiva was incised approximately 4mm posterior to the limbus dorso-temporally using Stevens tenotomy scissors, and the incision was extended parallel to the limbus for a length of 12mm. The episcleral tissue including tenon’s fascia was incised to expose the scleral surface and using tenotomy scissors, a pocket was bluntly dissected posteriorly taking care to avoid the orbital venous sinus. The silicone sensor ring and its polymethylmethacrylate retainer (PMMA) retainer were placed in the subconjunctival
pocket dorsotemporally. The PMMA retainer was positioned over the sensor ring to ensure optimal scleral contact. The PMMA retainer was sutured to the sclera using two interrupted sutures of 8-0 nylon placed to encircle the suture tabs on the retainer. The anterior suture was placed approximately 2mm posterior to the limbus (figure 2.1, 2.2). The conjunctiva was apposed over the unit in a simple continuous pattern using 8-0 Vicryl. Prior to recovery, the unit was tested by measuring IOP both with the TSS reader and TonoVet®. The rabbits were recovered from anesthesia and an Elizabethan collar was placed for 14 days. The first two rabbits did not receive post-operative anti-inflammatory medications; however, at the recommendation of supervising University Laboratory Animal Resources (ULAR) veterinarians, a dose of 0.2mg/kg subcutaneous meloxicam (Boehringer Ingelheim, St. Joseph, MO) was instituted prior to recovery in the final 8 rabbits. All rabbits received neomycin-polymixinB-gramicidin ophthalmic solution (Bausch & Lomb, Rochester, NY) in both eyes every 8 hours for 14 days.

Intraocular pressure monitoring:

Intraocular pressure (IOP) was monitored in each rabbit twice daily for 14 days at approximately 7am and 6pm using both the TSS reader and TonoVet® (Figure 2.3). IOP was measured first using the TSS reader with a wireless sensor, followed by TonoVet® and then again the TSS reader. Three readings were recorded using each technique. Minimal manual restraint was used when handling the rabbit for IOP readings. After 14 days, IOP was monitored twice daily on Monday and Friday in the same manner until the time of sacrifice.
Ophthalmic examinations:

Both eyes of each rabbit received one drop of 1.0% tropicamide for dilation. Each eye was examined with biomicroscopy and indirect ophthalmoscopy twice weekly for 14 days, then once weekly until sacrifice. Minimal manual restraint was used for examination. The results including any abnormal findings were recorded and quantified using the modified Hackett-McDonald grading system (Figure 2.4).

Enucleation:

At two weeks post-implantation, two rabbits were euthanized and globes were enucleated without prior manometric testing. Euthanasia was performed with 100mg/kg intravenous pentobarbital (Butler, Dublin, OH). Then, both eyes were enucleated via a standard transpalpebral approach. The conjunctiva over the implant unit was incised, and the sensor ring and PMMA retainer were carefully dissected from the underlying sclera. Data recorded included the following: exact clock hour location where the center of the implant unit was located; distance between edge of PMMA retainer and limbus; integrity and attachment of both anterior and posterior suture; position of sensor ring in the PMMA retainer; and the degree of scleral/implant unit contact. After the sensor ring and PMMA retainer were dissected from the globe, the superficial sclera was tagged with a suture to demarcate the location of the implant unit for histologic processing. The control eye was tagged with suture in the same location as the test eye. The eyes were then placed in 10% formalin.
Manometric procedure:

At 4, 8, 12 and 16 weeks two rabbits underwent manometric evaluation prior to euthanasia. The rabbits were sedated with intramuscular ketamine (50mg/kg) and xylazine (10mg/kg) and placed in left lateral recumbency. An eyelid speculum was used, and a stay suture of 6-0 silk was placed ventronasally. A 24g Teflon® catheter was inserted into the anterior chamber at the limbus dorsonasally. The stylet was removed and the catheter was connected to a closed system containing sterile LRS solution infused to manually increase the IOP. An additional 24g catheter was placed in the same manner temporally. This catheter was attached to a direct arterial pressure monitor (Datascope PassportXG) to obtain a direct measurement of IOP (Figure 2.5).

A baseline IOP was taken using the TSS reader. The IOP was then increased in 5 mmHg increments from 20-70mmHg using the pressurized LRS system, and the pressure was maintained for a period of 3 minutes at each interval. At the beginning and end of the 3-minute period, direct IOP measurements were taken via the direct pressure monitor as well as with the TSS reader. After all readings were obtained, the rabbits were euthanized via an intracardiac injection of pentobarbital (100mg/kg), enucleated as previously described, and the eyes prepared for histologic evaluation.

Tissue preparation for histologic evaluation:

Enucleated eyes were fixed in 10% buffered formalin for a minimum of 2 weeks. All eyes were cut along the vertical meridian through the center of the site of TSS explantation, which was demarcated by prior suture placement. The control eyes were cut in the same location as the test eye. The two hemispheres from each eye were
embedded in paraffin, and 4 um sections were cut using a rotary microtome from each hemisphere. The sections were stained with hematoxylin and eosin in a routine manner. Three sections from the test eye and two from the control eye were evaluated by light microscopy.

Histologic scoring and definitions:

All slides from both eyes were examined by light microscopy. Histologic specimens were evaluated based on three categories: Grade and thickness of fibrosis present under and around the implant unit; grade of inflammatory response including predominant cell type; and notation of any intraocular or adnexal disease relevant to the study.

Histologically it was not possible to distinguish the location of the PMMA retainer vs. the silicone encased sensor ring, so the term “implant unit” will be used to describe the surface of the entire retainer/sensor unit that contacted the sclera. Three sites around the area of implant-to-sclera contact were graded as follows: Base (directly under the implant unit); Walls (the elevated region immediately adjacent to the base); and Periphery (any fibrosis present at distant locations on the sclera and surrounding adnexa) (Figure 2.6). The thickness of the fibrosis was measured in micrometers at three locations within the base: the center and at the most posterior and anterior aspect of the base. The thickness of the sclera was also measured at one location, directly in the center of the base (Figure 2.7). The degree of inflammation was graded subjectively on a scale of 0-4, where 0 = none; 1 = Minimal; 2 = Mild; 3 = Moderate; 4 = Marked. Criteria for
grading included the relative density of each of the following inflammatory cells: granulocyte, histiocyte, lymphocyte and plasma cell.

The coefficient of variation (CV) was determined for all rabbits for both the TonoVet® in the test and control eye, as well as the TSS readings over the study period. Coefficient of Variation is defined as a quantity designed to give a relative measure of variability around the mean, and was calculated as CV = SD/mean. Coefficient of variation is a measure of variation which indicates the consistency of a series of readings. The lower the CV, the more consistent or less variable the values are. The higher the CV, the less consistent, or more variable the values are.

A student’s t test was performed to compare the thickness of sclera in the test eye vs. the control eye. Additionally, the same test was used to compare the thickness of sclera under the implant vs. the thickness of fibrosis at the same location. Values of p ≤0.05 were considered significant.

Intraocular and adnexal lesions noted were as follows: retinal atrophy, ciliary body hemorrhage or congestion, ciliary body edema, anterior chamber fibrin, hyphema, and extraocular muscle atrophy. Lesions were assessed as present or absent for each eye.
Figure 2.1: An illustration of the TSS implant unit. The unit consists of two separate pieces, a polymethyl methacrylate retainer (A), and a gold antenna ring encased in silicone (B). A pressure sensitive membrane, depicted by the arrow, required close contact to the sclera.
Figure 2.2: Intraoperative photo of surgical implantation of the implant. The implant is positioned in the dorsotemporal quadrant, with the anterior most portion approximately 2mm posterior to the limbus (arrow).
Figure 2.3: Photo demonstrating use and position of the TSS reader (A) and the TonoVet® (B). Minimal restraint is needed for either unit, though eyelid manipulation is not required for the TSS as it is for the TonoVet®.
Figure 2.4: A modified Hackett and McDonald grading scheme was used to record clinical findings. Each animal was graded on a 0-4 scale for the following changes: conjunctival abnormalities including congestion, swelling and discharge; Aqueous flare; Iris abnormalities including pupillary light reflex and involvement of iris stroma; corneal cloudiness including severity and area affected; pannus; fluorescein stain; lens abnormalities.
Figure 2.5: Photograph of an anesthetized rabbit undergoing manometric testing. An eyelid speculum is used to retract the eyelids, and two 24g Teflon® catheters were inserted into the anterior chamber through the limbus.
Figure 2.6: Photomicrograph demonstrating the location of implant-to-sclera contact. The region of implant fixation is indicated by the star. The degree of fibrosis was subjectively graded on a 0-4 scale at three locations around the implant. B=Base, W=wall, D=distant. H&E 4x.
Figure 2.7: Photomicrograph demonstrating the location of implant-to-sclera contact. The region of implant fixation is indicated by the star. The thickness of fibrosis was measured at three locations within the base. The anterior most portion (1), the central region (2), and the posterior most portion (3). The thickness of the sclera under the implant was also measured (arrow). H&E 4x.
CHAPTER 3

CLINICAL AND HISTOLOGIC EVALUATION OF BIOCOMPATIBILITY
OF TELEMETRIC SCLERAL SENSOR: RESULTS

Clinical findings:

According to the Hackett-McDonald grading scheme, a score of 0-4 was assigned to each clinical category based on degree of clinical signs. In no rabbits was a score of 2 exceeded in any category. The most common clinical signs noted were conjunctival swelling, congestion and ocular discharge, which were noted in all 10 rabbits. These findings occurred within one day post-operatively, and resolved in 9 rabbits within 17 days of surgery. These clinical signs were observed in the remaining rabbit throughout the study period, likely a result of the sensor being dislocated and contacting the corneal surface.

Uveitis or keratitis was not clinically observed in any of the rabbits. Additional findings of the anterior segment noted in the rabbits included conjunctival overgrowth in 1/10 rabbits, conjunctival erosion over the PMMA retainer in 5/10, and a clinically apparent sensor dislocation in 1/10 (Figure 3.1). Fundic examination revealed suture placement through sclera, choroid and retina in 4/10 rabbits, and a focal retinal detachment associated with a suture in 6/10 (Figure 3.2).
After the rabbits were euthanatized, the test globe was enucleated, the position of the implant unit was evaluated and the unit was surgically dissected away from the globe. The first two rabbits served as a pilot study and limited data were collected. The experience from the pilot data produced a detailed questionnaire that was used during explantation of the remaining 8 rabbits. Blunt dissection using Westcott and Steven’s Tenotomy scissors was used to free the implant units from the adjacent conjunctiva and sclera. The anterior portion of the implant unit was easily dissected from any surrounding connective tissue, whereas the posterior antenna ring was tightly bound to the surrounding connective tissue in all rabbits. Findings associated with the implant-to-scleral contact were noted in the last 8 rabbits. All implants were positioned in the dorsotemporal quadrant of the globe, between the 8 and 11 o’clock positions. The anterior-most aspect of the implant was located between 2-7mm from the limbus, with a mean of 4.7mm. The presence and subjective tight adherence of the sutures were assessed upon manipulation of the implants. Four out of 8 implants still had both anterior and posterior sutures visibly intact through sclera and around the PMMA retainer. Of these, 1 of 8 anterior sutures appeared tight, and 3 of 8 posterior sutures appeared tight. As noted previously, only one implant was clinically noted to be dislocated and contacting the cornea. However, upon reflection of the conjunctiva, poor to absent implant-to-scleral contact was discovered in a total of 5 globes. Two of 8 implants showed improper apposition between the PMMA retainer and the sensor ring, both of which were implants with poor scleral contact noted at explantation.
Histologic lesions:

None of the control eyes had any histologic lesions. No lesions were noted in the cornea, iris or lens of the implanted eyes. Some degree of fibrosis and inflammatory response was found at the site of implantation in all test eyes with no apparent association with the duration of implantation.

The grade of fibrosis was recorded at three sites within the area of implant-to-sclera contact (Base, Walls and Distant) (Figure 2.6). The grading was based on a 0-4 scale, where 0 = None; 1 = Minimal; 2 = Mild; 3 = Moderate; 4 = Marked. The walls showed the most degree of fibrosis (range 3-4, mean 3.5), followed by base (range 1-4, mean 2.5) and periphery (range 1-4, mean 2.3). The thickness of fibrosis was measured using a micrometer eyepiece at three locations within the base: the center and at the most posterior and anterior aspect of the base (Figure 3.3). These three points were averaged for each globe, which ranged from 29.3-440.0μm (mean 250.4μm).

The thickness of the sclera under the base of the implant-to-sclera contact site in the test eye ranged from 168-488μm (mean 221.3μm)(Figure 3.3). The thickness of the sclera in the same location in the control eye ranged from 240-400μm (mean 313.2μm). The thickness of sclera in the test eye was significantly less than that of the control eye (p = 0.002). The average thickness of the sclera under the implant was not statistically different than the thickness of fibrosis at the same site (p=0.302). The entire thickness of tissue under the implant (fibrosis + sclera) was measured with a range of 309.3-706.7μm (mean 471.7μm). The total thickness of tissue under the implant (fibrosis + sclera) was statistically different than the scleral thickness in the control eye (p=0.002).
The relative density of inflammatory cells present at the site of sclera/implant contact was subjectively graded on a scale of 0-4 for severity. Granulocytes were the most common cell type found, with a score range from 0-3 (mean 1.7). The remaining cells were as follows: lymphocytes range 0-3 (mean 1.3), histiocytes range 0-3 (mean 1.1), plasma cells range 0-3 (0.6) (Figure 3.4, 3.5).

Focal retinal atrophy was noted in 3/10 rabbits. The location of this atrophy was presumed to be at the site of suture penetration, though no suture material was histologically visible at these sites. Extraocular muscle atrophy and fibrosis was noted underneath and immediately adjacent to the implant site in 7/10 rabbits (Figure 3.6). Evidence of acute uveitis including fibrin and erythrocytes in the anterior chamber and ciliary body congestion was detected in 4 of 10. This was likely associated with anterior chamber cannulation for manometric testing. Granulomatous inflammation surrounded residual suture material in 2 globes and focal granulomatous and heterophilic scleritis was observed at the site of implant in one globe.
Figure 3.1: Clinical photographs of post-operative findings in 4 rabbits. Conjunctival hyperemia noted in 10/10 rabbits (A), conjunctival overgrowth in 1/10 rabbits (B), conjunctival erosion over the PMMA retainer in 5/10 rabbits (C), and a clinically apparent sensor dislocation in 1/10 rabbits (D).
Figure 3.2: Clinical photographs of post-operative fundic examination findings. Suture visible through the sclera and retina in 4/10 rabbits (A). Focal retinal detachment depicted by the arrow noted in 6/10 rabbits (B).
Figure 3.3: Photomicrograph of a region of the Base under the implant. The area of implant fixation is noted with a star. The arrow corresponding to (A) refers to the thickness of the fibrosis present between the implant and sclera, the arrow corresponding to (B) shows the thickness of the sclera. H&E 10x.
Figure 3.4: Photomicrograph depicting a focus of inflammatory cells located between the region of implant-to-scleral contact. The inflammatory cells indicated are lymphocytes (L), granulocytes (G), and histiocytes (H). H&E 40x.
Figure 3.5: Photomicrographs demonstrating the grades of inflammation present. Grade 1, Minimal inflammation (A); Grade 2, Mild inflammation (B); Grade 3, Moderate inflammation (C); Grade 4, Severe inflammation around suture material (D). H&E 40x.
Figure 3.6: Photomicrographs illustrating pathology associated with the implant.

Normal retina (A) is shown to illustrate the degree of retinal degeneration of all layers at the site of suture placement through the sclera and retina (B). Normal extraocular muscle (C) in comparison with extraocular muscle atrophy (D) adjacent to the implant. H&E 40x.
CHAPTER 4

INTRAOCULAR PRESSURE DETERMINATION
USING TELEMETRIC SCLERAL SENSOR: RESULTS

In vivo testing:

Five of 10 implants continued transmitting throughout the entire study period. Failure of transmission in the remaining 5 implants occurred at days 0, 12, 17, 49 and 71 post-implantation. Before transmission failed in these implants, values in 2 were close in range to the TonoVet® (Rabbit 277 and 280), values in one were consistently 5-10mmHg lower than the TonoVet® (Rabbit 278), and values in one never showed any correlation with the TonoVet® (Rabbit 279), and one implant never successfully transmitted any data (Rabbit 281). Of the five implants that continued to transmit data through the end of the study, four showed similar values to the TonoVet® with a 1-5mmHg offset (Rabbits 198, 199, 276 and 283), and one initially transmitted with good correlation to the TonoVet® (3-4mmHg offset) but dropped to a 6-11mmHg offset by day 50 (Rabbit 282). When assessing the IOP values obtained from the 5 implants that continued transmitting, the average difference between the TSS and TonoVet® values in the test eye ranged from 0.1-8.7mmHg (mean 3.2mmHg) (Figures 4.1-4.5). The TSS reader unit was difficult to obtain readings during the first few weeks of testing. After the operator became more...
comfortable with the positioning and angle that was required to obtain a reading, the values were easier to obtain. There was no association between instability of the implant and ease of obtaining a reading with the TSS unit.

The coefficient of variation (CV) was determined to measure the overall variability of IOPs in 9/10 rabbits. Rabbit #281 was not included in CV analysis, as no numerical values were ever transmitted from this implant. Interpretation of the CV is implied as the lower the CV, the more consistent or less variable the values are. The higher the CV, the less consistent, or more variable the values are. When comparing the TonoVet® to the TSS values in the test eye, the CV was low (<25) in 8/9 rabbits using the TonoVet®, and 4/9 rabbits using the TSS. This indicates more consistent readings using the TonoVet® in these rabbits than the TSS. Of the rabbits that had a low CV in the TSS, all 4 also had low TonoVet® values as well. When comparing the TonoVet® in the test eye (OD) and the control eye (OS), the TonoVet® had a low CV in 8/9 test eyes, and 9/9 control eyes. The reason for this disparity in Rabbit #276 was not apparent (CV = 41 OD; 19 OS). When assessing the CV of all rabbits combined, the TonoVet® showed low variability (low CV) in both eyes, and the TSS showed high CV (high variability) (Figure 4.6).

**Manometry:**

At the time of manometric testing, 3/8 implants continued to transmit data through this testing period. Only 2 of these transmitted data that compared favorably to manometric readings. Only the implant in Rabbit 276 was not statistically different when compared to manometry values (p=0.12). The data from the other two implants was
statistically different than the manometric values (p<0.05). The IOP measurements were consistently lower than manometric values in all 3 rabbits (Figure 4.7).
Figure 4.1: Graphical representation of IOP recordings from Rabbits 198 and 199. The X axis shows the days post-implantation. The Y axis shows the intraocular pressure (mmHg). The solid blue line indicates TonoVet® readings, the dotted pink line indicates TSS readings.
Figure 4.2: Graphical representation of IOP recordings from Rabbits 276 and 277.

The X axis shows the days post-implantation. The Y axis shows the intraocular pressure (mmHg). The solid blue line indicates TonoVet® readings, the dotted pink line indicates TSS readings.
Figure 4.3: Graphical representation of IOP recordings from Rabbits 278 and 279. The X axis shows the days post-implantation. The Y axis shows the intraocular pressure (mmHg). The solid blue line indicates TonoVet® readings, the dotted pink line indicates TSS readings.
Figure 4.4: Graphical representation of IOP recordings from Rabbits 280 and 281. The X axis shows the days post-implantation. The Y axis shows the intraocular pressure (mmHg). The solid line blue indicates TonoVet® readings, the dotted pink line indicates TSS readings.
Figure 4.5: Graphical representation of IOP recordings from Rabbits 282 and 283. The X axis shows the days post-implantation. The Y axis shows the intraocular pressure (mmHg). The solid blue line indicates TonoVet® readings, the dotted pink line indicates TSS readings.
Figure 4.6: Graphical representation of coefficient of variation. The X axis identifies each rabbit by number and the data for the entire group. The Y axis shows the coefficient of variation.
Figure 4.7: Graphical representation of all implants that transmitted data for manometric testing. The X axis shows time in minutes. The Y axis shows the intraocular pressure (mmHg). IOP values for rabbit 276 (squares, wide dotted line) were not statistically significantly different than manometric values ($p=0.12$). The remaining two rabbits were statistically significantly different than manometric values ($p<0.05$).
The rabbit is the most common animal model for ophthalmic research, as evidenced by the volume of ophthalmic reports in the literature utilizing this species. Only slight anatomical differences from human eyes are noted and include the following: smaller globe size, thinner cornea, larger corneal diameter, prominent anterior globe position, and a merangiotic retinal vascular pattern. Despite these differences, rabbits are common research models for glaucoma, intraocular lens placement, keratoprosthesis, intravitreal drug administration, and solution and material biocompatibility studies. In the present study, the greatest anatomic variable noted was the smaller globe size compared to the intended human patient. There are multiple reports of axial globe length in rabbits based on post-mortem studies, generally showing a range of 14-16mm in adult New Zealand White rabbits, though one report goes as high as 16-19mm with no notation of gender, age or breed of rabbits studied. The axial length range of 14-16mm was obtained from rabbits of similar age and weight to the animals in the present report, though we regretfully did not measure the axial globe length in this study. A mean measurement of 23-24mm and 21.87-25.01mm were reported for the average human axial globe length in two studies, respectively.
report measured enucleated rabbit eyes as well as human eyes, and reported a statistically
significant difference in axial globe length ($p<0.0001$), with rabbits measuring 16.12-
17.08 mm, and humans 24.52-25.40 mm. Overall, the average axial globe length of a
human eye is larger than that of a rabbit, making the size of an implant such as the TSS
an important parameter. In the present study, the two-piece TSS implant unit had an
anterior-posterior total length of 15 mm from the edge of the PMMA retainer to the caudal
most aspect of the sensor ring. In a human eye, the dimension of the TSS unit studied
would be considered large, but in the juvenile rabbit used in this study the size of the
implant unit was excessive. Although, the implant was secured to the globe in all study
rabbits, the orientation of the implant had to be angled to position it closer to the limbus
to reduce the posterior extension (Figure 5.2).

Clinically, the presence of the sensor was well tolerated by the rabbits. There was
no evidence of self-trauma to the area, though they wore protective Elizabethan collars
for the first 2 post-operative weeks. The minimal degree of conjunctivitis noted was
considered in the normal range for adnexal surgery, and it regressed within $2\frac{1}{2}$ weeks
post-operatively as expected. The aberrant conjunctival overgrowth noted in one rabbit
was not totally unexpected. This is a syndrome that has been reported in dwarf rabbits
with an unknown etiology. It is also seen in rabbits on ocular irritancy studies and as
sporadic finding in pet rabbits. It is possible that the presence of the implant
stimulated conjunctival growth, or it could be an incidental finding. The fact that it was
unilateral in this particular rabbit may support the idea that it was due to irritation, as this
condition is more commonly reported as a bilateral condition in rabbits.
The normal thickness of the rabbit sclera is 500μm at the limbus, and thins to 250μm at the equator.\textsuperscript{96, 97} The human sclera is reported to be similar in size, with a limbal thickness range from 390-670μm, and equatorial thickness 220-560μm.\textsuperscript{105} These two locations are where the anterior and posterior sutures were placed around the PMMA retainer respectively. Post-operative indirect examination of the rabbits revealed 4/10 with a visible pre-retinal equatorial suture, and 6/10 with a focal retinal detachment at the site of the posterior suture. The size of the suture (8/0) required to anchor the large PMMA retainer, the need for a broad-based suture due to the implant footplate design, as well as the location of the posterior suture in the region of thin sclera likely contributed to these complications. The anterior and posterior anchoring footplates on the PMMA retainer were broad-based (3mm) requiring a larger suture and a needle with a large radius of curvature (6.9mm, ½ curvature needle). This design was felt to contribute to the scleral perforation, focal retinal detachment and implant displacement. Multiple (3-4) single point fixation eyelets, as used for glaucoma filtration devices, would have potentially avoided these complications.\textsuperscript{88} Most glaucoma drainage devices are sutured to the sclera using 7-0 to 10-0 suture for fixation.\textsuperscript{91} These drainage devices are typically sutured 8mm posterior to the limbus, which in a human is still anterior to the equator, and in the thicker range of the sclera, though scleral perforation and retinal detachment are reported complications with glaucoma drainage surgeries.\textsuperscript{91, 106, 107} A similar situation occurs with attachment of scleral buckles used for surgical treatment of retinal detachment. One report claims a 2.5% risk of scleral puncture, causing potential complications such as retinal tears, detachment and endophthalmitis.\textsuperscript{108}
The average thickness of the sclera located under the implant in the test eye was measured in histologic sections and ranged from 160 to 488μm (mean 221.3μm). Measurements were obtained in the center of the implant-to-scleral contact. The implant was located approximately 3-6mm posterior to the limbus in all rabbits, so the actual point of scleral measurement was within 3mm of each other when comparing all rabbits. When compared to the thickness of the sclera in the same location of the control eye (240-400μm, mean 313.2μm), the scleral thickness in the TSS test eye was significantly different. This was likely due to tissue remodeling and atrophy of scleral collagen in response to pressure, presumably due to the relative size and force of the implant on the tissue causing physical compression of the sclera. Additionally, it is possible that the presence of inflammatory cells and the release of proteases and growth factors may have led to apoptosis of scleral tissue leading to thinning.109

Similar problems have been noted with encircling scleral buckle procedures used for treatment of retinal detachment in humans. Scleral buckles are made of various materials, and are sutured directly to the sclera while encircling the globe. One study evaluated the effect of silicone and hydrogel scleral buckles on scleral thickness and fibrous capsular response in rabbits.110, 111 The results were very similar to the present study, indicating a compression of the sclera under the implant resulting in a mean scleral thickness of 221μm, compared to scleral thickness under the TSS implant of 221.3μm. The normal sclera in the present study measured similar to that in the buckle study: 313.2μm in the TSS study compared to 320μm in the buckle study. Though the normal scleral measurement was taken at different locations in the two studies, they were both significantly thicker than the sclera under the implant.111 This was explained to be a
result of scleral erosion from the buckle implant. Another study was performed by the same author looking at similar parameters human eyes with a scleral buckle that were later enucleated for various reasons. Though the numbers can not be compared to our study due to normal species differences in scleral thickness, it also showed a significant thinning of sclera under the buckle when compared to normal adjacent sclera. Caution must be taken when comparing results of scleral buckle studies to the TSS implantation, as the encircling band is placed under tension to purposely compress the globe, so the forces would be greater with the scleral buckle technique than the TSS implantation, but the results indicate that the sclera may respond in a similar manner under the TSS implant.

The inflammatory response was graded subjectively on a 0-4 scale of severity which was modeled after previous studies. Two reports from Ayyala et al. addressed biocompatibility of four subconjunctival implants in rabbits, and these reports show the same inflammatory cell populations present, with similar order of frequency to the present study. The inflammatory grading was noted to be in the mild-to-moderate range for all materials studied at the 3 week point in these reports, as well the present study. The mean inflammatory grade was highest for polypropylene (mean 3.7 in 2000 report, and 2.2 in 1999 report), followed by PMMA (mean 2.8), Vivathane (mean 2.4), and silicone (mean 2.0 in 2000 report, and 1.6 in 1999 report) in the Ayyala et al. studies. Our mean inflammatory grade was found to be 1.2 for all rabbits throughout the entire study period. While no rabbits were sacrificed at exactly 3 weeks, comparison of this study's 2 week (0.7) and 4 week (1.4) means still falls below the range that was reported for both silicone and PMMA. These are subjective grading schemes, so
direct comparison should be interpreted with caution, but the overall inflammatory response to the implanted devices seems relatively low in this study.

A granulocytic response was used to describe the presence of heterophils, though special stains to rule out eosinophils were not performed. This type of inflammation was present in 9/10 rabbits, and at all time points in the present study. The reason for a granulocytic inflammatory response is not known, but it could be speculated that this was due to a break in the conjunctival surface over the area of implant, allowing granulocytes from the tear film to enter the site of implantation. The rabbit who did not have any granulocytes present did not have a break in the conjunctiva, but rather was the one rabbit noted to have conjunctival overgrowth, also known as aberrant conjunctival overgrowth, pseudopterygium, and conjunctival stricture. The limits of this theory lie in the fact that of the 9 rabbits with a granulocytic response, only 4 of them were noted to have a gross break in their conjunctival lining. Alternatively, the inflammatory cells may gain access to the region hematogenously as a result of irritation from the implant.

Another unexpected finding was the relative lack of histiocytic response, especially in the rabbits sacrificed at 12 and 16 weeks. Histocytic inflammation includes giant cells, which are often present with any chronic implant.\textsuperscript{84,91,114} The early onset of histiocytic inflammation could be the result of a foreign-body response, presence of suture material, or simply the physical irritant response of having the implant in place. Macrophage and giant cells are present with foreign material as an attempt to phagocytose the material, and therefore should have been present throughout the study period. Alternatively, if the fibrotic material present sufficiently encapsulated the foreign material, then it would be possible that the stimulus for histiocytic inflammation may be
absent in chronic stages, though more often histiocytes tend to remain on the surface of
the foreign material.\textsuperscript{84, 114} The lymphocytic and plasma-cell response is a non-specific
inflammatory response, and is to be expected with any surgical inflammation or antigenic
stimulation.\textsuperscript{84}

When comparing the present study to other biocompatibility reports, the
inflammatory response was consistent at all time points. The basic timeline of healing
around an implant should start with an initial inflammatory cellular response to the
foreign material as well as surgical trauma, starting with neutrophils and then later
macrophages. With time, this cellular response should cease, followed by a fibrotic
response, usually with subsequent formation of a capsule around the implant.\textsuperscript{84, 89, 91} A
biocompatibility study comparing a silicone Baerveldt shunt to a new ePTFE compound
shunt showed an almost acellular fibrotic response to both shunts at 8 weeks post-
implantation.\textsuperscript{89} In the present study, there were inflammatory cells present at all time
points. This supports the theory that the inflammatory response was not solely a result of
the materials used, but likely mechanical factors of the implant as well. An evaluation of
biocompatibility of implants in ocular tissues found that the surface of the globe is in
constant motion with the muscular control, so even an appropriately designed implant
would have some degree of micromovement which may contribute to increased fibrosis
during wound healing.\textsuperscript{91}

The previously mentioned biocompatibility studies also assessed the thickness of
fibrosis under shunts implanted in rabbit eyes, with no mention of the thickness of sclera
under the implant. The Boswell et al. study was comparable to the present study,
showing a mean thickness of approximately 100\(\mu\)m with the ePTFE shunt, and 420\(\mu\)m
with the silicone Baerveldt shunt, while Jacob et al. found the thickness of capsule beneath an unmodified silicone Baerveldt shunt to be 170\(\mu\)m.\(^8\),\(^9\) In the present study, the mean thickness of fibrosis under the implant was 250.4\(\mu\)m which falls between these reported values. The TSS implant consisted of two parts, a PMMA retainer and a silicone covered antenna ring. Because the unit had to be removed prior to processing, it was difficult to determine what region of fibrosis corresponded to which material. Other reports compared silicone to similar polymers, and showed silicone to be the least reactive when compared to polypropylene, vivithane and polymethyl methacrylate in terms of cellular and fibrotic responses.\(^1\)\(^1\),\(^2\)\(^1\),\(^3\) In reference to the scleral buckling procedure, a silicone buckle elicited a fibrotic capsule under the implant with a mean thickness of 113\(\mu\)m.\(^1\)\(^1\) This was less than the thickness of fibrosis noted in the present study, which may indicate that the degree of fibrosis was not only a result of material, but also due to movement and shear forces from the implant.

Implant-associated fibrosis can be detrimental in glaucoma drainage devices as it impairs the ability of the shunt to drain aqueous or of the bleb to resorb aqueous.\(^8\),\(^9\) It was hypothesized that the degree of fibrosis around a TSS implant could impair the implant’s ability to sense changes in IOP. Rabbits with low coefficient of variation (CV), or less variability in the TSS had fibrosis under the implant ranging from 176 to 400\(\mu\)m (mean 268.7\(\mu\)m), while rabbits with a high CV, or greater variability, had fibrosis ranging from 29.3 to 440.0\(\mu\)m (mean 232.9\(\mu\)m). It stands to reason that rabbits with thicker fibrosis between the implant and sclera would have a high CV (greater variability in readings), but this was not shown in this study. Rabbits with a high CV actually had a lower mean thickness of fibrosis than those with a low CV.
Greater central corneal thickness as well as corneal fibrosis can cause artificially elevated IOP obtained using applanation tonometry, while decreased central corneal thickness can cause lower intraocular pressure readings. The mechanism of IOP determination with the TSS implant is that the pressure sensitive membrane on the scleral side of the antenna ring will absorb the applied force of sclera, which is proportional to IOP. This type of IOP monitor has never been reported, so the effect of thickness and fibrosis under the implant is unknown, though it was hypothesized that the effect of fibrosis would alter the ability of the TSS to accurately report IOP. Rabbits with low CV using the TSS had a total tissue thickness under the implant (sclera + fibrosis) ranging from 448-706.7μm (mean 560.7), while rabbits with a high CV had total tissue thickness ranging from 309.3-664.0μm (mean 450.6μm). This also does not seem to correlate with the principles of applanation, and again further support the theory of implant instability and size leading to variable IOP recordings.

The principles of applanation involve flattening of the cornea using a known force over a fixed area. The TSS implant does not follow these principles instead it senses the forces the globe applies to a pressure sensitive membrane. Standard theories known to affect applanation such as degree of fibrosis and thickness may not affect a pressure sensor of this type as there is no requirement to compress or flatten the underlying tissue. The fibrotic capsule located between the implant and sclera in this study is likely similar in density to the natural fibrous sclera, which may not affect the ability to record pressures using this device. The fibrotic capsule likely increased in thickness over time for each rabbit, and there was no difference noted in the IOP readings between the TSS and TonoVet®, other than those cases where the TSS ceased transmission, which further
supports the idea that fibrosis did not significantly affect the ability of the TSS implant to
detect pressure.

An additional theory is that the implant design was inadequate to function for an
extended period of time. Rabbits with a low CV had an implant duration of an average of
8 weeks, whereas rabbits with a high CV had implant duration of 9.6 weeks. These
timepoints are similar, which doesn’t support this theory.

The most plausible theory is that of implant instability leading to failure. Of the
rabbits with low CV (less variability) using the TSS, 1/4 was noted to have implant
instability at the time of explantation, whereas of the rabbits with a high CV using the
TSS, 4/5 (80%) were noted to have implant instability, suggesting that instability of the
TSS contributed to variable pressure readings.

In 9/10 rabbits, the CV was higher for the TSS unit than the TonoVet®. The
exception was rabbit #198 where the CV for TonoVet® in the test eye was 17.6 and TSS
was 14.49. There is no definitive explanation for this unexpected change, as there was no
keratitis which might lead to altered TonoVet® readings, and no other physical or
mechanical differences associated with the sensor in this rabbit. This rabbit had low CV
values for all methods, so the slight difference between the two units may just be
individual variation in how measurements were taken.

Three rabbits were noted to have focal retinal atrophy under the site of
implantation involving all layers of the retina. This area of atrophy was located in the
posterior aspect of the implant-scleral contact. No suture material was noted
histologically at the site of retinal atrophy, though the location was presumed to be in the
area of fixation of the posterior nylon suture. The choroid in this region was also
atrophyed, and the retinal pigmented epithelium immediately adjacent to the area of retinal atrophy was hypertrophied as well (Figure 5.2). As mentioned previously, 4/10 rabbits had a pre-retinal suture visible and 6/10 rabbits had a focal retinal detachment noted on clinical fundic examination. The focal retinal atrophy was likely a result of detachment of the retina in this focal zone, which is supported by the focal hypertrophy of retinal pigmented epithelium in this region. The additional rabbits with clinical retinal lesions likely had similar histologic retinal atrophy which was not included in the section that was evaluated.

Seven of ten rabbits demonstrated extraocular muscle atrophy and fibrosis below and immediately adjacent to the implant site. This was most likely a result of the size of the implant and associated muscle entrapment or mechanical damage. Though care was taken to avoid the extraocular muscles while suturing the retainer, the 12mm width of the entire implant unit prevented complete avoidance of muscle entrapment. No strabismus was noted in any rabbit, which is an uncommon but reported complication associated with glaucoma drainage devices secondary to capsule formation and extraocular muscle entrapment.88 Additionally, the inflammation at the site of the implant may have contributed to release of inflammatory mediators which may have affected muscles adjacent to the area of implantation, but not necessarily under the implant itself.109

Histologically, four rabbits had evidence of acute anterior uveitis including fibrin and erythrocytes in the anterior chamber as well as ciliary body congestion. During the manometric procedure, Teflon® catheters were inserted into the anterior chamber, which likely stimulated anterior uveitis. Rabbits are models for uveitis research and blood-aqueous-barrier breakdown can be induced by paracentesis. The effects of paracentesis
are similar to anterior chamber cannulation performed for manometry. Anterior uveitis in rabbits is known to result in fibrin production, supporting the idea that the mild acute signs of uveitis found histopathologically were likely a result of the manometric procedure rather than the implant. Further, none of the rabbits showed clinical evidence of uveitis such as miosis, aqueous flare or photophobia prior to the manometric procedure.

Intraocular pressure monitoring obtained with the TSS compared favorably with the TonoVet®. The major limitation was that 50% of the implants ceased transmission of data during the study period. Of the 5 implants that ceased transmission, all were noted to be dislocated at the time of explantation. The average difference between the TSS and TonoVet® values in the test eye ranged from 0.1-8.7mmHg (mean 3.2mmHg). Though there was some offset between the two instruments, this does not limit the value of the unit. It is expected to have some degree of offset when comparing to different tonometers, but important factors to consider are whether a consistent trend is followed and whether values can be extrapolated. For example, a study comparing the standard Goldmann tonometer with the rebound Icare® tonometer in humans showed a difference of approximately 3mmHg, except in the higher IOP range (23-60mmHg) when the range was twice as large.52 Similarly, in studies comparing Goldmann to the applanation tonometer, Tono-Pen® showed a similar offset of 2-3mmHg in normal pressure ranges, but lacked good correspondence in the 31-45mmHg intervals.47 More specifically, another evaluation of Goldmann vs. Tono-Pen® showed that the Tono-Pen® underestimated high IOPs (≥30mmHg) and overestimated low IOPs (≤9mmHg).45 In canine studies the portable tonometers have been compared, showing that the values
obtained from the rebound tonometer (Icare®) were significantly lower than the Tono-Pen®
though they showed good correlation to one another, and an overall mean IOP difference of 1.905mmHg.\textsuperscript{53}

At the time of manometric testing, only 3/8 implants were able to transmit data. Of these, the values of only one implant was statistically similar to the manometric values (p=0.12). The other two implants that transmitted were statistically different (p<0.05), with one showing a curve which trended toward the manometric values, and one showing values that never went above 15.8mmHg despite the intraocular pressure rising to 70mmHg. The implant that was statistically similar to manometric values showed promise at reporting similar values even at extremely elevated pressures. This is important when considering clinical application of any type of tonometric device, as underestimation of high IOP values has been described in commercially available devices including the Tono-Pen®, Mackay-Marg.\textsuperscript{115, 116}

The dorsotemporal position of the TSS implant unit proved to be an easily accessible location for surgical implantation. This region shows the most scleral exposure, and gentle ventronasal rotation of the globe provided an adequate surgical window for implantation. The lateral position of the implant was useful for transmission of data to the reader unit, as it did not require the reader unit to cross into the visual axis, limiting stress and handling of the rabbits. The reader unit was relatively large in size and would benefit from being smaller, as well as having a longer range. The unit needed to be held approximately 3-5 cm away from the eye, which still required some restraint of the rabbit. The globe of the rabbit is well seated into the orbit, and is protected circumferentially by bone, as they do have a complete orbital rim.\textsuperscript{96} This also may have
limited transmission of data if the signal had to be transmitted through orbital bone. Redesign of the antenna or the reader unit to extend the distance of transmission would be beneficial to limit any stress response on IOP.

The overall size of the TSS implant unit was considered to be the major limitation of this study. As previously mentioned, the dislocation of the implant from the sclera in 5/10 rabbits was likely due to mechanical size of the implant placing a large amount of force on the fine-gauge suture material. The dislocation was a result of the suture pulling through the sclera rather than breakage of the suture. At the time of explantation, it was noted that all knots were intact and no suture was broken. Size of the retainer footplates also contributed to the inappropriate suture placement through the sclera and retina noted in 6/10 rabbits. No suture appeared to be broken; rather they tore through the scleral collagen, which would require a great force to break down such a fibrous structure. All of these factors likely induced a chronic inflammatory response that persisted much longer than is reported in similar surgeries such as glaucoma drainage device. Another complication that likely resulted from the size of the implant was the erosion of the PMMA retainer through the conjunctiva in 5/10 rabbits, which could have led to infection around the implant site.

This study demonstrates a novel idea for telemetric, continuous IOP monitoring in patients who have, or are at risk for glaucoma. Telemetric IOP monitoring will likely play an important part in the future of glaucoma therapy, and research in this area is becoming more common. A transscleral method provides the patient with a discreet and relatively non-invasive means of continuous IOP monitoring and should be further investigated. The design of the current implant needs to be reconsidered.
Recommendations include decreasing the overall diameter and thickness by at least 75% of the original implant. In addition, redesign of the PMMA retainer should include multiple areas with a smaller base for suture fixation. The current model requires the suture to be tied around a 3mm surface, which made secure suture placement very difficult. Designing the retainer with 3-4 eyelet holes similar to the holes present in a glaucoma drainage device would be ideal. The last recommendation would be to design the implant unit into a single piece design. Currently it is the surgeon’s responsibility to carefully align the silicone ring into the PMMA retainer at the time of fixation. This was technically difficult to accomplish, and 2/8 sensor rings had been noted to have slipped out of alignment by the time of explant. The single piece design would eliminate this variable. With the recommended changes and further evaluation of the device, the non-invasive telemetric scleral sensor could prove to be very beneficial in both research and clinical practice and could provide important information about the behavior and treatment of glaucoma across the species.
Figure 5.1: Illustration of the TSS implant unit in two different orientations. Initial desired position of the implant unit oriented 90° from limbus (A). Due to the length of the implant unit, the entire unit was rotated approximately 45° to position it closer to the limbus and reduce the posterior extension of the unit (B).
Figure 5.2: Photomicrograph illustrating focal retinal atrophy with associated choroidal atrophy and adjacent retinal pigmented epithelial hypertrophy. H&E 20x.


