Aqueous Humor Dynamics

Aqueous humor (AH) is the fluid that fills the anterior chamber of the eye. This fluid is produced by the epithelial cells of the ciliary body, flows through the pupil, and circulates in the anterior chamber. Aqueous humor is optically clear, but contains various compounds such as carbohydrates, amino acids, glucose, lactate, small proteins, ions, and urea, which provide the nutritional support to the avascular lens and cornea. In addition, waste products from these tissues are drained along with this fluid. Drainage of AH occurs through the iridocorneal angle (ICA), which is a complex structure formed by the junction of the peripheral iris and cornea. The pectinate ligament spans this small angle and is composed of small fiber-like strands through which the aqueous humor drains. The balance between AH formation and drainage determines the intraocular pressure (IOP).

Pathophysiology of Glaucoma

The definition of glaucoma has evolved over the years as the understanding of the condition in veterinary medicine has improved. Traditionally, glaucoma was defined simply as an elevation in IOP above the normal range. However, acute and temporary elevations in IOP (e.g. excessive restraint, jugular vein compression, or post-cataract surgery) do not lead to the same physiologic changes and thus are more properly termed “ocular hypertension.” Currently, the definition of glaucoma encompasses a group of conditions that lead to damage to the retinal ganglion cells, progressive optic nerve fiber death, and vision loss. Glaucoma is thus most appropriately considered a neuro-degenerative condition, which has multiple underlying etiologies. In veterinary medicine, glaucoma is always due to an elevation in IOP secondary to a decreased drainage of AH. Increased production of AH does not occur.

Classification and Etiology of Glaucoma

Classification of glaucoma is important to allow for proper diagnostic and therapeutic recommendations. Glaucoma should be classified based upon the underlying cause for the decreased AH drainage, specifically as congenital, primary, or secondary. In addition, the duration of the glaucoma should be determined and classified as acute or chronic.

Congenital Glaucoma

Congenital glaucoma is rare in both dogs and cats, and is caused by developmental abnormalities in the AH outflow pathways. Affected animals generally present young (3 – 6 months) with an acute onset of buphthalmia and corneal edema. The disease may be unilateral or bilateral, and
may be associated with other ocular anomalies such as cataract, persistent pupillary membranes, and retinal dysplasia.

**Primary Glaucoma**
Primary glaucoma is the most common type of glaucoma in the dog, and is due to an inherited malformation in the ICA that, over time, leads to a reduced capacity for AH drainage without any other underlying cause. The pectinate ligament that spans the ICA is misshapen – often a broader sheet of tissue with aberrant flow holes that replace the normal thin fibers and large openings. In addition, the width of the ICA is often significantly narrowed in primary glaucoma. Primary glaucoma is strongly breed-related, and the most commonly affected breeds include the Beagle, Basset Hound, Boston terrier, Cocker Spaniel, and Shar Pei. Mixed breed dogs are also affected with primary glaucoma. Although primary glaucoma is less commonly seen in cats, breeds at risk include Siamese, Burmese, Persian, and domestic shorthairs.

**Secondary Glaucoma**
Secondary glaucoma results from a physical obstruction to AH drainage, most often occurring at the ICA. Alternatively the AH flow can also be obstructed prior to the ICA (i.e. if the pupil becomes blocked by posterior synechia (iris bombe), a luxated or swollen lens, or vitreous). Reduced AH drainage through the ICA is seen commonly with inflammatory conditions leading to excessive protein, white blood cell, and red blood cell exudation into the anterior chamber. Neoplastic cells may also accumulate in the ICA and lead to a reduction in AH drainage. Secondary glaucoma is the most common form of glaucoma in cats.

**Duration of Glaucoma**
Acute glaucoma is defined as an elevation in IOP of < 24-48 hours duration. Intermittent spikes in IOP often occur prior to the development of a sustained elevation, but are not usually detected clinically. Once the IOP elevates persistently, clinical signs of glaucoma develop. If patients are treated during this phase, vision may be salvageable. Unfortunately, the subclinical spikes in IOP are quite detrimental, thus only 50% of patients regain sight even when treated in the acute phase.

Chronic glaucoma develops after the IOP elevation is sustained for days or longer. Medical therapy may be effective at reducing the IOP, however vision cannot be regained. With time, many of the ocular structures undergo both physiologic and morphologic changes in response to the persistently high IOP. Many dogs and almost all cats present with chronic glaucoma, as the acute phase is either misdiagnosed or overlooked completely by the owners.

**Clinical Signs of Glaucoma**
Most dogs will exhibit blepharospasm, epiphora, head-shyness, and an elevated third eyelid as glaucoma is a painful condition. Clinical signs in cats are exceedingly subtle and they will very rarely show overt signs of pain with glaucoma. Owners may complain of lethargy, decreased appetite, or sleeping more but may not directly contribute these signs to the ocular discomfort. Ophthalmic findings consistent with glaucoma include episcleral congestion and conjunctival hyperemia. Corneal edema will be present in dogs with IOPs > 40 mmHg, however the corneal
endothelium of the cat is more resistant to the elevated pressure, thus edema may be mild even with IOPs > 60 mmHg. Finally, a dilated, non-responsive pupil and negative menace response develop with glaucoma. Asymmetrical pupil sizes, or anisocoria, is the most common presenting complaint in cats with glaucoma. The presence of a consensual PLR (light shone into the affected eye with constriction of the contralateral pupil) and dazzle reflex are positive prognostic indicators for the visual potential of the affected eye.

The ophthalmic exam will also allow determination as to the etiology of the glaucoma. Primary glaucoma will lack significant inflammation such as aqueous flare or hemorrhage. The retina should appear fairly normal aside from cupping of the optic nerve. Secondary glaucoma will have evidence of chronic inflammation, such as corneal vascularization, aqueous flare, hyphema, hypopyon, iris color change, synechia formation, cataracts, vitreal debris or hemorrhage, and possibly chorioretinal lesions. It is important to determine the position of the lens, as anterior lens luxations will lead to acute glaucoma requiring emergency surgery.

Unfortunately, subtle or transient increases in IOP lack overt clinical signs in the acute phases, and many patients will present with chronic glaucoma. There are key findings on ocular exam that indicate a chronically elevated IOP. Buphthalmia, or enlargement of the globe, develops over weeks to months of uncontrolled glaucoma. Almost all buphthalmic eyes are permanently blind. Lens subluxations or luxations may develop with chronic glaucoma as the lens zonules are not elastic and break as the globe enlarges. Finally, the fundic exam will help to determine the duration of glaucoma and the visual prognosis of the eye. The optic nerve may appear slightly hyperemic and sunken during acute elevations in IOP, however with time the optic nerve begins to degenerate and appears pale and very cupped. Vascular attenuation and diffuse tapetal hyperreflectivity are additional indications of retinal degeneration and chronic glaucoma.

**Diagnosis of Glaucoma**

Measurement of IOP is indicated in any patient with an inflamed eye. A dilated pupil and decreased vision are even further suggestions that glaucoma may be present. Determination of IOP is called tonometry, and is truly just an estimation using various measuring devices. It is crucial that tonometry be performed with proper restraint and correct use of equipment to obtain accurate measurements. Multiple studies have demonstrated large variations in IOP with jugular pressure, excessive eyelid manipulation, and even changes in body position.

There are three available methods to measure IOPs: indentation, applanation, and rebound tonometry. Indentation tonometers, such as the Schiotz®, indent the corneal surface and the IOP is obtained following conversion of the tonometer reading using the accompanying human conversion table. This is a very inexpensive method, however is challenging to perform due to patient positioning requirements and the tonometer requires careful cleaning and storage to maintain accuracy. Applanation tonometers, such as the Tono-Pen VET® measure IOP by flattening the corneal surface and are commonly used in general practice. This method requires minimal patient positioning or restraint and provides a digital display of the IOP and percent error. The TonoVet® is a rebound tonometer that measures IOP by projecting a small probe at the corneal surface and analyzing the characteristics of its rebound. Rebound tonometers have been shown to be as accurate and easy to use as applanation tonometers. These tonometers are
slightly more expensive, but do not require topical anesthetic prior to use. Although minimal, variation in IOP measurements obtained using different instruments does occur, so it is recommended to maintain consistency when monitoring IOP over time.

**Treatment of Glaucoma**

Glaucoma can be treated both medically and surgically; the decision is often based upon the duration of the disease. Additionally, the underlying cause, availability of equipment, and financial constraints of the owner will contribute to the final decision. The goals of medical glaucoma therapy are to normalize IOP to preserve or regain vision, or to simply alleviate pain if vision has been permanently lost. Medical therapy of glaucoma is broadly categorized into medications that reduce the formation of AH, and those that improve outflow of AH. Unfortunately, in most cases medical therapy eventually becomes ineffective at controlling the IOP, and surgery is necessary to control discomfort. If secondary glaucoma is diagnosed, treating with anti-glaucoma medications alone is unlikely to be effective long term. It is important to address the specific underlying cause that ultimately led to the decreased AH outflow.

**Osmotic Diuretics**

Hyperosmotic agents reduce the formation of aqueous humor by reducing plasma flow through the ciliary body, and also cause dehydration of the vitreous. The main indication for the use of hyperosmotic agents in glaucoma is in cases of acute glaucoma with a positive dazzle reflex and/or consensual PLR, where vision is salvageable. For maximum efficacy, water should be withheld for 4 hours after hyperosmotic treatment.

Mannitol is an osmotic diuretic that has been shown to significantly reduce IOP within 15 minutes of administration and can remain effective for 6 - 10 hours. Mannitol can be used safely in most dogs, but should be used with caution in dogs with cardiac or renal disease, or in dehydrated patients. The use in cats is not well documented, likely due to the rarity of acute glaucoma. The author usually begins with 1 gram/kg IV over 30 – 45 minutes.

Oral glycerin causes a significant decrease in IOP within 30 minutes of administration, and can persist for 10 hours. Glycerin should not be used in dogs with diabetes mellitus. The most common side effect of oral administration is gastrointestinal upset. The reported effective dose is 1-2 gram/kg PO, however the author rarely uses this medication.

**Carbonic Anhydrase Inhibitors (CAIs)**

Both systemic and topical CAIs are available. Inhibition of carbonic anhydrase decreases aqueous humor production by reducing synthesis of bicarbonate in the ciliary body.

Acetazolamide is an oral CAI that is no longer recommended due to the high incidence of systemic side effects. Methazolamide is an alternative oral CAI, however still has potential to cause unwanted systemic effects, including gastrointestinal upset, metabolic acidosis, and hypokalemia. The author uses this medication for treatment of glaucoma in dogs that are unable to be treated topically.
Topical CAIs have the advantage of providing adequate ciliary body concentrations of the drug but reduce the risk of systemic adverse effects. Brinzolamide (Azopt®) and Dorzolamide (Trusopt®) are commercially available and have both been shown to reduce IOP effectively in dogs and cats. Dorzolamide is available in a generic form, which makes it more cost effective. The degree of IOP reduction observed with topical CAI is comparable to that of the oral CAI, and no additional decline in IOP is obtained from the combination of the two. The most common adverse effect of topical dorzolamide is transient blepharospasm after instillation, and this is less commonly seen with brinzolamide. Topical CAI are most often used every 8-12 hours.

A solution of 2% dorzolamide and 0.5% timolol (Cosopt®) is available in generic form. This combination therapy is as efficacious in reducing IOP as concurrent use of each drug, but the commercially available combination improves client compliance as it only requires twice daily administration.

**Beta-Blockers**

Beta-blockers reduce the formation of AH via their effects on beta receptors present in the ciliary body. Undesirable cardiac and respiratory effects can be seen with topical beta-blockers, including bradycardia, and bronchoconstriction. Thus, these medications should be avoided in patients with cardiovascular disease and asthma.

Betaxolol is a selective β₁-antagonist and has been shown to prolong the onset of glaucoma in the fellow eye when used twice daily. Timolol is a non-selective β-antagonist and is also often used as glaucoma prophylaxis. The degree of IOP reduction with beta-blockers is mild, thus these medications are often combined with other anti-glaucoma therapy.

**Prostaglandin Analogs**

Prostaglandin analogs are the newest modality of topical glaucoma therapy used in dogs. These medications are ineffective in cats due to their lack of appropriate receptor types in their ciliary body epithelium. Prostaglandin analogs are thought to lower IOP primarily by increasing AH outflow via their action on iris and ciliary body musculature. They induce a profound miosis and may physically open the ICA and improve flow. Prostaglandin analogs should be avoided in cases of glaucoma secondary to anterior lens luxation or uveitis.

Latanoprost (Xalatan®) is a selective prostaglandin-F₂α receptor agonist that results in a dramatic decrease in IOP within 20 minutes. Often used to treat acute glaucoma, this is the most commonly utilized prostaglandin analog and is available in generic form. Travoprost and bimatoprost are newer prostaglandin analogs that have also been shown to be effective in the dog. Prostaglandin analogs are administered every 8-24 hours.

**Surgery for Glaucoma**

Multiple surgical options are available to address glaucoma when medical therapy can no longer control the IOP. As with medical therapy, the surgical procedures can be classified into procedures that reduce aqueous humor production or improve aqueous humor outflow. The chosen procedure will depend upon the patient’s visual status and the desired cosmetic outcome. If vision has been permanently lost, surgical procedures can alleviate pain associated with end-stage glaucoma and eliminate the need for topical medications.
Cyclodestruction, or destruction of the ciliary body, decreases the production of aqueous humor and can be performed using cryotherapy, transscleral lasers, or endoscopic techniques. These surgeries are performed by veterinary ophthalmologists most often on visual eyes in which IOP control is not ideal with the use of medications alone.

Chronic end-stage glaucoma may be painful and buphthalmic globes are predisposed to exposure keratitis, ulceration, and infection. Surgical options for chronic glaucomatous globes include enucleation, evisceration with intrascleral prosthesis, and chemical ablation.

Enucleation is relatively inexpensive and has few complications. The main disadvantage of enucleation is the postoperative appearance of the patient, however the benefits include the potential for histopathologic examination of the globe, and immediate pain control. The postoperative recovery is simple and there is no long-term monitoring necessary. This is the recommended option for cats with end-stage glaucoma.

Evisceration and intraocular placement of a prosthetic, silicone ball is performed to achieve the best cosmetic outcome. Proper case selection is imperative for a good outcome, and globes with chronic inflammation, suspected intraocular neoplasia, or corneal disease are poor candidates. The post-operative recovery requires both oral and topical medications, and long-term follow up is necessary. Post-operative complications include corneal ulcers, implant rejection, and corneal scarring. Owners must be made aware that the remaining ocular tissues (eyelids, conjunctiva, cornea, third eyelid) are still susceptible to disease and can require treatment. This procedure should not be performed in cats due to the potential for the presence of underlying malignant neoplasia as well as a high rate of surgical rejection of the implant.

Chemical ablation, or pharmacologic destruction of the ciliary body, is accomplished by injecting gentamicin into the vitreous cavity. A steroid (dexamethasone or triamcinolone) is often injected concurrently into the vitreous, or subconjunctivally at the conclusion of the procedure. This technique does not require general anesthesia, and is the least expensive of the salvage procedures. Most dogs develop cataracts, however the cosmetic outcome is usually acceptable. Complications include inadequate control of IOP, hyphema, uveitis, retinal detachment, and phthisis bulbi. This procedure is contraindicated in cats due to the risk of development of a traumatic intraocular sarcoma.

**SUMMARY**

Glaucoma is diagnosed by measuring an elevated intraocular pressure in conjunction with appropriate clinical signs. Every glaucoma case should be categorized by the etiology (primary or secondary) and duration (acute or chronic). The diagnostics, treatment, and prognosis will vary greatly depending upon these classifications.

Canine glaucoma is common in clinical practice and both primary and secondary glaucoma will present as red, painful eyes. Primary canine glaucoma is strongly breed related and the contralateral eye should be treated and monitored. The underlying cause of secondary glaucoma should be identified and addressed. Multiple medications are effective for the treatment of
glaucoma in dogs, and emergency IOP reduction is crucial for restoration of vision in cases of acute glaucoma. Various surgical options are available for visual eyes to improve IOP control and prolong vision. Surgery for blind eyes is indicated when medications are no longer effective at controlling IOP. Enucleation, intrascleral prosthesis, and chemical ablation are options for most dogs, although careful case selection is necessary for prosthetic implantation.

Feline glaucoma is almost always secondary, and usually presents in the chronic state. Dorzolamide is the best topical anti-glaucoma medication for cats, as latanoprost is ineffective, and timolol may exacerbate underlying cardiac or respiratory conditions. Enucleation is the best surgical choice for cats with uncontrollable glaucoma.

REFERENCES