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Recovery of canine retina and optic nerve function after acute elevation of intraocular pressure: implications for canine glaucoma treatment

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Abstract

Purpose To characterize the timing and extent of functional recovery in healthy canine eyes exposed to acute elevation of intraocular pressure (IOP).

Methods Acute elevation of IOP was induced in 14 healthy Beagles by elevating IOP above the levels of systolic blood pressure for 60 min (average elevation was between 100 and 160 mmHg). Menace, dazzle and pupillary light reflexes (PLR) were tested at 1, 7, 14 and 28 days post elevation. Optical coherence tomography was used to evaluate retinal thickness preoperatively and at 15 and 30 days post elevation.

Results One day post elevation all animals were blind in the operated eye (no positive menace), 5/14 had positive PLR and 10/14 had positive dazzle response. Seven days post elevation 4/14 animals had positive menace response and all animals (14/14) had positive dazzle and PLR responses. Fourteen and 28 days post elevation all animals had positive menace, PLR and dazzle responses. Optical coherence tomography analysis revealed significant thinning of the inferior retina (pre elevation: 156.3 ± 4.8 μm; 15 days post elevation: 125 ± 10.4 μm; 30 days post elevation 123 ± 11.9 μm; $P < 0.01$, ANOVA). The superior retina, however, did not show any detectable decrease in thickness compared to control eyes (pre elevation: 193.8 ± 2.6 μm; 15 days post elevation: 176.9 ± 8.5 μm; 30 days post elevation 176.9 ± 7 μm; $P = 0.057$, ANOVA).

Conclusions Detailed functional and morphologic analysis revealed precise information about retinal damage after acute elevation of IOP. Canine retina has the capacity to recover at least some visual function even at 14 days after acute elevation of the IOP. More aggressive medical and surgical treatment of canine glaucomatous patients may be indicated despite complete loss of visual function, PLR and dazzle responses in early days after development of an acute glaucomatous attack.

Key Words: dog, glaucoma, function, structure, recovery, ischemia

INTRODUCTION

Glaucoma is one of the most frequent blinding diseases in dogs. Numerous etiologies have been established as a cause of glaucoma. However, the most frequently used classifications of canine glaucoma are based on characterization of abnormalities in the aqueous humor outflow pathways.[1–8] Primary glaucoma is a disease characterized by abnormal structure of the aqueous humor outflow pathways, is most likely a result of a hereditary genetic abnormality,[8–11] and is frequently characterized by the presence of narrow or closed iridocorneal angles or an abnormally narrow or closed ciliary cleft.[9,12–16] In some dog breeds gonioscopic examination does

not reveal narrowing or closure of the iridocorneal angle. However, abnormalities in the pectinate ligament structure or posterior aqueous humor outflow structures, such as trabecular meshwork endothelial cells and collector channels, have been proposed as possible causes for increased aqueous humor outflow resistance.[3,17–24] Secondary glaucoma can be a result of chronic intraocular inflammation (primary or secondary to intraocular surgery), neoplasia, pigment dispersion, lens instability, trauma, retinal detachment and/or intraocular hemorrhage.[2,4,25–31]

Regardless of the cause of glaucoma, elevated intraocular pressure (IOP) is considered the major factor causing retinal neuronal damage. Elevated IOP may cause abnormalities in

retinal and optic nerve oxygenation and, in combination with direct mechanical effects, may result in retinal degenerative changes.[32–34] Glaucomatous conditions characterized by degenerative retinal ganglion cell death in the absence of elevated IOP have not been recognized in canine patients. In veterinary patients reduction of IOP is the major therapeutic strategy for the treatment of glaucoma, while prophylactic treatment with different antiglaucoma medications significantly delays the onset of symptoms of disease in fellow normotensive eyes in glaucomatous dogs that have not developed elevated intraocular pressure.[35–43] While glaucoma in human patients is usually not associated with clinical signs of ocular pain and discomfort, glaucoma in veterinary patients is usually recognized when aggressive clinical signs of the disease are present. These are usually the result of extremely high IOP and are accompanied by excessive ocular discomfort. While numerous studies in human patients have described methodologies for evaluation of functional outcomes in glaucomatous patients, similar prognostic data are sparsely reported in the veterinary literature.[44,45] Considering the frequently poor prognosis and the associated long-term management, along with medical and surgical treatment costs, needed to preserve vision of canine glaucomatous patients, there is a great need for descriptions of reliable prognostic factors to determine visual outcome in canine glaucomatous patients. The main purpose of this study was to establish objective parameters that can help determine the potential for visual recovery in normal canine eyes exposed to acute and short-term elevation of IOP by using menace, dazzle (photopic blink reflex) and pupil light reflex (PLR) response.

MATERIALS AND METHODS

All animal studies were conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Visual Research and the Iowa State University Committee on Animal Care.

Fourteen healthy dogs (Beagles) of 6 months of age were used in this study. An ocular examination (slit-lamp biomicroscopy, IOP measurements, indirect ophthalmoscopy) was performed on all animals to rule out any possible presence of ocular disease before inclusion in the study.

Functional testing

Pupil light reflex and dazzle response were evaluated by use of a custom-made fiber-optic light source with a maximal output light intensity of 2000 kcd/m^2 (BioMed Vision Technologies, Ames, IA, USA) pre IOP elevation and at 1, 3, 7, 14 and 28 days post elevation. Animals were dark adapted for 1 min before testing responses. Because of the possible effect of ischemia on the iris sphincter muscle of the operated eye, only indirect pupil light responses were evaluated (light stimulus was delivered to the operated eye, while the pupil response was observed from the nonoperated, control eye). Dazzle responses were evaluated by observing positive blink reflex of the operated eye when light stimulus was applied for 5 s.

Menace response was tested by eliciting palpebral responses in the control and operated eye, then eliciting the menace response in the control (nonoperated eye), and finally by eliciting a response from the operated eye by using a hand motion toward the eye from different directions (temporal, frontal and nasal).

Acute elevation of the intraocular pressure in dogs

Dogs were anesthetized with halothane 2.5% and a mixture of nitrous oxide and oxygen (30 : 70 ratio) and body temperature was maintained using a heating pad. The pupils were dilated with topical 10% phenylephrine hydrochloride (Ak-dilate™, Akorn Inc., Buffalo Grove, IL, USA) and 1% tropicamide (Tropicamide, Falcon Pharmaceuticals, Forth Worth, TX, USA). Prior to anterior chamber cannulation the eye was surgically prepped and the 0.5% propracaine hydrochloride (Falcon Pharmaceuticals, Forth Worth, TX, USA) was instilled. The anterior chamber was cannulated with a 25-gauge needle connected to a reservoir containing 0.9% NaCl. The IOP in experimental eyes was controlled by adjusting the height of the reservoir to maintain a level of systolic blood pressure for 60 min. The systolic blood pressure was evaluated with an ultrasonic Doppler flow detector (Model 811-L, Parks Medical Electronics Inc., Las Vegas, NV, USA) every 5 min. The average elevation of intraocular pressure was between 100 and 160 mmHg. After 60 min, the needle was removed from the anterior chamber and topical antibiotic ointment (Vetropolycin, Pharmaderm Inc., Melville, NY, USA) was applied on the cornea. Postoperative treatment included one dose of hydromorphone HCl (0.1 mg/kg, Dilaudid, Abbott Laboratories, Lake Forest, IL, USA) subcutaneously and application of topical antibiotic ointment to the operated eye twice daily for 2 days.

Optical coherence tomography

Optical coherence tomography analysis was performed using an optical coherence tomography scanner (OCT-1) unit (Carl Zeiss Meditec Inc., Dublin, CA, USA) in eight dogs.

Dogs were anesthetized with halothane 2.5% and a mixture of nitrous oxide and oxygen (30 : 70 ratio), and body temperature was maintained using a heating pad. Neuromuscular paralysis was achieved using intravenous atracurium besylate (0.2 mg/kg BW, Bedford Laboratories, Bedford, OH, USA) and mechanical positive pressure ventilation was established to provide respiratory support and maintain oxygen saturation above 95%. The pupils were dilated with topical 10% phenylephrine hydrochloride and 1% tropicamide. Corneas were kept moist by using eye wash solution every 30–60 s to avoid corneal dessication, which can significantly affect quality of OCT scans. Linear scans were performed in the dorsolateral retinal region (area centralis, tapetal retina) and inferiolateral region (nontapetal retina) to obtain retinal thickness data preoperatively, and at 15 and 30 days post elevation.

Statistical analysis

Statistical analysis was performed by using ANOVA test with the GraphPad (GraphPad, San Diego, CA, USA) software. A P-value of < 0.05 was considered significant.

RESULTS

Functional analysis

Analysis of the photopic blink (dazzle) response revealed recovery in 10 dogs 1 day post elevation, while all dogs displayed a positive dazzle response at 7, 14 and 28 days post elevation (Fig. 1). Analysis of PLR activity showed recovery of responses in five dogs 1 day post elevation, while all dogs had positive responses (of variable intensities) at 7, 14 and 28 days post elevation (Fig. 2). Analysis of the menace response showed the slowest recovery dynamics compared to dazzle and PLR responses. Menace response was absent in all animals 1 day post elevation, recovered in four animals at 7 days post elevation and was present in all animals at 14 and 28 days post elevation (Fig. 3).
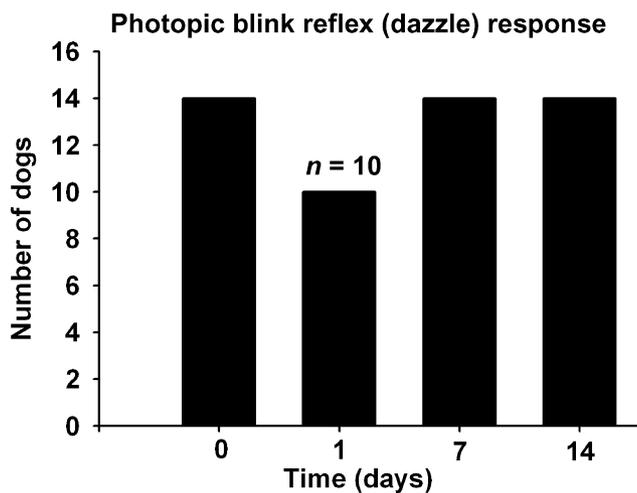
Optical coherence tomography

Optical coherence tomography analysis showed a small but significant thinning of the nontapetal retina at 15 and 30 days post elevation compared to preoperative values (pre elevation: $156.3 \pm 4.8\,\mu m$; 15 days post elevation: $125 \pm 10.4\,\mu m$; 30 days post elevation: $123 \pm 11.9\,\mu m$; $P = 0.0024$, ANOVA, Fig. 4). While total retinal thickness data for the tapetal retina showed a trend of retinal thinning, statistical analysis revealed no significant difference at 15 and 30 days post elevation compared to the preoperative values (pre elevation: $193.8 \pm 2.6\,\mu m$; 15 days post elevation: $176.9 \pm 8.5\,\mu m$; 30 days post elevation: $176.9 \pm 7\,\mu m$; $P = 0.057$, ANOVA, Fig. 4). Individual dog data for different time points are shown in Table 1.

Figure 1. Recovery dynamics of dazzle response. Seven days after acute ischemic insult all animals recovered dazzle response.

Figure 3. Recovery dynamics of visual function. Fourteen days after acute ischemic insult all animals had positive menace response. While all animals recovered dazzle and PLR responses at 7 days after acute elevation of IOP, only four animals had detectable recovery of some visual function.
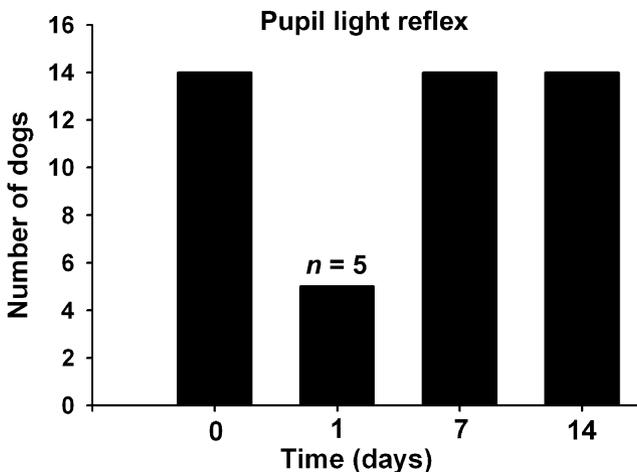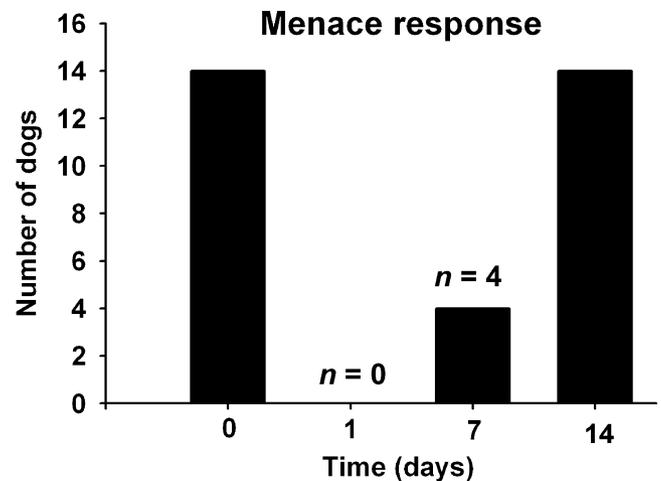

Figure 2. Recovery dynamics of the PLR response. Seven days after acute ischemic insult all animals recovered PLR response, despite only five animals having positive response 1 day post elevation.
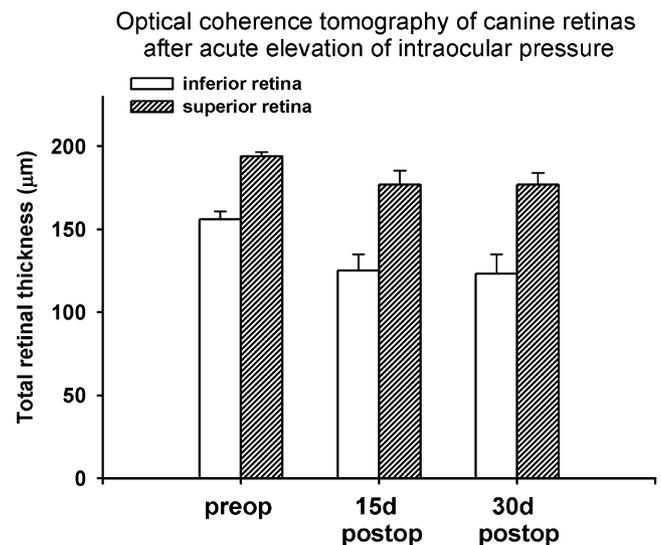

Figure 4. Optical coherence tomography analysis showed significant thinning of the inferior retina after acute elevation of IOP.

Table 1 Optical coherence tomography data (thickness is expressed in μm)

Dog number	Preop nontapetal	Preop tapetal	15 days nontapetal	15 days tapetal	30 days nontapetal	30 days tapetal
1	165	180	140	200	150	190
2	165	190	150	200	130	190
3	175	200	150	200	160	200
4	150	200	125	165	120	160
5	155	200	155	190	165	200
6	130	190	100	170	80	160
7	160	190	100	150	90	160
8	150	200	80	140	90	155

Tapetal retinal scans were performed through the area centralis (dorsotemporal region of the optic nerve), while the nontapetal retinal scans were performed through the nontapetal region (ventrotemporal region of the optic nerve).

DISCUSSION

Canine glaucoma is a blinding disease in which aggressive medical and/or surgical therapy may restore vision. As long-term preservation of vision is directly related to the control of intraocular pressure, aggressive medical and surgical strategies usually result in better visual outcomes, if treatment is initiated soon after clinical symptoms of blindness have developed. Glaucomatous canine patients are frequently presented as emergencies with severely impaired or completely absent visual function in the affected eye. While currently available medical and surgical strategies can decrease acutely elevated IOP, the major concern for owners and veterinary ophthalmologists remains the prospect of visual recovery after ocular hypertensive episodes. Obviously, a poor prognosis for visual recovery will guide the decision toward more conservative treatment where the ultimate goal is alleviation of ocular discomfort rather than preservation of visual function. Traditionally, absence of dazzle and PLR responses in canine patients, once IOP has decreased to normal levels, are considered poor prognostic factors for visual recovery. This frequently guides ophthalmologists and owners to pursue eye salvaging/pain-alleviating procedures. This is particularly so in cases where long-term medical IOP control is poor without introduction of surgical procedures (diode laser treatment and/or shunt placement).[42,46,47]

Dazzle and pupil light reflex responses are nonvisual responses due to subcortical localization of their centers, while menace response is mediated via activation of the visual cortex and represents a crude estimate of visual function. Dazzle, PLR and menace responses are mediated by photosensitive pigments in outer segments of photoreceptors (opsins) and specific populations of intrinsically photosensitive RGCs (melanopsin, cryptochromes).[48–50] This study demonstrates that the healthy canine retina has a remarkable physiologic capacity to recover at least some retinal function after being exposed to severe elevation of IOP. We have demonstrated that recovery of dazzle responses was most robust, followed by recovery of PLR. However, recovery of some visual function (observed by positive menace response) even at 14 days after acute elevation of the IOP was relatively unexpected. While experimental acute elevation of IOP is not the ideal model for studying canine patients with spontaneously occurring glaucoma, complete absence of vision, PLR and dazzle responses, and predominant structural deficits in the nontapetal (inferior retina) region are frequently observed features in canine glaucoma. Previous studies suggest that severe, acute elevation of intraocular pressure causes retinal damage by mechanical and ischemic components. Therefore, a direct comparison of our results with spontaneously occurring canine glaucoma, where elevation of IOP is chronic and never so severe, is not strictly possible.[51] However, we hypothesize that results of this study can be extrapolated to some extent to canine glaucomatous patients. It is our clinical experience that glaucomatous dogs with complete absence of menace, dazzle and PLR responses can recover some visual function days or weeks after occurrence of the glaucomatous attack. This controlled study has confirmed our clinical observations. More aggressive medical and surgical therapy for canine glaucomatous patients in the early days after IOP elevation is therefore warranted despite complete functional absence of traditionally observed parameters such as menace, PLR and dazzle responses.

Other objective diagnostic modalities with a prognostic value in canine glaucoma

The need to quantify structural damage to the optic nerve has led to the development of imaging devices for measuring the number and distribution of retinal ganglion cell (RGC) axons. The imaging techniques presently available for measuring the number of retinal cells are optical coherence tomography (OCT), retinal thickness analysis (RTA), and scanning laser polarimetry (Gdx); the latter measures retinal birefringence (retinal depolarization of light).[52–55] OCT provides the most direct measurement of the thickness of the inner superficial retinal layer where the RGC axons are located, and has been used extensively in the diagnosis of early glaucoma.[52,54,56] Furthermore, OCT has been used extensively to obtain detailed topographic '*in vivo* histology' of retina in different ocular diseases.[57–60] In this study OCT was used to provide the primary retinal structural information in canine eyes after acute elevation of IOP. We previously
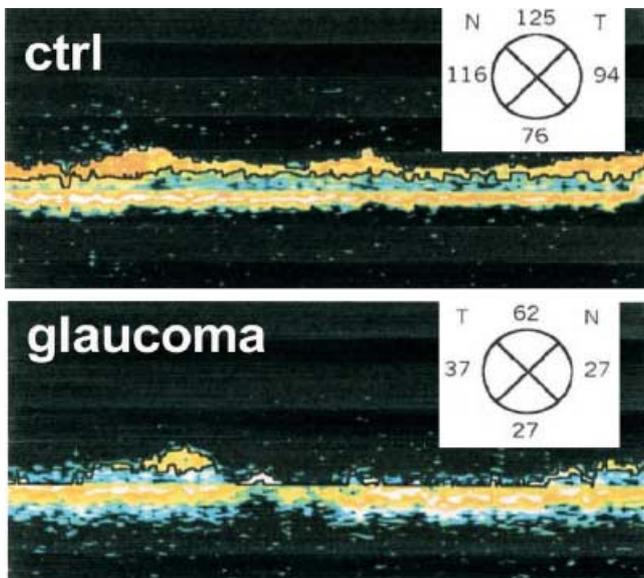
Figure 5. Optical coherence tomography (OCT) analysis of the glaucomatous eye. The scan is from the right eye of a 6-year-old Shiba Inu. This eye was medically treated for primary glaucoma for 6 months using latanoprost (Xalatan, Pharmacia and Upjohn, Kalamazoo, MI, USA) and brinzolomide hydrochloride 1% (Azopt, Alcon Laboratories Inc., Forth Worth, TX, USA). The left eye was enucleated 1 year prior to this treatment. One day prior to OCT examination, this patient presented with acute elevation of IOP (76 mmHg), which was reduced with intravenous mannitol infusions and anterior chamber centesis. One day after presentation, menace, dazzle and PLR responses were absent and OCT was performed to evaluate the status of the nerve fiber layer (NFL). Significant NFL loss was detected in all quadrants; however, the superior quadrant still displayed 50% of the NFL thickness preserved. Following the OCT session, diode laser cyclophotocoagulation combined with the shunt placement was performed. Vision recovered 10 days after surgery. This patient is visual in bright light conditions and poorly visual in dim light conditions 8 months after surgery.

used morphometric analysis of retinal tissue sections and demonstrated significant asymmetry between superior and inferior retina (superior retina is approximately 10–15% thicker than the inferior retina) in healthy canine eyes. The same physiologic difference has been confirmed *in vivo* by using OCT (Fig. 4). In this study we detected significant thinning of the inferior retina after pressure-related insult, which corresponds to the histologic appearance of canine glaucomatous eyes. While OCT can be used to monitor progression of retinal damage in glaucoma or in experimental models of retina and optic damage, structural imaging can also be used to obtain better prognostic information about the status of the optic nerve prior to making any decision whether or not to pursue more aggressive therapeutic options for treatment of glaucoma (Fig. 5).

CONCLUSIONS

We have demonstrated that the canine retina has excellent potential for visual function recovery even at 14 days after exposure to a dramatic elevation of intraocular pressure. Furthermore, we have shown that the absence of dazzle and PLR responses in the first 7 days after a hypertensive insult does not necessarily rule out functional visual recovery at later time-points. While this study was performed in healthy dog eyes, we can draw a possible conclusion that aggressive medical and surgical treatment for visual recovery should be pursued in glaucomatous patients for at least 14 days prior to deciding to convert to salvaging procedures.

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