Comparison of ultrasound biomicroscopy and standard ocular ultrasonography for detection of canine uveal cysts

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OBJECTIVE
To compare ultrasound biomicroscopy (UBM) with standard ocular ultrasonography for detection of canine uveal cysts and to determine the sensitivity, specificity, and interobserver agreement for detection of uveal cysts with UBM.

SAMPLE
202 enucleated eyes from 101 dogs.

PROCEDURES
2 examiners examined 202 eyes by means of UBM (50 MHz) to identify uveal cysts. A board-certified radiologist then examined 98 of the 202 eyes by means of standard ocular ultrasonography (7- to 12-MHz linear transducer). Subsequently, 1 examiner dissected all 202 eyes under magnification from an operating microscope to definitively identify uveal cysts. Each examiner was masked to other examiners' findings. Sensitivity, specificity, and interobserver agreement were calculated for detection of cysts by UBM.

RESULTS
Cysts were detected by use of UBM in 55 of 202 (27%) eyes by one examiner and 29 of 202 (14%) eyes by the other. No cysts were detected in the 98 eyes examined with standard ocular ultrasonography. Dissection results revealed that cysts were present in 64 of 202 (32%) eyes, including 29 of 98 (30%) eyes examined by standard ocular ultrasonography. Mean sensitivity of UBM for cyst detection was 47%; mean specificity was 92%. Uveal cysts not identified with UBM were often small (mean diameter, 490 μm). Interobserver agreement was high ($\kappa = 0.81$).

CONCLUSIONS AND CLINICAL RELEVANCE
UBM was more effective than standard ocular ultrasonography for detection of uveal cysts in enucleated eyes. Small-diameter cysts were difficult to visualize even with UBM. (*Am J Vet Res* 2015;76:540–546)

Uveal cysts in dogs were previously considered to be a benign, incidental finding.[1] In 1998, uveal cysts were reported to cause glaucoma in Great Danes.[2] In each affected eye, cysts could be visualized filling the posterior chamber and anteriorly displacing the iris, resulting in a shallow anterior chamber and difficulty visualizing the iridocorneal angle.[2] At approximately the same time, Deehr and Dubielzig[3] described an association between the presence of uveal cysts and the development of glaucoma in Golden Retrievers. Uveal cysts in Golden Retrievers were found to originate from the ciliary body epithelium and were typically located within the iridociliary sulcus on histologic examination.[4] Uveal cysts have become a hallmark histologic finding in the condition now described as Golden Retriever pigmentary uveitis.[4,5] Clinically, the cysts typically appear round, are pigmented, and transilluminate; may be single or multiple; and are located within the anterior chamber, at the pupillary margin,

or within the posterior chamber.[6] In Golden Retrievers, cysts at the pupillary margin or in the posterior chamber are most often located nasally.[6] Clinical identification of these uveal cysts has been difficult, with detection rates as low as 1 of 15 to 3 of 13 in eyes with cysts confirmed histologically.[3,5]

The development of UBM, which uses a high-frequency (50-MHz) transducer for the imaging of eyes, provides a noninvasive technique that enables 360° visualization of the anterior segment, including the cornea, iridocorneal angle, iris, posterior chamber, iridociliary sulcus, and ciliary body.[7] Ultrasound biomicroscopy has a resolution 5 to 10 times that of a 10-MHz ultrasound probe.[7] With UBM, resolution to 200 μm is possible, although penetration is limited to 4 to 5 mm. Therefore, the posterior segment cannot be visualized with this method.[8] Physician ophthalmologists have successfully used UBM to detect uveal cysts within the iridociliary sulcus, typically in the inferior or temporal quadrants.[8] Through the use of UBM, an association has been identified between the presence of uveal cysts and development of angle closure glaucoma in humans.[9,10] Cysts within the posterior cham-

ABBREVIATIONS
CI	Confidence interval
UBM	Ultrasound biomicroscopy

ber have been shown to mechanically displace the iris anteriorly, thereby compromising the filtration angle.[10]

In the veterinary literature, UBM has been described as an effective tool for evaluation of corneal disease, anterior uveal neoplasia, and iridocorneal angle morphology.[11-13] Examinations via UBM have been performed successfully in dogs and cats with manual restraint and application of a topical anesthetic.[11,13] In 1 report,[11] bilobed cysts within the posterior segment causing anterior iridal displacement were identified with this method. In a recent clinical report[14] describing glaucoma associated with uveal cysts in 3 American Bulldogs, UBM allowed detection of multiple cysts within the iridociliary sulcus. It appears that UBM could be a useful tool to further elucidate the role of uveal cysts in glaucoma and in Golden Retriever pigmentary uveitis.

Most veterinarians do not currently have access to UBM technology; instead, most use a 7.5- to 10-MHz standard ultrasound probe to perform examination of intraocular structures.[15] Whether the difference in resolution between UBM and standard ocular ultrasonography results in one imaging modality being superior to the other for detection of uveal cysts is not known. To our knowledge, the accuracy and reproducibility of UBM or standard ocular ultrasonography for detection of uveal cysts in any species have not yet been determined. The objectives of the study reported here were to compare the use of UBM versus standard ocular ultrasonography to detect uveal cysts; to determine the sensitivity and specificity of each method for this purpose, compared with dissection; and to determine interobserver agreement for detection of these cysts with UBM. We hypothesized that UBM would have a higher sensitivity and specificity for detection of uveal cysts, compared with standard ocular ultrasonography.

Materials and Methods

Animals

Two hundred two eyes were collected from 101 dogs immediately following euthanasia for reasons unrelated to this study. Because limited historical information was available, the age of each dog was estimated on the basis of dentition and lenticular changes. Dogs were classified in 3 groups according to estimated age: < 4 years, 4 to 8 years, and > 8 years. This study conformed to the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Visual Research.

Preliminary study

Because the effect of tissue autolysis on uveal cysts was not known, a pilot study was performed. An eye with a solitary uveal cyst identified by UBM was immersed in distilled water and stored at 4°C for 48 hours. The eye was serially examined with UBM at 0, 12, 24, 36, and 48 hours after enucleation. The cyst could be visualized at 0, 12, 24, and 36 hours, but not 48 hours, after enucleation. Additionally, marked tissue

autolysis was noted on dissection of the eye 48 hours after enucleation, and this made examination of the uveal tract impossible. On the basis of results from the pilot study, the maximum time allotted from sample collection to ultrasonographic examination and dissection of each eye was 24 hours.

Sample collection

All eyes were enucleated immediately following euthanasia of the dog. Eyes were excluded if obvious pathological changes were noted on examination with a Finoff transilluminator. The presence of visible uveal cysts did not result in exclusion from the study. The pupil size was midrange in all eyes. A suture was
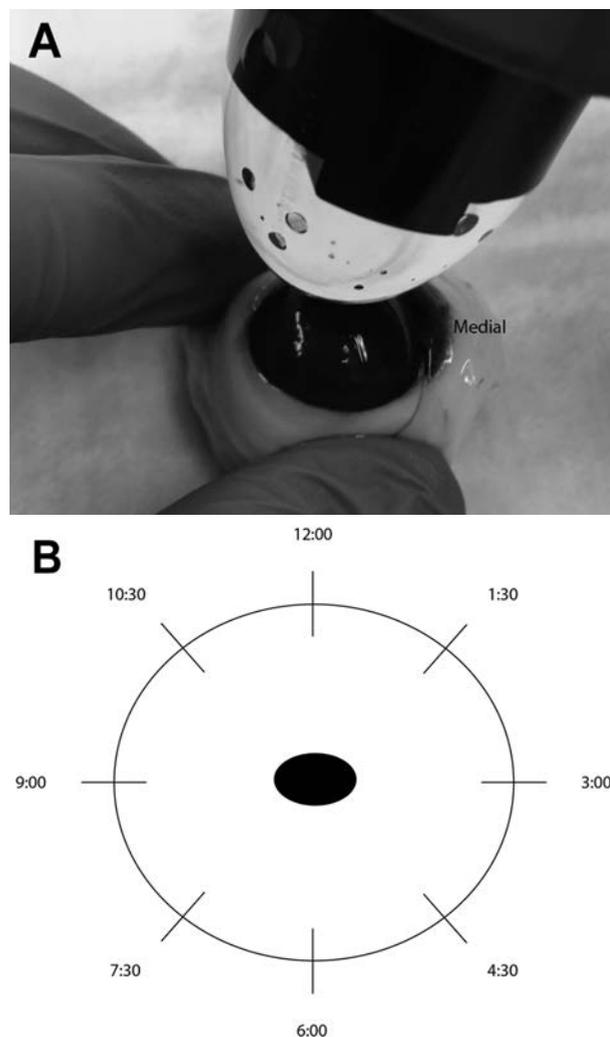

Figure 1—Images depicting a UBM technique used to assess the presence or absence of uveal cysts in 202 enucleated eyes from 101 dogs. A—Photograph showing the tip of the transducer gently applied to the corneal surface of an eye placed on a flat surface. B—Schematic illustration showing the circumference of the ciliary body divided into 8 sites according to a clockface analogy. The medial bulbar conjunctiva of each eye was identified by a suture placed at the time of enucleation; the right eye was scanned with the suture placed at the 3:00 position and the left eye was scanned with the suture placed at the 9:00 position to replicate the position of the globes within the skull.

placed to identify the medial bulbar conjunctiva. Each eye was individually stored in distilled water at 4°C. Ultrasonographic examinations and dissection were performed ≤ 24 hours after enucleation.

Ultrasonography

Two examiners (LNT and WMT) each performed UBM and were masked to each other's findings. Examiner 1 (LNT) had < 1 year of experience; examiner 2 (WMT) had 4 years of experience. A clear, single-use, disposable cover[a] filled with distilled water was placed over the end of the 50-MHz mechanical linear scan transducer.[b] Each eye was placed on a flat surface with the corneal surface of the eye turned upward. The covered transducer was gently applied perpendicular to the globe at 8 sites along the limbus (Figure 1).[8] The transducer was held with the scan plane perpendicular to the limbus. The expected UBM appearance of a uveal cyst was a thin-walled, round structure lacking internal reflectivity (Figure 2).[8] If a suspected cyst was noted, the probe's scan plane was rotated 90° to ensure the structure persisted in both planes. The cyst's anatomic location (iris, ciliary body, or iridociliary sulcus), site according to a clockface analogy, quadrant (dorsal, temporal, ventral, or nasal), and number of cysts per eye were recorded. The medial bulbar conjunctiva was placed as the globe would be positioned in vivo. For the clockface analogy, the medial aspect was at the 3:00 position for the right eye and the 9:00 position for the left eye.

Standard ocular ultrasonography was performed by a board-certified veterinary radiologist (HGH) by means of B-mode ultrasonography with a 7- to 12-MHz linear transducer.[c] The examiner was masked to the results of the UBM findings. A direct transcorneal method was used. The eyes were examined in vertical and horizontal planes. Power, gain, time gain compensation, and depth were adjusted to image the anterior segment of the eye. When detected, the number of cysts per eye, anatomic location, quadrant, and site were recorded in the manner described for UBM.

Dissection

After ultrasonographic examination, the eyes were dissected by 1 examiner (WMT). A 360° corneolimbal incision was made, and the cornea was removed. Examination of the anterior uveal tract was performed under magnification from an operating microscope.[d] A Bishop-Harmon forceps was used to elevate the iris, allowing visualization of the posterior iridal epithelium, iridociliary sulcus, and ciliary body (Figure 3). The globe was rotated as needed to al-

low visualization of the entire iris and ciliary body. Digital calipers[e] were used to determine the size of each cyst. The calipers had a resolution of 10 μm and accuracy of 20 μm. The number of cysts and their anatomic location, site by clockface analogy, quadrant, and diameter in micrometers were recorded. Cysts ≤ 750 μm in diameter were categorized as small, and those > 750 μm in diameter were categorized as large.

Statistical analysis

All statistical analysis was performed with the aid of a commercial statistical software package.[f] On the basis of a priori analysis for an estimated sensitivity of UBM of 85%, a sample size of 200 eyes was calculated as necessary to obtain precision of 0.07 and α = 0.05.[16] A Pearson χ^2 test was used to determine the association between sex and the presence of cysts on an individual animal basis. A univariate relationship between age categories and the presence of cysts on an individual animal basis was examined by means of a Fisher exact test owing to expected frequencies < 5. Comparison of factor frequencies between eyes, including in the same dog, was tested with the χ^2 test.[17] Comparison of factor frequencies (eg, quadrant location) within the same eye was assessed with the
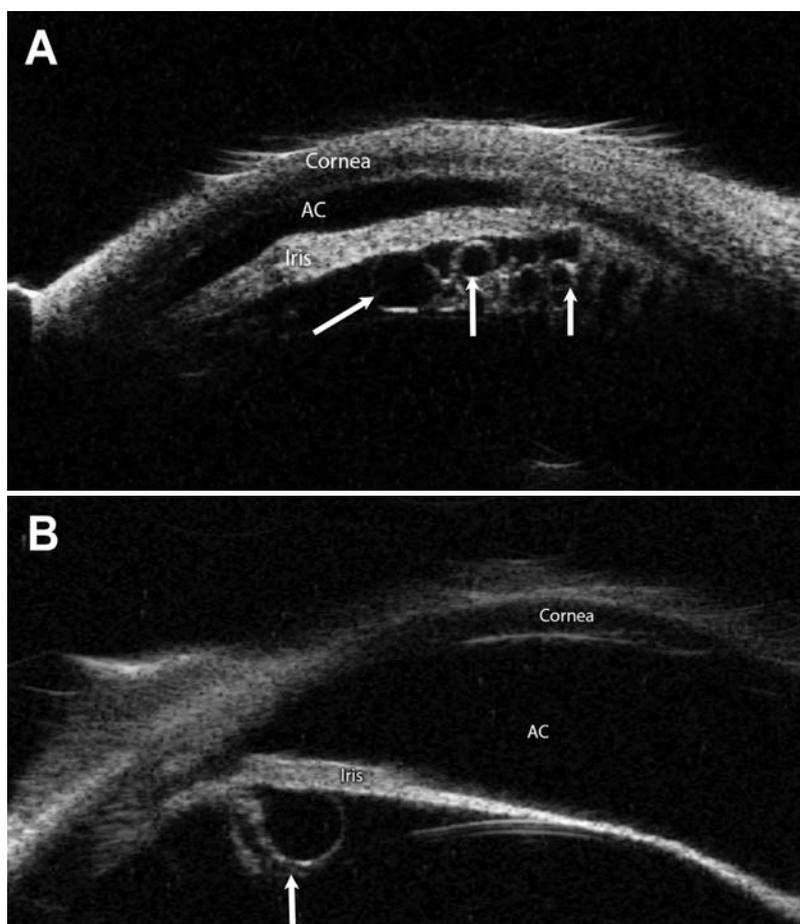

Figure 2—Images of uveal cysts in canine eyes as viewed by UBM. A—Several thin-walled cysts (arrows) with no internal reflectivity are visible extending from the posterior iridal epithelium and ciliary processes. B—A solitary cyst (arrow) localized to the iridociliary sulcus can be seen. AC = Anterior chamber.
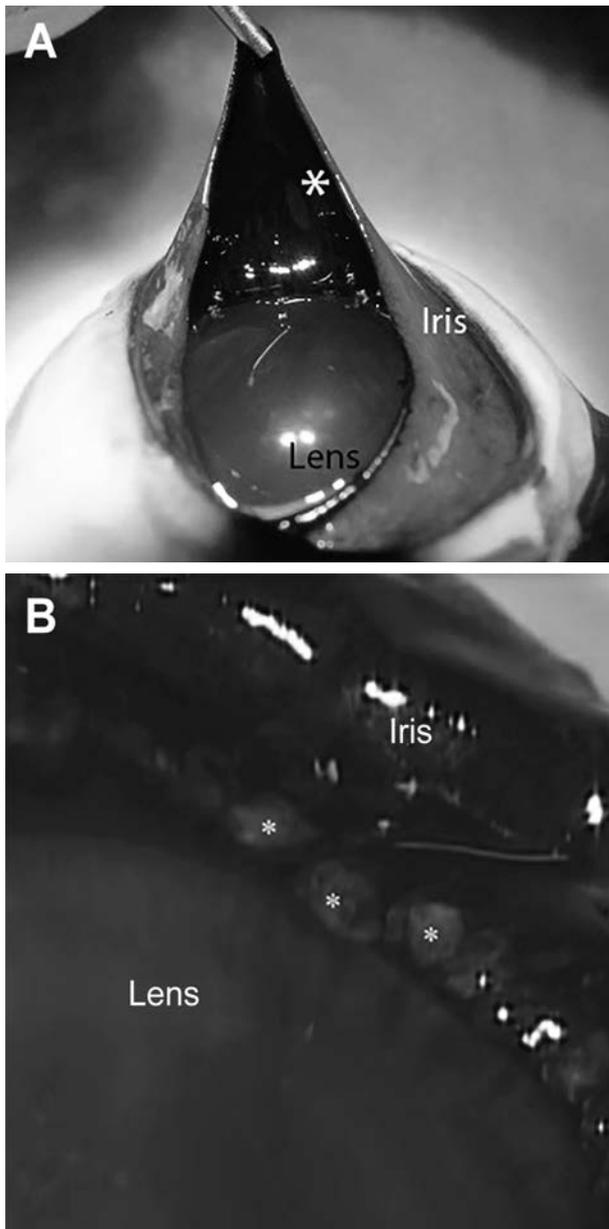
Figure 3—Photographs of canine eyes at the time of dissection. A—A thin-walled cyst is evident within the iridociliary sulcus (asterisk). B—Higher magnification image showing multiple thin-walled cysts within the iridociliary sulcus (asterisks) of another dog.

McNemar test. To determine the specificity and sensitivity of UBM and standard ultrasonography, compared with dissection, 2 X 2 contingency tables were created by use of data from individual eyes. A recent report by Bunce et al[17] indicated that if an ocular study involves an outcome measured at the ocular level and the condition can be unilateral, then analyzing the data on a per-eye basis instead of a per-patient basis is appropriate; because uveal cysts can be unilateral and canine globes vary little in size or architecture, we elected to analyze most of the data on a per-eye basis. Negative and positive predictive values were calculated for UBM.[g] A simple κ statistic was calculated to determine

the interobserver agreement when UBM was used for detection of uveal cysts. Agreement was classified as poor (κ ≤ 0.2), fair (κ > 0.20 to 0.40), moderate (κ > 0.40 to 0.60), substantial (κ > 0.60 to 0.80), and almost perfect (κ > 0.80).[18]

Results

Descriptive data

A total of 202 eyes from 101 dogs (86 mixed-breed dogs, 2 Golden Retrievers, 2 Labrador Retrievers, 2 Treeing Walker Coonhounds, and 1 each of the following breeds: Alaskan Malamute, Beagle, Bichon Frise, Boxer, Chihuahua, Pembroke Welsh Corgi, Dachshund, German Shepherd Dog, and Rottweiler) were evaluated. There were 36 females and 65 males. Dogs were categorized by age group as follows: 59 (58%) were < 4 years, 17 (17%) were 4 to 8 years, and 25 (25%) were > 8 years of age. Ages of 76 dogs were estimated because exact age was unknown. Two eyes from 1 dog each had a solitary, free-floating cyst observed in the anterior chamber by examination with the Finoff transilluminator.

On the basis of UBM, cysts were identified as present in 55 of 202 (27%) eyes by examiner 1 and 29 of 202 (14%) eyes by examiner 2. Dissection revealed that cysts were present in 64 of 202 (32%) eyes (95% CI, 25% to 39%) including 29 of 98 (30%) eyes examined by standard ocular ultrasonography (examination by the latter method was truncated after the first 98 eyes were examined because no cysts were detected with this method, regardless of size). There was no difference in the frequency of confirmed cysts between males (26/65) and females (14/36; P = 0.916). Of the 64 eyes with confirmed cysts, 36 (56%) had cysts present at 1 site, 11 (17%) had cysts present at 2 sites, 9 (14%) had cysts present at 3 to 7 sites, and 8 (13%) had cysts at all 8 sites according to clockface analogy. Of the 29 eyes with dissection-confirmed cysts that were not detected with standard ultrasonography, 16 (55%) had cysts present at 1 site, 4 (14%) had cysts present at 2 sites, 1 (3%) had cysts present at 3 sites, and 8 (28%) had cysts at > 5 sites according to clockface analogy.

Solitary cysts were detected by dissection in 36 of 202 (18%) eyes (including 16/98 [16%] eyes examined by standard ocular ultrasonography). Solitary cysts were more likely to be detected in the nasal quadrant (20/36 [56%] eyes) than in the dorsal (7/36 [19%] eyes; P = 0.028), temporal (7/36 [19%] eyes; P = 0.028), or ventral (2/36 [6%] eyes; P < 0.001) quadrants. Of the 101 dogs, 16 (16%) had unilateral cysts, 24 (24%) had bilateral cysts, and 61 (60%) had no cysts detected. Dogs with bilateral cysts typically had cysts located at the same quadrant in each eye. Dogs > 8 years of age were significantly (P = 0.02) more likely to have cysts involving ≥ 4 sites (5/25 [20%] dogs) than were dogs ≤ 8 years of age (3/76 [4%]).

Mean sensitivity for cyst detection with UBM was 47%, and mean specificity was 92%. Sensitivity and specificity for detection of uveal cysts with UBM were

summarized for each examiner individually **(Table 1)**. The smallest-diameter cyst identified by an examiner with UBM was 110 μm (range, 110 to 1,860 μm). Positive and negative predictive values for cyst detection with UBM were 62% and 80%, respectively, for examiner 1 versus 90% and 78%, respectively, for examiner 2. There was a high degree of interobserver agreement (κ = 0.81) for this method. Because no cysts were detected with standard ocular ultrasonography, sensitivity and specificity for this method were 0% and 1%, respectively.

For each examiner, a comparison of UBM findings versus dissection results is shown **(Table 2)**. The more experienced examiner (examiner 2) had fewer false-positive results for identification of cysts with UBM than did the other examiner (examiner 1), although the differences were not evaluated statistically. Commonly, false-positive results were recorded for eyes collected from older dogs in which cyst-like structures arising from the ciliary processes were observed by UBM **(Figure 4)** but were not confirmed as cysts on dissection. Twenty-six of 64 (41%) eyes with dissection-confirmed cysts were recorded as having none detected with UBM by both examiners. Of 30 false-negative results for individual eyes recorded by examiner 1, 16 (53%) were for eyes with solitary cysts and 14 (47%) were for eyes with multiple cysts. Examiner 2 recorded 38 false-negative results for the same sample, including 17 (45%) for eyes with solitary cysts and 21 (55%) for eyes with multiple cysts. Most false-negative results were recorded for cysts that were ≤ 750 μm in diameter (26/30 [87%] by examiner 1 and 32/38 [84%] by examiner 2) versus cysts > 750 μm in diameter (4/30 [13%] by examiner 1 and 6/38 [16%] by examiner 2). The mean diameter of all cysts not detected by UBM was 490 μm, with a range from 110 to 1,300 μm **(Table 3)**. The mean diameter of cysts not detected by standard ocular ultrasonography was 540 μm (range, 130 to 1,860 μm).

Table 1—Sensitivity and specificity (%) for detection of uveal cysts with UBM in 202 eyes from 101 dogs, reported for each of 2 examiners who performed the evaluations independently and were masked to confirmatory test results.

Examiner	Sensitivity	Specificity
1	53.1 (40.2–65.7)	84.8 (77.7–90.3)
2	40.6 (28.5–53.6)	97.8 (93.8–99.5)

The UBM results were compared with the number of uveal cysts confirmed via dissection. Values are median (95% CI).

Discussion

In the present study, UBM was more sensitive for detection of uveal cysts in enucleated eyes from dogs than was standard ocular ultrasonography. Mean sensitivity and specificity of UBM for detection of uveal cysts were 47% and 92%, respectively. No cysts were detected with standard ocular ultrasonography. On the basis of dissection findings in dogs euthanized for reasons unrelated to the study, the prevalence rate of uveal cysts was 64 of 202 (32%).

Extensive clinical application of UBM has resulted in a better understanding of the formation of and diseases associated with uveal cysts in humans. Investigators have determined that, in people, the iridociliary junction is the most common site for cyst formation.[19,20] Cysts in humans are also typically noted in the inferior and temporal quadrants.[8] In the present study, solitary uveal cysts were most commonly identified in the nasal quadrant (20/36 eyes). The nasal quadrant was also the most common site for cyst detection, accounting for 74 of 80 (93%) cases, during clinical examination of Golden Retrievers in another study.[6] The reason for this site predilection for cyst formation has not been determined.

In humans, uveal cysts may be present in ophthalmologically normal eyes,[8] but their formation has also been associated with underlying diseases such as uveitis.[21] Future UBM investigation of eyes of dogs with Golden Retriever pigmentary uveitis may help determine whether low-grade uveitis causes cyst formation or whether the cysts are a primary pathological lesion. Considering that ciliary body cross-sectional area was increased in uveitic eyes of people,[21] assessment of the same measurement in the eyes of Golden Retrievers could provide useful information.

In the present study, cysts as small as 110 μm in diameter were detected with UBM. The smallest diameter of cysts detected with this method in a previous human study[8] was 200 μm. Detection of these small-diameter cysts notwithstanding, sensitivity for cyst detection in the present study was moderate. Not surprisingly, the lowest sensitivity of UBM in this study was found when used by examiner 2, whose results also reflected the highest specificity of UBM for detection of uveal cysts. Use of more stringent criteria to identify a cyst increases false-negative results while diminishing false-positive results. The cysts most commonly overlooked during UBM examination were small in

Table 2—Contingency table showing results for the presence or absence of uveal cysts as assessed by 2 examiners by means of UBM versus dissection findings for the same sample as in Table 1.

	UBM			
	Cyst present		No cyst present	
Dissection	Examiner 1	Examiner 2	Examiner 1	Examiner 2
Cyst present (n = 64)	34	26	30	38
No cyst present (n = 138)	21	3	117	135
Total	**55**	**29**	**147**	**173**

diameter. In a population of dogs that typically have larger-diameter cysts, such as Golden Retrievers,[6] we speculate that sensitivity would likely be improved.

Our results indicated that the interobserver agreement for UBM was high. This value was calculated to determine the potential accuracy with which an inexperienced examiner might detect the presence of uveal cysts with UBM, compared with a more experienced examiner. In this study, the less experienced examiner had a subjectively higher number of false-positive results than did the more experienced examiner. This was most likely attributable to the misdiagnosis of cyst-like structures as true cysts. Kunimatsu et al[8] described these cyst-like structures as waving ciliary processes. In the present study, on dissection, the ciliary processes of some dogs were no longer tightly and regularly folded, which resulted in ciliary processes of varying length and width that occasionally overlapped. Furthermore, these ciliary processes were found to be dilated at their distal aspect. These findings likely produced the echogenic patterns misdiagnosed as cysts.

The current literature suggests that a 7.5- to 10-MHz probe can be useful to detect cysts arising from the iris and ciliary body.[22,23] However, Verbeek[22] reported that such cysts must be > 350 μm in diameter to be detected with a 10-MHz transducer.[22] In the present study, a 7- to 12-MHz linear transducer was not useful for detecting uveal cysts, even those > 350 μm in diameter.

In the present study, only 98 eyes were examined with standard ocular ultrasonography because of the inability to detect any confirmed cysts, even larger-diameter cysts. In accordance with a recent report,[17] much of our data were analyzed on a per-eye basis (treating these as independent data points) rather than a per-dog basis (to account for potential clustering of data). This potentially introduced bias into the study, particularly for those dogs with bilateral uveal cysts. In addition, all eyes were enucleated. Therefore, effects of skull shape, the third eyelid, and movement of the eye by the animal were removed as confounding factors. According to the literature[11,12] and the experience of one of the authors (WMT), most dogs can undergo UBM with only manual restraint and a topical anesthetic agent. However, the nasal region of the eye can be more challenging to image in vivo owing to the presence of the more prominent orbital rim and the third eyelid. Although the compressible probe cover used in this study facilitates positioning in the nasal region, sedation would likely be needed to accurately image this region.

The gold standard for detection of uveal cysts in this study was dissection of all eyes under 18X magnification from an operating microscope. Cysts were easily seen, as were the posterior iris epithelium, iridociliary sulcus, ciliary processes, zonular fibers, and anterior lens capsule. The entire circumference of the iris and ciliary body could also be evaluated with this method, unlike histologic examination of the eye in which only a few representative sections are reviewed. During dissection, it was noted that some cysts were deflated. Whether this occurred prior to the ultrasonographic examination due to globe hypotony or when the cornea was removed was not known. Collapsed cysts can be seen in some clinical cases and have also been observed in formalin-fixed eyes.[3-6,14]

In our study, UBM was superior to standard ocular ultrasonography with a 7- to 12-MHz linear transducer for detection of canine uveal cysts in enucleated eyes. Therefore, in studies to determine
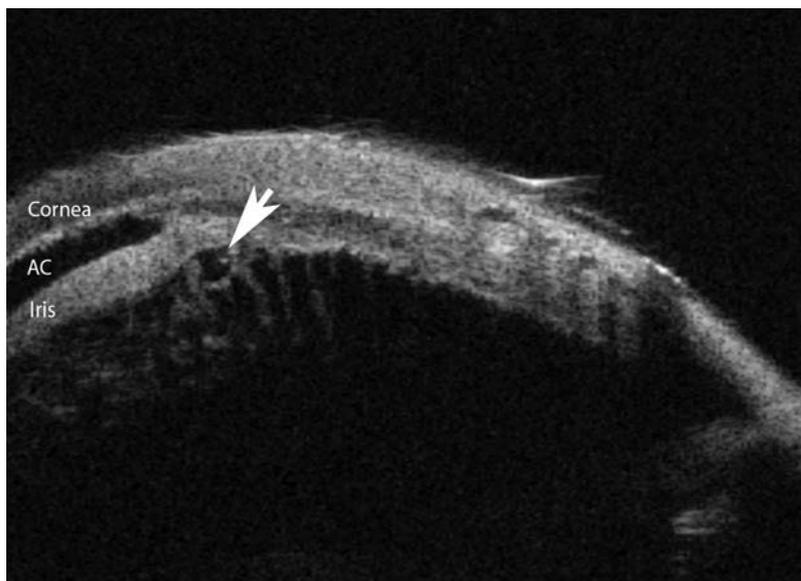

Figure 4—Image showing a cyst-like structure (arrow) viewed by UBM. The structure was associated with the ciliary processes and observed in one scan plane (transverse) but not the other (longitudinal). The lesion was not a cyst but could be mistaken for one. AC = Anterior chamber.

Table 3—Results of descriptive analysis of dissection-confirmed cysts not detected by 2 examiners when UBM was used.

| | Cysts not detected by UBM | |
Variable	Examiner 1 (n = 30)	Examiner 2 (n = 38)
Single cyst (No.[%])	16 (53)	17 (45)
Cyst ≤ 750 μm (No.[%])	26 (87)	32 (84)
Cyst > 750 μm (No.[%])	4 (23)	6 (16)
Mean (range) cyst size (μm)	488 (110–1,200)	492 (110–1,300)

whether cyst detection could serve as an early marker for Golden Retriever pigmentary uveitis or to identify cysts causing glaucoma in breeds such as American Bulldogs or Great Danes, UBM may be the imaging modality of choice.

Footnotes

a. ClearScan ultrasound cover, ESI Inc, Plymouth, Minn.
b. 50-MHz linear scan transducer, Aviso, Quantel Medical, Cedex, France.
c. iU22 Ultrasound, Philips, Andover, Mass.
d. Leica F40, Leica Microsystems, Buffalo Grove, Ill.
e. Digimatic 500-151-20 caliper, Mitutoyo Corp, Aurora, Ill.
f. STATA/SE, version 12.1, StataCorp, College Station, Tex.
g. MedCalc for Windows, version 12.5, MedCalc Software bvba, Ostend, Belgium. Available at: www.medcalc.org/calc/diagnostic_test.php. Accessed Nov 10, 2014.

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