

Use of indocyanine green and sodium fluorescein for anterior segment angiography in ophthalmologically normal cats

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OBJECTIVE

To assess and compare results of anterior segment angiography of ophthalmologically normal cats following IV injection with indocyanine green and sodium fluorescein dyes.

ANIMALS

10 client-owned cats.

PROCEDURES

Anterior segment angiography was performed in anesthetized cats following administration of 0.25% indocyanine green (1.0 mg/kg, IV) or 10% sodium fluorescein (20 mg/kg, IV) solution. All cats received both treatments. Imaging (1 eye/cat) was performed with a full-spectrum digital single-lens reflex camera equipped with an adaptor (1 image/s for 30 seconds) immediately following IV dye injection and 1, 2, 3, 4, and 5 minutes after injection. Onset and duration of arterial, capillary, and venous phases of iris vasculature were identified and compared statistically between treatments. Degree of iridal pigmentation, leakage of dye from iris vasculature, and image quality were subjectively assessed.

RESULTS

No differences were found in onset or duration of vascular phases between treatments. Visibility of the iris vasculature was not impaired by poor or moderate iridal pigmentation with either method. Indocyanine green provided subjectively better vascular detail and image contrast than sodium fluorescein. No vascular dye leakage was observed following indocyanine green administration. Leakage of dye from blood vessels in the stroma (in 10 cats) and presence of dye in the anterior chamber (in 5 cats) were detected after sodium fluorescein administration.

CONCLUSIONS AND CLINICAL RELEVANCE

Images obtained with either fluorescent dye were considered to be of diagnostic quality. Lack of leakage following indocyanine green administration suggested this treatment may have better diagnostic utility for anterior segment angiography. The photographic equipment used provided a cost-effective alternative to existing imaging systems. (*Am J Vet Res* 2015;76:897-903)

Angiographic techniques are widely used, valuable diagnostic imaging modalities in human ophthalmology. Despite this, anterior segment angiography, used to allow examination of the iris vasculature, is considered to be an important but underutilized imaging technique.^{1,2} Sodium fluorescein and indocyanine green dyes are commonly used for angiography. Sodium fluorescein is a low-molecular weight (376-Da), hydrophilic molecule with peak absorption (485 to 500 nm) and emission (520 to 530 nm) characteristics occurring within the visible spectrum.^{3,4} In the presence of pathological changes, ASSFA can be used

to identify a variety of anterior segment disease processes, including uveitis of various etiologies, diabetic microangiopathy, glaucoma, and neoplasia.⁵⁻⁸ It is considered to be more sensitive than slit lamp biomicroscopy at detecting proliferative vasculature disorders.¹ However, because of the spectral properties of sodium fluorescein, inherent limitations exist. A high degree of pigmentation within the iris stroma (eg, the concentration of melanin resulting in brown irises) blocks fluorescence of sodium fluorescein, limiting its usefulness for ocular hemodynamic evaluations.⁹

Indocyanine green can be used as an alternative to sodium fluorescein dye for angiography. It provides greater tissue transmission and penetration, compared with fluorescein, owing to unique molecular and spectral properties.¹⁰⁻¹² Indocyanine green allows visual detection of the iris vasculature, regardless of the degree of iridal pigmentation present,² and has intense

ABBREVIATIONS

ASIGA	Anterior segment indocyanine green angiography
ASSFA	Anterior segment sodium fluorescein angiography
dSLR	Digital single-lens reflex
MAC	Major arterial circle

protein binding characteristics, which limit its extravasation.¹³ Use of indocyanine green in angiography has been fundamental in the diagnosis and treatment of a variety of ocular diseases affecting humans and has allowed identification of vascular abnormalities undetected by use of sodium fluorescein.^{2,9,14-18}

Ocular angiography remains an underutilized imaging modality in veterinary medicine. Previous publications¹⁹⁻²⁶ have focused primarily on imaging of the posterior segment following sodium fluorescein administration. Recently, our research group performed ASSFA with an inexpensive dSLR camera adaptor system to assess iris vasculature in dogs and cats.^{27,28} Although the method was shown to be a potentially useful means of diagnostic imaging, the concentrations of melanin present in moderate to heavily pigmented irises, particularly in dogs, resulted in substantial masking of sodium fluorescein fluorescence. These findings mimicked those observed in humans, limiting hemodynamic assessment of the iris vasculature to poorly pigmented eyes in dogs.^{2,27} While melanin concentration (ie, iris color) was not found to be an important limiting factor in ASSFA of cats, vascular leakage and the presence of sodium fluorescein in the anterior chamber were common and impacted its potential diagnostic utility.²⁸

Indocyanine green has been rarely used for angiography in veterinary medicine, with reports^{26,29-33} limited to imaging of the posterior segment. Specifically in regard to cats, most studies³⁰⁻³² have involved absorptive angiography, as opposed to fluorescence angiography. The former technique relies on the light absorbing properties of indocyanine green, producing a negative contrast image (in which vessels appear black) by use of high-speed infrared-sensitive film. The latter technique exploits the fluorescent properties of indocyanine green, selectively isolating its near-infrared emission (by which vessels appear white) through use of an excitation and barrier filter. Fluorescence angiography is considered to be a superior imaging modality, providing greater image resolution and better vascular detail, compared with the absorption technique.³⁴ Recently, our research group compared results of ASIGA and ASSFA of ophthalmologically normal Beagles.³⁵ Images in that study³⁵ were obtained by use of the aforementioned camera adaptor with a modified (full spectrum) dSLR camera. Indocyanine green allowed for the assessment of the iris vasculature regardless of iridal pigmentation and was not found to leak from blood vessels in clinically normal canine eyes, whereas these were not characteristics of sodium fluorescein.³⁵ On the basis of those findings, and considering its spectral and protein binding properties, we speculated that indocyanine green would have greater diagnostic utility for anterior segment angiography, compared with sodium fluorescein, in cats.

To the author's knowledge, there are currently no published reports of studies investigating the use of indocyanine green for evaluating the iris vasculature in cats. As such, the purpose of the study reported here

was to assess and compare the use of ASIGA and ASSFA of ophthalmologically normal cats. We also aimed to identify normal angiographic findings of the feline anterior segment with each of these methods.

Materials and Methods

Animals

Ten client-owned cats were enrolled in the study between May 20, 2013, and September 30, 2013. All cats were considered to be free of systemic and ocular disease as assessed by complete physical and ophthalmic examinations. Ophthalmic examination included evaluation of menace responses, dazzle and pupillary light reflexes, and fluorescein staining of the ocular surface^a; slit-lamp biomicroscopy^b; applanation tonometry^c; and indirect ophthalmoscopy.^d Fluorescein staining of the ocular surface was performed approximately 2 hours prior to angiographic imaging. The study was approved by the Cummings School of Veterinary Medicine at Tufts University Clinical Science Review Committee, which has oversight for use of client-owned animals in research, and adhered to the Association for Research in Vision and Ophthalmology statement for the use of animals in vision research. Prior to enrollment, informed consent was obtained from the owner of each cat.

Study protocol

Twenty minutes prior to anesthetic induction, all cats received butorphanol tartrate^e (0.2 mg/kg, IM), maropitant citrate^f (1.0 mg/kg, SC), and diphenhydramine hydrochloride^g (2.0 mg/kg, SC). A 20-gauge IV catheter was aseptically placed in the right or left cephalic vein, and all cats were subsequently anesthetized with propofol^h (IV bolus [4.0 mg/kg] followed by a constant rate infusion [0.2 mg/kg/min]). Cats were placed in sternal recumbency and intubated, and supplemental oxygen was administered. Heart rate, respiratory rate, ECG tracings, and pulse oximetry data were monitored, and a body conforming positioning padⁱ was used to aid appropriate head positioning. The left or right eye of each cat was arbitrarily selected for angiographic purposes. A Barraquer wire lid speculum was used to maintain eyelid retraction. Two stay sutures (5-0 nylon) were placed within the ventronasal and lateral bulbar conjunctiva near the limbus and gently anchored to center and stabilize the globe. All globes were lubricated every 30 seconds with a sterile ophthalmic saline (0.64% NaCl) solution^j during imaging. The degree of iridal pigmentation was subjectively assessed as poor, moderate, or strong.

Angiography was performed following rapid IV bolus administration of 0.25% indocyanine green solution^k (1.0 mg/kg) or 10% sodium fluorescein solution^l (20 mg/kg) in a crossover design. Five cats were arbitrarily selected to receive indocyanine green initially, and the remaining 5 cats received sodium fluorescein first. Each cat received 1 injection of each dye, with a total of 15 minutes allotted between injections of

angiographic dyes to allow for dye and equipment preparation. All injections were performed manually, during which time the photographic sequence and timer were initiated simultaneously. Imaging was performed at a rate of 1 image/s for the first 30 seconds, then subsequent images (1/time point) were obtained at 1, 2, 3, 4, and 5 minutes. Upon completion of the imaging sequences, stay sutures were removed and the cats were recovered from anesthesia. Cats were monitored during recovery, and reexamination (complete physical and ophthalmic examination) was performed upon recovery to ensure no sustained adverse effects had occurred. Animals were monitored for 2 hours following recovery and then returned to their owners.

Photographic equipment

Image acquisition was performed by use of a dSLR adaptor system^{28,35,36} that consisted of a modified (full spectrum) dSLR camera,^m dSLR camera adaptor (developed at Tufts University),³⁶ camera lens,ⁿ and an accessory flash.^o Modification of the dSLR camera was performed by an infrared camera conversion company^p and encompassed removing the hot mirror overlying the camera sensor, designed to block UV and infrared light, and replacing it with clear glass.

ASIGA

For ASIGA, excitation^q and barrier^r filters were inserted within the illumination and optical pathways of the adaptor, respectively. Camera settings used on the basis of another study³⁵ included a shutter speed of 1/100 second, effective aperture (effective focal length ratio) of f/8, and a sensitivity (International Standards Organization) setting of 6,400. Prior to indocyanine green administration, images were obtained with the excitation and barrier filters in place to determine the degree of background autofluorescence or pseudofluorescence, if any.

ASSFA

For ASSFA, excitation^s and barrier^t filters were inserted into the adaptor as described above. Camera settings used on the basis of a previous study²⁸ included a shutter speed of 1/30 second, effective aperture of f/8, and a sensitivity (International Standards Organization) setting of 800. To assess background fluorescence, prior to the administration of sodium fluorescein, imaging was performed with the excitation and barrier filter in position.

Angiographic evaluations

Measurements obtained included the time to onset of the arterial, capillary, and venous phases as previously described.³⁷ Briefly, the times to onset of the arterial, capillary, and venous phases were identified by the initial dye filling of the MAC, pupillary capillaries, and iridal veins, respectively. The arterial phase encompassed the time period from when the dye was first noted to enter the MAC until it reached the pupillary capillaries. The capillary phase included the time period from initial capillary filling until filling of the iridal veins were noted. The venous phase was defined by the onset of filling of iridal veins at the pupillary border. Phase intervals were

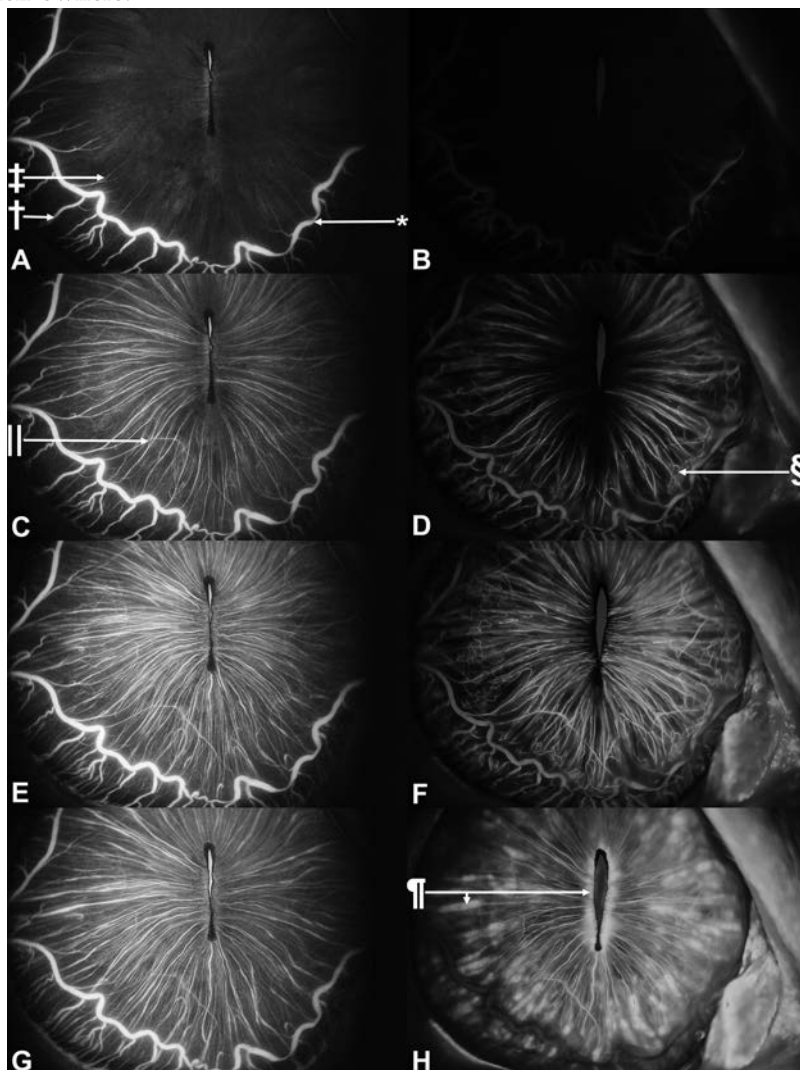


Figure 1—Representative ASIGA (A, C, E, and G) and ASSFA (B, D, F, and H) images of the right eye of a 6-year-old neutered male domestic shorthair cat with a yellow iris. A and B—Initial filling of the MAC with fluorescent dye (onset of the arterial phase) 5 seconds after injection. C and D—Onset of the capillary phase 7 seconds after injection. E and F—Early venous phase 9 seconds after injection. G and H—Venous phase at 20 seconds after injection. Notice the MAC (asterisk), radial ciliary arteries (dagger), and radial iris arteries (double dagger). Complex vascular networks within the ciliary zone (section indicator) and an incomplete minor arterial circle (double vertical bar) are also shown. Marked extravasation is evident from the capillaries and radial iris veins (paragraph indicator) in the venous phase after sodium fluorescein administration. The ASSFA images were converted to black and white with graphic image editing software for visual comparison.

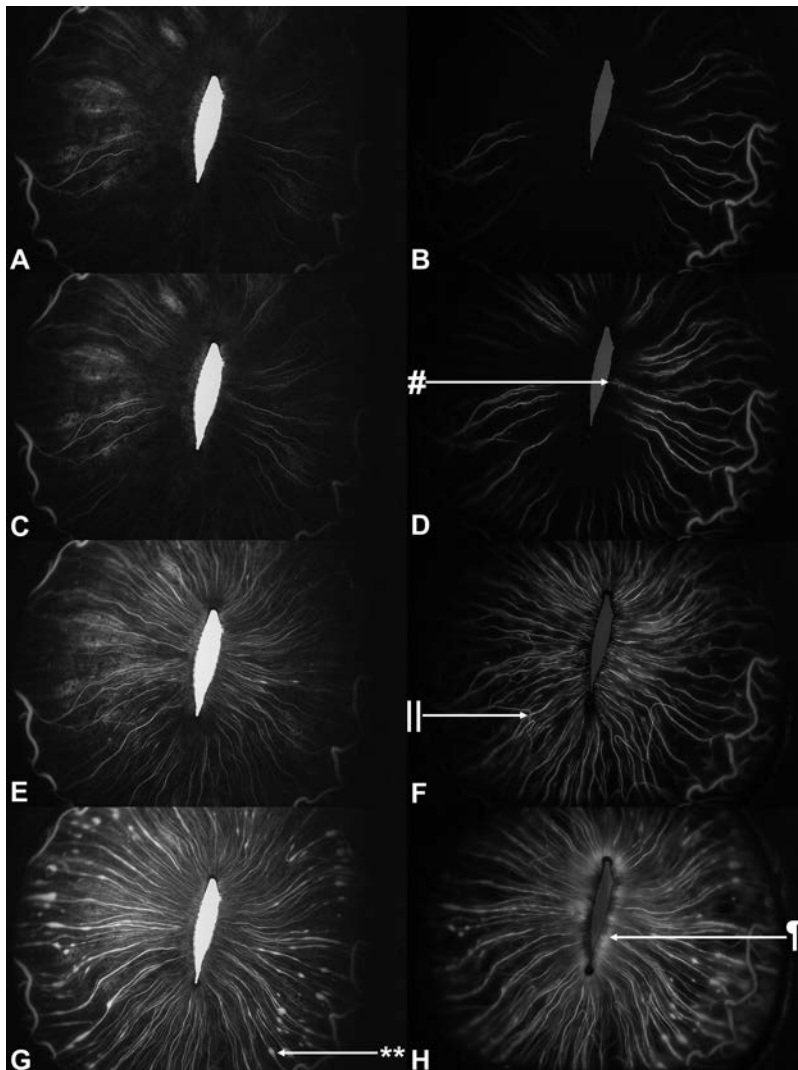


Figure 2—Representative ASIGA (A, C, E, and G) and ASSFA (B, D, F, and H) images of the right eye of a 5-year-old neutered male domestic shorthair cat with a blue iris. A and B—Arterial phase 7 seconds after injection. C and D—Onset of the capillary phase 8 seconds after injection. E and F—Early venous phase 12 seconds after injection. G and H—Venous phase 1 minute after injection. Terminal capillary loops (pound symbol) and an incomplete minor arterial circle (double vertical bar) are indicated. Marked extravasation from capillary and radial veins (paragraph indicator) is evident in the venous phase of ASSFA. Multifocal venous dilations are readily apparent (double asterisk). No extravasation of indocyanine green or sodium fluorescein from the dilated regions was observed. The ASSFA images were converted to black and white with graphic image editing software for visual comparison.

defined as the duration of time from the beginning of one phase to the beginning of the next phase. All time measurements were performed in duplicate by 1 author (CGP), and means for the 2 values were calculated on completion of the study. The ASIGA and ASSFA images were subjectively compared by 1 author (CGP) to assess the observer's ability to visualize the iris vasculature and to determine the appearance of recognizable dye leakage from the iris vasculature or within the anterior chamber. The ASSFA images were converted to black and white by use of a black and white adjustment tool (entire image) with graphic image editing software¹¹ for comparison purposes.

Statistical analysis

Normality of the data sets was evaluated by examination of histograms, calculation of skew, and comparisons between means, medians, and modes. Results indicated normality assumptions were met. The time to onset of the arterial, capillary, and venous phases, in addition to the arterial and capillary phase intervals for ASIGA and ASSFA were compared via a 2-tailed paired *t* test.¹² Data are shown as mean \pm SD. A *P* value < 0.05 was considered statistically significant.

Results

Animals

Cats enrolled in the study included 7 domestic shorthair, 2 Siamese, and 1 domestic longhair. Mean \pm SD age and weight were 5.1 ± 1.9 years and 5.4 ± 0.9 kg, respectively. Six cats were castrated males, and 4 were spayed females. Iridal pigmentation of cats evaluated varied from poor (blue, $n = 4$) to moderate (yellow, $n = 6$). Photographs obtained prior to the injection of indocyanine green or sodium fluorescein with the described filter combinations revealed no evidence of pseudofluorescence or autofluorescence.

Angiographic imaging

Images obtained during ASIGA and ASSFA allowed assessment of the iris vasculature, which was clearly visible, and its hemodynamic characteristics in all eyes, regardless of the degree of iridal pigmentation present. Comparable vascular patterns in each cat were noted, regardless of the fluorescent dye used; however, marked differences were subjectively observed between cats. Representative ASIGA and ASSFA images depicting individual variations between 2 cats are shown (**Figures 1 and 2**). No

significant differences were detected in time to onset of the arterial, capillary, or venous phases for the 2 fluorescent dyes. Further, no significant differences were noted in the arterial or capillary phase intervals between the 2 fluorescent dye treatments.

Times to onset of the arterial phase for ASIGA and ASSFA were 5.1 ± 1.1 and 5.7 ± 0.7 seconds, respectively, with intervals of 2.7 ± 0.7 seconds and 2.7 ± 0.5 seconds, respectively. Filling of the MAC was noted to be rapid and uniform (Figures 1 and 2). Fluorescence of the radial ciliary arteries and radial iris arteries occurred shortly thereafter. The radial ciliary arteries had an array of branching patterns as they coursed toward

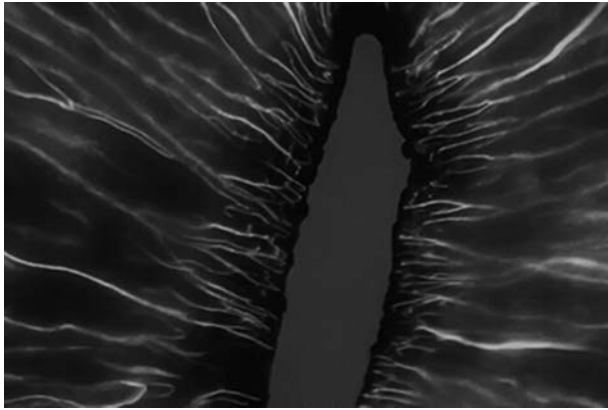


Figure 3—Magnified view (400X enlargement) of the same image as in panel F of Figure 2. Notice terminal capillary loops at the pupillary edge.

the iris base upon leaving the outer aspect of the MAC. Radial iris arteries primarily emanated from the inner aspect of the MAC; however, some were observed to originate directly from radial ciliary arteries. Radial iris arteries arising from the MAC had relatively straight courses and subjectively decreased in caliber as they progressed centripetally toward the pupillary zone. Radial iris arteries arising directly from the radial ciliary arteries typically formed complex networks, terminating deep within the stroma of the ciliary zone and continuing on as radial veins. Filling of the radial iris arteries was not uniform, with a detectably segmental filling pattern. Additionally, in some eyes, the presence of an incomplete minor arterial circle was noted in the iris collarette.

Capillary phases began 7.9 ± 1.3 and 8.4 ± 1.0 seconds after injection for ASIGA and ASSFA, respectively, with capillary phase intervals of 1.0 ± 0.0 seconds for both treatments. Capillaries formed abrupt terminal loops at the pupillary edge (**Figure 3**).

Times to onset of the venous phase were 8.9 ± 1.3 and 9.5 ± 0.8 seconds after injection for ASIGA and ASSFA, respectively. This phase was characterized by centrifugal dye movement in radial veins toward the iris base, with pattern mimicking those of neighboring arteries (Figure 2). No lamination of vessel walls (ie, radial iris veins) was observed during this phase. However, in 3 cats, all with poor iridal pigmentation (blue iris color), multifocal venous dilations were detected within the ciliary zone of irises. No dye leakage was associated with these dilations on or after detection.

On subjective comparison of the study techniques, ASIGA was found to provide greater vasculature detail and image contrast, compared with ASSFA. Additionally, although not specifically measured, luminal diameters of iris arteries and veins appeared smaller on images produced during ASIGA than on those obtained during ASSFA. No leakage of indocyanine green into the iris stroma or into the anterior chamber was detected. However, leakage of sodium fluorescein from iris vasculature (10 of 10 cats) and its presence in the anterior chamber (5 of 10 cats) were noted during ASSFA. Vessel leakage occurred primar-

ily during the venous phase, involving the capillaries and radial iris veins within the ciliary zone (Figures 1 and 2). Leakage progressed throughout the remainder of the imaging sequence, obscuring vasculature detail, often forming a negative contrast image, (ie, the iridal vessels appeared black and stroma appeared white) during the late time periods (3 to 5 minutes). Leakage of sodium fluorescein into the anterior chamber was observed to originate from within the pupillary opening in 4 cats.

No complications attributable to ASIGA or ASSFA were detected. All cats recovered from anesthesia without complications.

Discussion

Angiographic techniques rely upon unique fluorescent properties of a dye to observe and assess the vasculature present within a structure of interest. Timed studies with contrast agent administration provide insight into vascular function, perfusion, and tissue integrity. The use of anterior segment angiography to visualize and characterize the vascular arcade within the iris has allowed for the early detection, diagnosis, and treatment of a variety of vision-threatening ophthalmic or systemic conditions in human medicine.^{2,5-9,14-18} In veterinary medicine, however, angiographic techniques are infrequently performed. This paucity could reflect the high capital costs of the equipment required, rather than limitations of the information it may provide. Additionally, the potential need for sedation or anesthesia may be a limiting factor increasing cost and possibly safety of these diagnostic procedures. In the present study, simple modification of a dSLR camera combined with use of a dSLR camera adaptor allowed for ASIGA and ASSFA to be performed and may serve as a viable cost-effective alternative to conventional fundus imaging cameras employed for this purpose.

Visibility of the feline iris vasculature was subjectively improved with ASIGA, compared with ASSFA, in the present study. The peak absorbance and emission of indocyanine green, unlike those of sodium fluorescein, occur within the near-infrared spectrum of light.¹⁰ This provides a high degree of tissue penetration and reduces fluorescence absorption from resident compounds (eg, melanin).⁹ In contrast to observations reported for people and dogs, fluorescence of sodium fluorescein was not substantially masked by the degree of iridal pigmentation in cats in the present or previous studies.^{9,27,37} Leakage of sodium fluorescein from the iris vasculature (capillaries and radial veins) and within the anterior chamber was a common finding in this study (detected in 10/10 and 5/10 cats, respectively). These observations were comparable to findings in a recent study of ASSFA in cats performed by our research group.²⁸ Extravasation of sodium fluorescein hinders visibility of the iris vasculature. Of greater importance, it confounds assessment of the blood-aqueous barrier integrity and may impede the early detection of pathological changes. The

authors do not believe that extravasation of sodium fluorescein noted in the current and previous studies indicates any disease process or age-related change. Ultrastructurally, the microvasculature of the feline iris consists of nonfenestrated capillaries.³⁸ However, wide intercellular spaces (40 Å) and macula occludens at the intercellular junctions of the capillaries and postcapillary venules have been identified.³⁹ The former provide a site of leakage for small molecules, such as sodium fluorescein (which has an effective diffusion radius of 5 Å unbound and 35 Å when bound to protein^{39,40}). Similarly, Bellhorn⁴⁰ used fluorescence microscopy to evaluate permeability of blood-ocular barrier in mature and immature cats and reported that vasculature within the iris and ciliary processes was permeable to dextran-labeled sodium fluorescein molecules with an effective diffusion radius of up to 85 Å.

In the present study, no extravasation of indocyanine green was observed, owing to its unique molecular and metabolic properties. As such, the authors believe that indocyanine green may have greater diagnostic potential for evaluation of the iris vasculature and determining the integrity of the blood-aqueous barrier in cats. For example, ASIGA could aid in the detection of perfusion abnormalities, similar to those shown to occur with certain posterior segment diseases.^{41,42} More importantly, ASIGA could potentially be used to identify pathological changes, such as pre-iridal fibrovascular membrane formation, early in development and prior to a stage discoverable by means of slit lamp biomicroscopy. Earlier detection could translate into improved management of a variety of ophthalmic conditions affecting cats, most notably uveitis and neoplasia, in addition to minimizing potential vision-threatening sequelae such as glaucoma.

We found no apparent differences in vascular flow patterns during ASIGA, compared with ASSFA, and no significant differences in time to onset of various vascular phases or phase intervals between the 2 treatments. In humans, onset of vascular phases during both anterior (ie, arterial phase) and posterior segment (ie, choroidal phase) angiography has been reported to occur more rapidly for indocyanine green than for sodium fluorescein.^{9,12} These temporal differences, up to 2 seconds depending on the filling phase, are believed to reflect the ability of indocyanine green to more accurately represent blood movement through the vasculature, as opposed to the delayed process of dye staining and diffusion that occurs with sodium fluorescein.⁴³ This inconsistency between results of the present study and human studies may reflect species differences, sample size effects, differences in imaging techniques, or a combination of these factors. The small number of cats included in our study and the temporal frequency of imaging (1 frame/s during the first 30 seconds) may not have allowed detection of significant differences between the treatments, if these existed.

In addition to the small sample size, limitations of the present study included the fact that all cats in the study were healthy and ophthalmologically nor-

mal. Further evaluation and use of ASIGA in a larger number of cats and in feline patients with various ophthalmic conditions is warranted to assess its potential diagnostic utility.

Acknowledgments

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Dr. Pirie is lead inventor of the camera adaptor described in this report, for which Tufts University holds the patent.

Presented in abstract form at the 44th Annual Meeting of the American College of Veterinary Ophthalmologists, San Juan, Puerto Rico, November 2013.

Footnotes

- a. Ful-Glo, Akorn Inc, Lake Forest, Ill.
- b. Kowa SL-15 Portable Slit-Lamp Biomicroscope, Kowa Co Ltd, Tokyo, Japan.
- c. TonoVet, Icare, Vantaa, Finland.
- d. Welch Allyn binocular indirect ophthalmoscope, Welch Allyn, Skaneateles Falls, NY.
- e. Torbugesic-SA, Zoetis, Florham Park, NJ.
- f. Cerenia, Pfizer, New York, NY.
- g. Diphenhydramine hydrochloride, Baxter Healthcare Corp, Deerfield, Ill.
- h. PropoFlow, Baxter Healthcare Corp, Deerfield, Ill.
- i. Vacu-positioner, Shor-Line, Kansas City, Kan.
- j. BSS, Alcon Laboratories Inc, Fort Worth, Tex.
- k. IC-Green, Akorn Inc, Lake Forest, Ill.
- l. AK-Fluor, Akorn Inc, Lake Forest, Ill.
- m. Canon 7D, Canon, Tokyo, Japan.
- n. Canon EF-S 60 mm f/2.8 macro lens, Canon, Tokyo, Japan.
- o. Canon 580EXII flash, Canon, Tokyo, Japan.
- p. Lifepixel Infrared, Mukilteo, Wash.
- q. 769/41 nm Bright Line, Semrock, Rochester, NY.
- r. 832/37 nm BrightLine, Semrock, Rochester, NY.
- s. MF479/40 nm, Thorlabs, Newton, NJ.
- t. MF525/39 nm, Thorlabs, Newton, NJ.
- u. Adobe CS5, Adobe Systems Inc, San Jose, Calif.
- v. Microsoft Excel 2010, Microsoft, Redmond, Wash.

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