Effect of reproductive status on intraocular pressure in cats

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Objective—To measure intraocular pressure (IOP) and progesterone concentrations in cats and to examine their reproductive organs to determine whether reproductive status affects IOP in cats.

Animals—Seventy-five sexually intact domestic shorthair cats scheduled to be neutered, including 28 males, 47 females not in estrus, 13 females in estrus, and 13 pregnant females.

Procedures—Applanation tonometry was conducted to measure IOP, and radioimmunoassay was used to determine progesterone concentrations. Reproductive organs were examined at time of surgery.

Results—The IOP in female cats that were in estrus was significantly higher than IOP in female cats that were not in estrus. Progesterone concentrations significantly affected IOP in pregnant cats.

Conclusions and Clinical Relevance—In cats, IOP is affected by changes in reproductive status. Such changes should be considered when interpreting tonometry results in this species. (Am J Vet Res 2002;63:159–162)

Aqueous humor is a transparent fluid that fills the anterior and posterior chambers of the eye. It is produced in the ciliary processes and exits the eye through the iridocorneal (conventional) and uveoscleral (unconventional) pathways. Dynamic equilibrium between production and drainage of aqueous humor results in intraocular pressure (IOP). Disruption of outflow of aqueous humor results in elevation of IOP. This elevation is a major risk factor for glaucoma, a condition characterized by progressive damage to the optic nerve of affected eyes, and decrement and function of retinal ganglion cells, progressive visual field loss that may result in blindness. Therefore, the measurement of IOP (tonometry) is an important diagnostic and prognostic tool in the management of animals with glaucoma.

Nonpathologic changes in IOP may be caused by numerous anatomic and physiologic factors. For example, substantial short-term changes in IOP are induced by the diurnal cycle. In dogs, values of IOP obtained in the evening tend to be 2 to 4 mm Hg higher than values obtained in the morning, and a similar pattern has been reported in humans. This rhythmic fluctuation in IOP is generally believed to be caused by daily changes in concentrations of adrenocorticosteroids that increase pressure. Support for this theory comes from the fact that animals with differing patterns of adrenocorticosteroid concentrations have differing diurnal cycles of IOP. For example, IOP in rabbits is lowest at 8 AM and highest at 10 PM, varying by 4 mm Hg throughout a 24-hour period. Rats and cats also possess diurnal cycles similar to that of rabbits, peaking in the evening or at night and decreasing by morning, which is opposite the pattern of dogs and humans.

Intraocular pressure also may be influenced by sex. In humans, studies have documented higher pressures in women, and our laboratory group recently reported significant differences in IOP between male and female lions (Panthera leo). To our knowledge, this was the first nonhuman species in which naturally occurring sex-based differences in IOP have been reported. Additional differences were detected between groups of lionesses, as determined on the basis of the luteal status of the animals. We documented that these differences in lionesses are attributable to increased concentrations of progesterone, which most likely lead to increased resistance to outflow.

Differences in IOP attributable to sex and reproductive status may contribute to our understanding of physiologic processes involving the dynamics of aqueous humor. However, they are obviously of limited value when conducted in exotic animals such as lions. The objective of the study reported here was to evaluate whether similar differences exist in a related species (ie, domestic cats).

Materials and Methods

Animals—Seventy-five domestic shorthair cats (28 males, 47 females) were included in the study. The cats had been caught in baited cages as part of a program to limit the population of feral cats in Tel Aviv. The cats were brought in separate cages to a special neutering clinic run by the Department of Veterinary Services, Tel-Aviv Yaffo Municipality. This study was reviewed and approved by the Institutional Animal Care and Use Committee of the Koret School of Veterinary Medicine.

Age of each cat was estimated by a single investigator (NS), as determined by examination of each cat’s dentition. Cats were neutered daily as part of the program; however, we randomly selected 1 day each month on which to conduct the study. All cats brought to the clinic on that day were eligible to be included in the study. Age, sex, and reproductive status of each cat were not used as selection criteria. Data collection lasted for a period of 1 year; thus, measurements were made throughout all seasons of the year. All measurements and samples were obtained between 8 AM and noon to minimize effects of diurnal variation.
**Data collection**—Food was withheld overnight. The following morning, cats were anesthetized by administration of an IM injection of ketamine hydrochloride' (10 mg/kg of body weight) and xylazine hydrochloride (1 mg/kg). Fifteen minutes after induction of anesthesia, each cat was removed from its cage and brought into the preparation room, where it underwent a routine physical examination and thorough ophthalmic examination. On the basis of the results of those examinations, 75 cats were included in the study.

Blood samples were collected for analysis of progesterone concentrations. A topical solution of 0.4% benoxinate hydrochloride was administered to each cornea, and IOP was measured, using a handheld applanation tonometer. Three sequential readings with a variance of ±10% (as determined by the applanation tonometer) were obtained for each eye. Order in which the eyes of each cat were tested was randomly determined.

Following collection of blood samples and tonometry measurements, cats were neutered in a routine manner. In female cats, the ovaries and uterus were surgically removed and examined to determine the animal's reproductive status. This examination was always conducted by the same investigator (NS), who categorized each cat into 1 of 3 groups: pregnant, in estrus, or not in estrus. Pregnancy was further classified as early (<6 weeks of gestation); uterus did not have evidence of conceptual swellings) or advanced (≥6 weeks of gestation; conceptual swellings were easily identified). Cats were classified as in estrus on the basis of identification of 1 or more visible follicles on the ovaries. Cats were classified as not in estrus on the basis that follicles were not visible on the ovaries. Of the 21 cats classified as not in estrus, 8 had recently given birth as determined by the appearance of the uterus and mammary glands, and the other 13 were judged to be cats that had never ovulated on the basis of lack of luteal structures (active or regressing).

After neutering surgery was complete, the pinna of the left ear of each cat was clipped so that it could be readily identified if recaptured. Cats were hospitalized overnight to allow monitoring of their recovery. Cats then were released the following day at the location where they were captured.

**Progesterone analysis**—Progesterone concentration was measured, using a radioimmunoassay. Each aliquot of serum (0.5 ml) was diluted with 3 volumes of 0.1M sodium acetate buffer, pH 5.0, and extracted on C-18 extraction columns. Columns then were eluted with 2 ml of 100% methanol, evaporated to dryness, and redissolved in 0.5 ml of the buffer used for the assays. Aliquots (100 μl) were used for the assays, and all determinations were performed in duplicate. Sensitivity of the assay was 5 pg/tube. Mean ± SD recovery as determined by addition of labeled steroid was 98 ± 5%; mean recovery as determined by addition of unlabeled steroid was 105 ± 15%. Intra- and interassay coefficients of variation were 11 and 15%, respectively.

**Effects of ketamine-xylazine anesthesia on IOP**—Because the cats used in the study were of unknown origin and temperament, we only performed tonometry after they were anesthetized by administration of ketamine-xylazine. To assess the possible effect of this anesthetic protocol on IOP measurements, we performed an additional study. Tonometry was performed on both eyes of 6 conscious domestic shorthair cats (matched on the basis of age and sex with the cats in the experimental group). Cats were anesthetized by administration of ketamine-xylazine. Fifteen minutes after induction of anesthesia, tonometry was repeated in these 6 cats.

**Statistical analysis**—Analysis of the data revealed a normal Gaussian distribution. Differences between groups were analyzed by use of Student 2-group t-tests or a 1-way ANOVA, when appropriate. Values of P ≤ 0.05 were considered significant.

**Results**

Estimated age of the 47 female cats ranged from 0.5 to 3.3 years (mean ± SD, 1.5 ± 1.0 years). Estimated age of the 28 male cats ranged from 0.3 to 3.0 years (mean, 2.0 ± 1.0 years). Age or time of year did not significantly affect variables for any of the cats; however, IOP was slightly lower in older male cats.

Results of tonometry and radioimmunoassay of progesterone concentrations in nonpregnant cats were summarized (Table 1). The IOP for females in estrus (20.7 ± 5.2 mm Hg) was significantly (P < 0.001) higher than for females not in estrus (16.9 ± 3.2 mm Hg). There was not a significant (P = 0.1) difference in progesterone concentrations between these 2 groups of nonpregnant females (estrus, 0.8 ± 0.7 ng/ml; not in estrus, 0.8 ± 0.4 ng/ml). The IOP did not differ significantly between the males (18.7 ± 3.2 mm Hg) and values for either group of nonpregnant females.

Results of tonometry and radioimmunoassay of progesterone concentrations in pregnant cats were summarized (Table 1). We did not detect significant (P = 0.1) differences in IOP between cats in early (18.8 ± 6.2 mm Hg) and advanced (17.5 ± 3.8 mm Hg) stages of pregnancy or in progesterone concentrations for these 2 groups. Furthermore, we did not detect significant differences in IOP between cats in early and advanced stages of pregnancy and any of the nonpregnant groups of cats.

Examination of progesterone concentrations of the 13 pregnant cats revealed a surprisingly large number (n = 5) of pregnant cats with low (<2.0 ng/ml) progesterone concentrations. Therefore, cats were allocated into 2 groups on the basis of progesterone concentrations (low progesterone, <2.0 ng/ml; high progesterone, >3.0 ng/ml). Intraocular pressure in the 8 cats of the high progesterone group (20.6 ± 4.0 mm Hg) was significantly (P < 0.001) higher, compared with IOP for the 5 cats in the low progesterone group.

**Table 1**—Comparison of mean ± SD progesterone concentrations and mean ± SD intraocular pressures (IOP) in sexually intact cats classified on the basis of reproductive status

<table>
<thead>
<tr>
<th>Group of cats</th>
<th>Progesterone (ng/ml)</th>
<th>IOP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpregnant females*</td>
<td>&lt; 0.3</td>
<td>18.7 ± 3.6</td>
</tr>
<tr>
<td>In estrus (n = 13)</td>
<td>0.8 ± 0.7</td>
<td>20.7 ± 5.2</td>
</tr>
<tr>
<td>Not in estrus (n = 21)</td>
<td>0.8 ± 0.4</td>
<td>16.9 ± 3.2</td>
</tr>
<tr>
<td>All pregnant females (n = 34)</td>
<td>3.6 ± 2.6</td>
<td>18.2 ± 5.1</td>
</tr>
<tr>
<td>Stage of pregnancy†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early (n = 7)</td>
<td>3.6 ± 2.9</td>
<td>18.8 ± 6.2</td>
</tr>
<tr>
<td>Advanced (n = 6)</td>
<td>3.6 ± 2.5</td>
<td>17.5 ± 3.8</td>
</tr>
<tr>
<td>Progesterone concentration*†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (n = 5)</td>
<td>0.3–1.99</td>
<td>14.4 ± 4.5</td>
</tr>
<tr>
<td>High (n = 18)</td>
<td>3.1–8.29</td>
<td>20.6 ± 4.0</td>
</tr>
</tbody>
</table>

*Values for IOP differed significantly (P < 0.001) between the 2 subgroups in this classification. †Early pregnancy was <6 weeks of gestation, and advanced pregnancy was ≥6 weeks of gestation. §Values reported represent the range. ||Value differed significantly (P < 0.05) from the values for males, nonpregnant females in estrus, and nonpregnant females not in estrus.
(14.4 ± 4.5 mm Hg). We did not detect significant differences in IOP between the high progesterone group and any nonpregnant group of cats. However, mean IOP in the low progesterone group was significantly lower than IOP in males or nonpregnant females.

The anesthetic protocol used in the study did not significantly (P = 0.30) affect IOP, as determined by measurements obtained for the 12 eyes of 6 age- and sex-matched domestic shorthair cats. Mean ± SD IOP in these cats was 15.5 ± 3.4 mm Hg prior to anesthesia and 16.5 ± 3.8 mm Hg 15 minutes after induction.

Discussion

The most remarkable finding in the study reported here was the fact that IOP in cats is affected by reproductive status. Cats in estrus had IOP that was significantly higher than that of nonpregnant cats not in estrus. Furthermore, IOP in pregnant cats with low progesterone concentrations was significantly lower than in males or any other group of females. In contrast, IOP in pregnant cats with high progesterone concentrations was the same as in female cats in estrus. We believe that this is the first report of a correlation between reproductive status and IOP in any domesticated species.

The relationship between reproductive status and IOP has been studied extensively in humans, with many investigators examining IOP changes during the menstrual cycle, pregnancy, and menopause. In general, IOP in women fluctuates during the menstrual cycle, decreases during pregnancy, and increases during menopause. These changes in IOP raise interesting questions regarding the physiologic mechanisms that regulate IOP. In some women, there is a correlation between the onset of menopause and primary open-angle glaucoma, and a beneficial, ocular hypotensive effect has been reported in women receiving hormonal replacement therapy.

It is suspected that changes in IOP reported in women are caused by fluctuations in concentrations of various hormones. Several investigators attribute these changes in IOP to progesterone, hypothesizing that excess progesterone during pregnancy blocks the ocular hypertensive effect of endogenous corticosteroids and increases aqueous outflow. However, other investigators have failed to find a correlation between changes in IOP and hormone concentrations during the menstrual cycle. The role of other reproductive hormones, including testosterone and estrogen, in IOP regulation is more controversial, and conflicting results frequently are reported.

The relationship between IOP, hormone concentrations, and reproductive status is unclear in animals. In contrast to the prevailing theory that progesterone has an ocular hypotensive effect in humans, topical treatment with progesterone causes an increase in IOP of rabbits. Administration of mifepristone, a progesterone antagonist, without prior treatment with exogenous progesterone induces ocular hypertension, thus implying that endogenous progesterone also increases IOP in this species. A similar hypertensive effect is suspected in lions. We reported that IOP in lionesses with luteal tissue is significantly higher than in lionesses without luteal tissue. The 10-fold increase in progesterone concentrations in luteal females was associated with a significant increase in IOP. In a study in rabbits, it was suggested that progesterone causes an increase in the synthesis of chondroitin sulfate in the iridocorneal angle. The accumulation of excess amounts of this glycosaminoglycan in the angle leads to increased resistance to aqueous outflow, resulting in ocular hypertension. Thus, it appears that there are species differences in the role that progesterone plays in IOP regulation, because the hormone may cause ocular hypertension in rabbits and lions but ocular hypotension in humans.

Analysis of results of the study reported here suggests that the effect of progesterone on IOP in domestic cats is similar to that observed in lions and rabbits. Significantly higher IOP was detected in pregnant cats with high progesterone concentrations, compared with values for pregnant cats with low progesterone concentrations, implying that progesterone may play a role in IOP regulation in this species (Table 1). However, similar to the situation in humans, hormonal regulation of IOP is probably complex and involves factors in addition to progesterone concentration. We did not detect significant differences in IOP between pregnant cats and nonpregnant females in estrus despite a 4.5-fold difference in progesterone concentrations between these 2 groups. Nor did we detect a significant difference in IOP between males and all pregnant cats despite a 12-fold difference in progesterone concentrations between these 2 groups. Furthermore, IOP in cats in estrus was significantly higher than in females not in estrus, even though progesterone concentrations in these 2 groups were extremely similar.

Although pregnant cats and female cats in estrus would be expected to have high estrogen concentrations, we are not aware of physiologic evidence that estrogen would have an effect on IOP. Unlike progesterone, estrogen has negligible mineralocorticoid action. In addition, estrogen does not have an effect on IOP during the menstrual cycle in women or during the luteal phase in lionesses. Additional studies are required to elucidate the physiologic factors involved in IOP regulation and the mechanisms responsible for differences in IOP during the reproductive cycle of cats.

An unexpected finding in our study was the fact that 5 of 13 pregnant cats had progesterone concentrations < 2.0 ng/ml, which most likely implies a compromised pregnancy. Although hypoluteoidism in cats has been described in the literature, there is a lack of information available on its incidence. However, an incidence of 5 of 13 (38%) cats is probably high and perhaps reflective of the poor nutritional status of feral cats. Effect of factors such as rigidity, curvature, and thickness; therefore, values obtained in nonhuman animals should be regarded as estimates of IOP. True IOP values can only be determined through direct manometry of the anterior chamber. The use of such a method has docu-
mented that the applanation tonometer used in this study consistently underestimates IOP in cats. However, it does so in a readily predictable manner, and formulas can be used to calculate the true IOP. Although another applanation tonometer is regarded by some as a more accurate device for measuring IOP, it is no longer manufactured. Therefore, despite its limitations, the applanation tonometer that we used is the most widely used tonometer in veterinary ophthalmology.

We measured IOP in cats anesthetized with ketamine and xylazine. Ketamine increases IOP in cats, whereas xylazine decreases IOP in this species. When administered together, xylazine and ketamine cause an insubstantial decrease in IOP of horses. In the study reported here, we detected a slight but not significant (P = 0.30) increase in IOP in 6 cats anesthetized with ketamine and xylazine, compared with IOP in the conscious state. We did not find evidence to suggest that anesthesia would have a differential effect on IOP for animals of varying reproductive status. Furthermore, we are not aware of any species in which such an observation has been reported. Therefore, we believe that the differences we documented between groups of anesthetized cats would be duplicated in similar groups of conscious cats.

References