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Circadian rhythm of intraocular pressure in cats

María J. Del Sole,* Pablo H. Sande,† José M. Bernades,† Marcelo A. Aba* and Ruth E. Rosenstein†

**Laboratorio de Fisiología del Sistema Nervioso y Endocrinología, Departamento de Fisiopatología, Facultad de Ciencias Veterinarias, Universidad Nacional del Centro de la Provincia de Buenos Aires, Tandil, Argentina; †Laboratorio de Neuroquímica Retiniana y Oftalmología Experimental, Departamento de Bioquímica Humana, Facultad de Medicina, Universidad de Buenos Aires, Cefybo, Conicet, Argentina*

Address communications to:

Dr Ruth E. Rosenstein

Tel.: +54 11 4508 3672 (ext. 37)
Fax: +54 11 4508 3672 (ext. 31)
e-mail: ruthr@fmed.uba.ar

Abstract

Objective To evaluate the rhythm of intraocular pressure (IOP) in healthy domestic cats with no evidence of ocular disease and to analyze the influence of photoperiod, age, gender and ocular diseases on diurnal-nocturnal variations of cat IOP.

Animals All animals were Domestic Short-haired cats; 30 were without systemic or ocular diseases, classified as follows: 12 male intact adult cats, five intact adult female, five adult spayed female, and eight male cats; the latter were less than 1 year of age. In addition, five adult cats with uveitis and three adult cats with secondary glaucoma were included.

Procedure IOP was assessed with a Tono-Pen XL at 3-h intervals over a 24-h period in 12 healthy adult male cats kept under a photoperiod of 12-h light/12-h darkness for 2 weeks. Eight animals from the same group were then kept under constant darkness for 48 h, and IOP was measured at 3-h intervals for the following 24 h. In addition, IOP was assessed at 3 p.m. and 9 p.m. in five intact females, five spayed females, and in eight young cats, as well as in five adult cats with uveitis and three glaucomatous cats.

Results Consistent, daily variations in IOP were observed in animals exposed to a light-dark cycle, with maximal values during the night. In cats exposed to constant darkness, maximal values of IOP were observed at subjective night. Differences of IOP values between 3 p.m. and 9 p.m. (diurnal-nocturnal variations) persisted in intact females, spayed females, and young animals, as well as in uveitic and glaucomatous eyes.

Conclusions The present results indicate a daily rhythm of cat IOP, which appears to persist in constant darkness, suggesting some level of endogenous circadian control. In addition, daily variations of cat IOP seem to be independent of gender, age, or ocular diseases (particularly uveitis and glaucoma).

Key Words: cats, circadian rhythm, glaucoma, intraocular pressure, uveitis

INTRODUCTION

Many physiological processes oscillate with a 24-h periodicity. These daily rhythms may be endogenous (driven by an internal clock) and entrained by the 24 h cycle of light and dark, or they may require the cycle of light and dark for their expression. Introduced by Halberg in 1959,[1] the term circadian rhythm defines a biological cycle with a period of approximately 24 h. In mammals, the biologic clock is genetically inherited and has the dominant pacemaker in the suprachiasmatic nuclei (SCN),[2,3] which is a paired nucleus, situated above the optic chiasm, on each side of the third ventricle. Because SCN neurons contain an internal pacemaker which generates an endogenous rhythm of electrical activity,[4] changes controlled by the SCN occur even in the absence of external stimuli. Nevertheless, the SCN are influenced by environmental changes, especially by the light-dark cycle. Light reaching the retina sends an input to the SCN through the retino-hypothalamic tract (RHT),[5] influencing various rhythms including body temperature, hormone levels, and activity. The period of the human circadian clock is not precisely 24 h;[6] however, the light-dark cycle and other environmental and behavioral rhythms act to modify the period to precisely 24 h, thereby supporting the circadian daytime activity-nocturnal sleep routine.[7]

The eye, the main source of photic information to the central pacemaker, expresses circadian rhythms in various processes at all levels of organization from the molecular

(e.g. melatonin synthesis)[8,9] through to the cellular (retinomotor movements, rod outer segment phagocytosis),[10] whole organ (intraocular pressure [IOP]),[11] and visual system (visual sensitivity).[12]

It has long been known that IOP is not constant and varies considerably throughout the day.[11] Although the physiological role and mechanisms of daily variation remain poorly understood, its importance is suggested by the observation that several aspects of the 24-h IOP pattern are altered in pathologic conditions, particularly in glaucoma.[13] Since it was first described[14] the variation of human IOP has been the subject of numerous investigations.[15,16] To provide better control for several factors, the 24-h IOP pattern has also been studied in animals. These studies have demonstrated 24-h IOP patterns in rabbits,[17,18] rats,[19,20] chickens,[21] and marmosets,[22] among other species.[23] In the absence of a detailed description of a circadian rhythm of IOP in cats, the present study was undertaken to determine the 24-h IOP pattern in cats maintained under a 12-h light/12-h dark cycle. In addition, circadian variations of IOP in cats exposed to a 48-h period of constant darkness, as well as the influence of age, gender, and two specific ocular diseases on diurnal-nocturnal variations of cat IOP were examined.

MATERIALS AND METHODS

Animals

All animal procedures were in strict accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. European Short-haired cats obtained from the colony for research at the Facultad de Ciencias Veterinarias, Universidad Nacional del Centro de la Provincia de Buenos Aires, Tandil, were housed individually in a temperature-controlled environment illuminated by fluorescent lights that were automatically turned on (from 8 a.m. to 8 p.m.) and off. Prior to their inclusion in the study, individual physical and ophthalmologic health conditions were determined on the basis of a general and ocular examination. Ocular examination included Schirmer tear test measurements (Schirmer tear test strips, Schering-Plough Animal Health Corp., Union, NJ, USA), fluorescein staining (Love Sudamericana Laboratory, Buenos Aires, Argentina), applanation tonometry (Tono-Pen XL, Mentor®, Norwell, MA, USA), biomicroscopy (slit lamp HLS 150, Heine Optotechnik, Herrsching, Germany) and direct ophthalmoscopy (Heine Beta 200, Heine Optotechnik).

Animals were adapted to human contact for 8–10 weeks. A total of 38 cats were used for the experiments, as follows: 12 intact adult male cats (mean age: 2.9 ± 0.3 years) were used to assess IOP throughout the 24-h cycle. For this purpose, animals were adapted to a 12-h light/12-h dark cycle for 2 weeks prior to determining IOP values over a 24-h period. Eight animals randomly selected from this group were then kept under constant darkness for 48 h and IOP was assessed during the following 24 h.

In addition, IOP was assessed at 3 p.m. and 9 p.m. in a group of five adult, intact, female cats, and five adult, spayed, female cats. Furthermore, IOP was assessed at 3 p.m. and 9 p.m. in eight juvenile male cats of < 1 year old, three adult male cats (#1, #2 and #3), two adult female cats (#4 and #5) diagnosed with uveitis, two adult female cats (#6 and #7) and one adult male cat (#8) diagnosed with secondary glaucoma (all of them ≥ 2 years old). All these animals were also entrained by the 12-h light/12-h dark cycle before the experiments.

IOP assessment

All tonometric measurements were performed by a single investigator using a Tono-Pen XL applanation tonometer (Mentor®) in awake cats. Cats were manually restrained, and a drop of topical anesthetic (0.5% sterile proparacaine hydrochloride ophthalmic solution, Anestalcon®, Alcon Laboratories, Buenos Aires, Argentina) was applied to the cornea immediately preceding tonometry. Five independent IOP readings (standard error (SE) < 5%) were obtained from each eye, and IOP was determined as the mean of these readings. In healthy animals, the paired data from right and left eye correlated significantly, regardless of time point. Thus, in statistical analyzes, the averages of the two eyes from individual healthy animals were pooled. Mean IOP from each cat was averaged, and the resultant mean value was used to compute the group mean IOP ± SE. The 24-h IOP pattern was assessed by collecting IOP measurements every 3 h ± 20 min at 9 a.m., 12 p.m., 3 p.m., 6 p.m., 9 p.m., 12 a.m., 3 a.m., 6 a.m. and 9 a.m. (day 2 of experiment). For IOP assessment during the nocturnal phase, measurements were performed under dim red light illumination (16-W bulb) to minimize alteration of IOP by light perception.[24] In another set of experiments, cats were kept under constant darkness for 48 h, and IOP was measured in each animal at 3-h intervals during the following 24 h.

Uveitic and glaucomatous animals

The study was performed with the owner's consent on clinical patients referred from specialty hospitals. These animals were maintained under controlled conditions for 2 days before the experiment. Uveitis and glaucoma were diagnosed through routine ophthalmic examination. The diagnosis of uveitis was based on low IOP, miosis, aqueous flare, and iridial hyperemia or tumefaction; in some cases accompanied with pain (lacrimation, blepharospasm and photophobia), hyphema, hypopyon, cataract, or vitreous flare. Uveitis was bilateral in three cats (#1, #3 and #4) and unilateral in two cats (#2 and #5). Secondary glaucoma diagnosis was based on a persistent (over 48 h) increase of IOP (≥ 25 mmHg),[25] buphthalmos, mydriasis, and conjunctival hyperemia. Glaucoma was bilateral in cat #8 and unilateral in cats #6 and #7. Most of the eyes (five out of eight due to uveitis; two out of four due to glaucoma) were already blind. Anterior uveitis accounted for secondary glaucoma in this population of patients. In these patients, IOP assessments were performed before initiating the pharmacologic treatment.

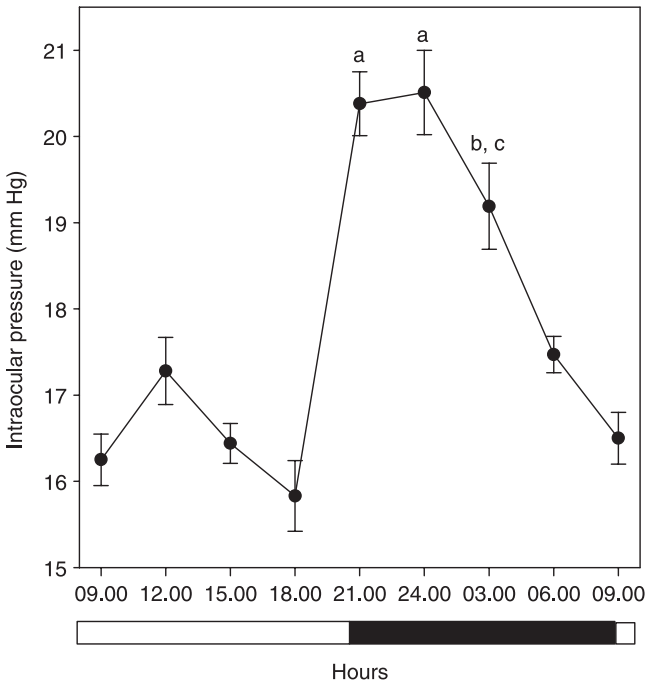

Figure 1. Daily variations of IOP in 12 adult male cats kept under a 12-h light/12 h dark cycle. Significant variations in IOP (mean ± SE, $n = 12$ animals) were observed among time points ($P < 0.001$, ANOVA). IOP values at 9 p.m. and 12 a.m. were significantly higher than those obtained at 9 a.m., 12 p.m., 3 p.m., 6 p.m. and 6 a.m. (a): $P < 0.01$, Tukey's test. At 3 a.m., IOP was significantly higher than at 9 a.m., 12 p.m., 3 p.m. and 6 p.m. (b): $P < 0.01$ vs. 9 a.m., 3 p.m., 6 p.m. (c): $P < 0.05$ vs. 12 p.m., Tukey's test).

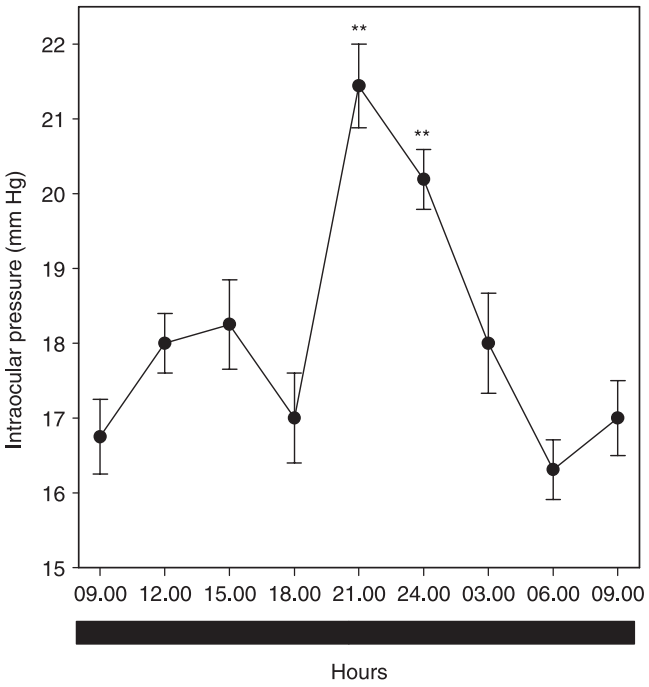

Figure 2. Circadian variations of IOP in eight male adult cats kept under constant darkness for 2 days before IOP assessment. There is significant variation among time points ($P < 0.001$, ANOVA). IOP values (mean ± SE, $n = 8$ animals) at 9 p.m. and 12 a.m. were significantly higher than at 9 a.m., 12 p.m., 3 p.m., 6 p.m., 3 a.m. and 6 a.m. (**$P < 0.01$, Tukey's test).

Statistical analysis

All data are presented as mean ± SE. Daily and circadian variations of IOP were assessed by one-way analysis of variance (ANOVA) followed by Tukey's test. Statistical analysis of diurnal and nocturnal (at 3 p.m. and 9 p.m., respectively) differences was performed using the Student's *t*-test. In the case of glaucomatous or uveitic cats, a paired Student's *t*-test was used. In each case, a *P*-value < 0.05 was considered statistically significant.

RESULTS

Cat IOP was assessed at 3-h intervals throughout the light-dark cycle in both eyes of 12 adult male cats (Fig. 1). IOP values were significantly higher at 9 p.m. and 12 a.m. than at 9 a.m., 12 p.m., 3 p.m., 6 p.m. and 6 a.m. After midnight, although a slight decrease was observed, IOP values still remained significantly higher at 3 a.m. than during the light phase. Mean ± SE IOP values (in mmHg) at different time points were as follows: 9 a.m. 16.2 ± 0.3; 12 p.m. 17.3 ± 0.4; 3 p.m. 16.4 ± 0.2; 6 p.m. 15.8 ± 0.4; 9 p.m. 20.4 ± 0.4; 12 a.m. 20.5 ± 0.5; 3 a.m. 19.2 ± 0.6; 6 a.m. 17.5 ± 0.2. The 24-h pattern of each individual cat was similar in magnitude and frequency to the group when considered as a whole (data not shown). Indeed, IOP cycles for these cats were largely synchronous, as peak IOP was observed predominantly between 9 p.m. and 12 a.m., while low values were detected between 9 a.m. and 6 p.m.

Figure 2 shows IOP values from eight cats exposed to constant darkness for 48 h. The IOP significantly varied throughout the following 24-h period, with maximal values during the subjective night (the segment of a circadian cycle during the free-run state that corresponds to the dark segment during entrainment by a light-dark cycle). Under constant darkness, IOP values at 3 a.m. were similar to those obtained between 9 a.m. and 6 p.m. Mean ± SE IOP values (in mmHg) at different time points were as follows: 9 a.m. 16.7 ± 0.5; 12 p.m. 18 ± 0.4; 3 p.m. 18.25 ± 0.6; 6 p.m. 17 ± 0.6; 9 p.m. 21.4 ± 0.6; 12 a.m. 20.2 ± 0.4; 3 a.m. 18 ± 0.7; 6 a.m. 16.3 ± 0.4. Again, the individual circadian rhythm was similar to the whole group (data not shown).

Figure 3 shows IOP values at 3 p.m. and 9 p.m. from five intact females, five spayed females, and 12 male cats. At 3 p.m., IOP was significantly higher in intact female than in spayed female cats. In addition, while no significant differences were detected in nocturnal values of IOP among these groups, significant diurnal-nocturnal variations of IOP were observed in each of them. Mean ± SE IOP values (in mmHg) were as follows: at 3 p.m. 16.4 ± 0.2, 17.5 ± 0.3, and 15.3 ± 0.3; for male, intact female and spayed female cats, respectively; at 9 p.m.: 20.4 ± 0.4; 19.7 ± 0.3; and 19.9 ± 0.4; for male, intact female and spayed female cats, respectively.

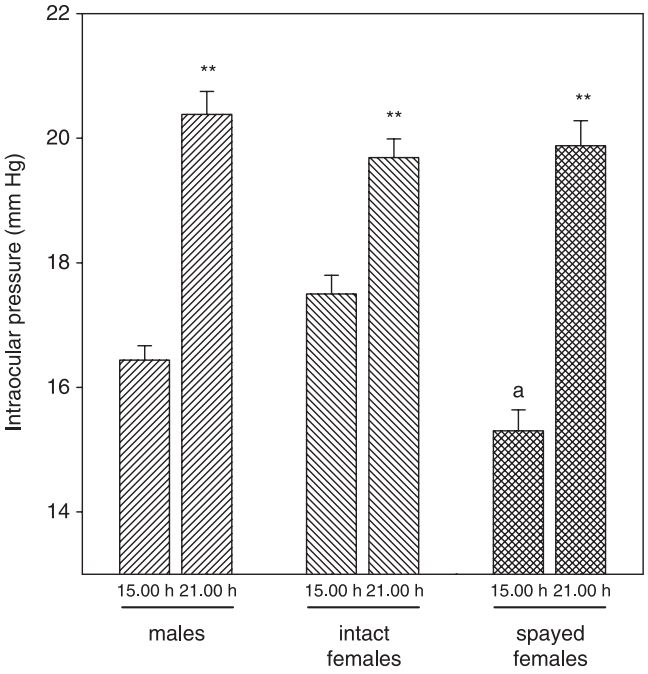

Figure 3. Diurnal-nocturnal (3 p.m. and 9 p.m., respectively) variations of IOP in age-matched male (n = 12 animals), intact female (n = 5 animals), and spayed female (n = 5 animals) cats. At 3 p.m., IOP was significantly higher in intact females than in spayed female [(a): $P < 0.05$ vs. intact female cats, Student's t-test)]. No differences in nocturnal values were observed among groups but IOP values at 9 p.m. were significantly higher than at 3 p.m. in each group (**$P < 0.01$, Student's t-test).

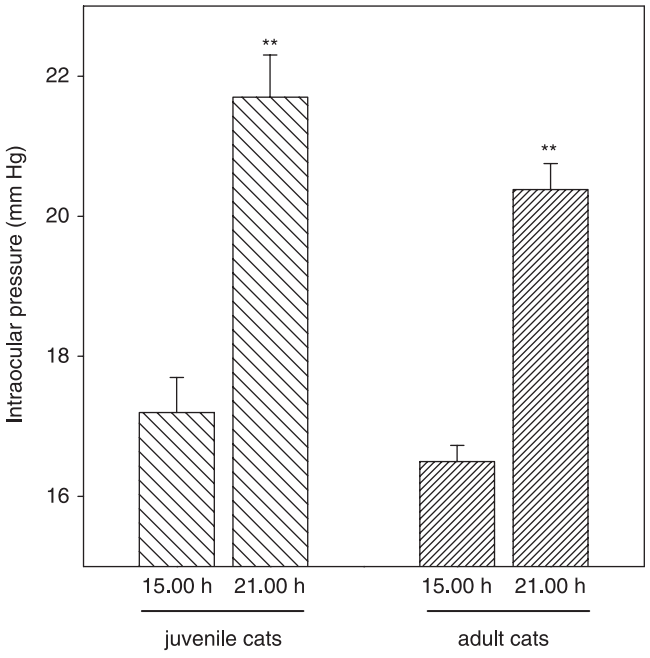

Figure 4. Influence of age on IOP. No significant differences in both diurnal and nocturnal values (mean ± SE, n = 12 for adult cats, n = 8 eyes for juvenile cats) were observed between groups but significant differences were found for IOP values at 3 p.m. and at 9 p.m. in each group (**$P < 0.01$, Student's t-test).

The IOP values at 3 p.m. and 9 p.m. from a group of eight intact male cats of less than 1 year old are shown in Fig. 4. In both juvenile and adult cats, IOP values at 9 p.m. were significantly higher than at 3 p.m. No significant differences were detected for diurnal (at 3 p.m.) or nocturnal (at 9 p.m.) values of IOP between both groups. Mean ± SE IOP values (in mmHg) were as follows: at 3 p.m. 17.2 ± 0.5 and 16.5 ± 0.2; and at 9 p.m. 21.7 ± 0.6 and 20.4 ± 0.4, for juvenile cats and adult cats, respectively.

The IOP values at 3 p.m. and 9 p.m. were assessed in diseased eyes. Cats #1 to #5 were diagnosed with uveitis, whereas cats #6 to #8 were diagnosed with secondary glaucoma. The mean age of the uveitic group was 3.8 ± 1.1 years, three were male and two were female. In the group of glaucomatous cats, mean age was 5 ± 1.9 years, two were female and one was male. The right eyes of cat #2 and #6 and the left eye of cat #7 were phthisical, while in cat #5 the disease was unilateral. Table 1 summarizes individual IOP values of these animals assessed at 3 p.m. and 9 p.m. In both uveitic and glaucomatous eyes, IOP values at 3 p.m. were significantly lower than at 9 p.m.

Table 1. IOP values (in mmHg) from uveitic (cats #1 to #5) and glaucomatous (cats #6 to #8) eyes. Mean IOP values ± SE at 3 p.m. and 9 p.m. in uveitic and glaucomatous eyes

Animal	Eye	3 p.m.	9 p.m.
1	OD	12 ± 0.58	18 ± 0.90
1	OS	10 ± 0.48	14 ± 0.70
2	OS	12 ± 0.58	18 ± 0.90
3	OD	14 ± 0.68	16 ± 0.80
3	OS	7 ± 0.33	9 ± 0.45
4	OD	14 ± 0.70	17 ± 0.85
4	OS	5 ± 0.23	6 ± 0.30
5	OD	15 ± 0.75	16 ± 0.80
6	OS	51 ± 2.55	57 ± 2.75
7	OD	26 ± 1.30	30 ± 1.50
8	OS	47 ± 2.35	50 ± 2.60
8	OD	48 ± 2.41	50 ± 2.51

The right eyes of cat #2 and #6 and the left eye of cat #7 were phthisical. In cat #5, the disease was unilateral. In both groups paired Student's t-test indicated significant differences between diurnal and nocturnal values of IOP ($P < 0.01$ for uveitic cats, $P < 0.05$ for glaucomatous cats). OS: left eye, OD: right eye.

DISCUSSION

The present results demonstrate statistically significant 24-h variations of IOP in cats housed under a light-dark cycle. Although daily rhythms of IOP have been documented in many species, the phase and amplitude of these rhythms differ among them. In rhesus macaques, an increase of IOP was reported in the early morning,[26] whereas studies in both rabbits and rats have consistently demonstrated that IOP increases during the night.[17,20] In Beagle dogs, the highest

IOP values were detected in the morning and the lowest IOP in the early evening.[27] From these results, it can be hypothesized that for each species, higher values of IOP correlate with the awakening or activity phase. In agreement, our results showed high values of IOP in cats during the night. Similar results were previously reported by Wilkie and Latimer.[28,29]

In the present report, readings were collected over one 24-h period. Although a longer study would have been more useful, it should be noted that to collect readings over more than a 24-h period could provoke alterations of ocular physiology (such as corneal edema, keratitis, and IOP changes, among others), induced by both mechanic and pharmacologic manipulations.

The normal range for IOP in adult cats has been reported to be 9–31 mmHg with a mean IOP value (± SE) of 19.7 ± 0.62 mmHg[30] while in the present study mean IOP was 18.1 ± 0.31 mmHg, over the entire 24-h period. Although it has been suggested that Tono-Pen XL could underestimate IOP in cat eyes,[31,32] our results are in close agreement with those obtained for felines by other authors using the same device,[33] and with those obtained by other authors using a pneumatic tonometer.[34,35] In contrast, using the Tono-Pen XL, Rainbow *et al.*[36] reported cat IOP values significantly lower than those obtained in the present study (12.6 ± 2.1 mmHg), while other authors reported mean values of 15.6 ± 3.68 mmHg.[37]

The difference between the peak (9 p.m. to 12 a.m.) and trough mean IOP (9 a.m. to 6 p.m.) in the light-dark cycle was approx. 4 mmHg. This value is similar to the amplitude reported in humans[38] and mice[39] (approx. 5 mmHg), but lower than those reported in rats and chickens (8–10 mmHg).[21,22] In contrast to the results reported herein, Gray *et al.*[37] did not observe a definable pattern of IOP variation across time in cats. There is no ready explanation for this discrepancy; however, the fact that these authors assessed IOP only between 9 a.m. and 5 p.m. could account for the difference. In addition, no details are provided about the photoperiod under which the animals were exposed.

As higher values of IOP were detected at night than during the light phase, it seems possible that the pupil size may influence this parameter. Although in the present report pupil size was not assessed, it was shown that topical application of tropicamide in cats caused a significant elevation of IOP.[33] However, this ocular hypertension was also observed in the contralateral untreated eye, in which no changes in the pupil size were observed, suggesting an unspecified or possible systemic effect of this drug.[33] Moreover, in the present study significant variations in IOP were observed between 9 p.m. and 6 a.m., both time points that occurred under darkness.

A daily ocular rhythm may be controlled by a circadian oscillator, by direct response to environmental lighting levels, or by a combination of these mechanisms. The observation that daily variations in cat IOP persisted under constant darkness supports the possibility of an endogenous clock-controlled function. While the possibility that light may influence cat IOP is not excluded, these results suggest that an actual light-dark cycle might not to be necessary for the generation of its rhythm.

Human and dog IOP has been shown to be equal between sexes.[40–43] However, some studies have found sex-specific differences (typically with higher IOP in female humans).[44] In this study, although we did not assess IOP in neutered male cats, significant diurnal-nocturnal variations in IOP were observed both in intact female cats and spayed female cats. Our results showed that diurnal IOP was significantly higher in intact female than in spayed female cats, while male diurnal IOP did not differ from that of either spayed or intact female cats. At present, we do not have an explanation for this observation. However, as no differences in this parameter were observed for intact and spayed females at 9 p.m., a hormonal influence on this parameter seems unlikely.

The influence of age on IOP has been studied in humans and dogs.[43,44] A decrease in IOP with cat age has previously been reported.[30,37] However, another study of 100 cats suggested that IOP does not vary significantly with age.[45] Our study agrees with the latter in that no differences in both diurnal and nocturnal IOP values were observed between young and adult cats, although significant diurnal-nocturnal variations of IOP were observed in both groups.

The importance of 24-h IOP monitoring is increasingly highlighted by numerous studies, particularly in ocular diseases.[46–48] In the present study, diurnal-nocturnal variations of IOP were assessed in a small number of cats with two ocular diseases, uveitis and glaucoma. Uveitis is a common clinical entity in cats, and is characterized by leakage of proteins and inflammatory cells into the anterior chamber, and in part by a decrease in IOP.[49] Although a small number of uveitic cats were included in this study, nocturnal values of IOP in these eyes were significantly higher than diurnal values. Remarkably, nocturnal IOP values in some uveitic animals (for example, cats #2, #3 and #5) were close to diurnal IOP in healthy eyes suggesting that, at least in some cases, the assessment of daily variations of IOP could contribute to a better uveitis diagnosis.

Some reports indicate that the 24-h IOP rhythm is significantly modified and even reversed in glaucomatous patients,[13] while in glaucomatous Beagles significant daily variations of IOP were observed.[50] Although glaucomatous cats showed a significant ocular hypertension, higher values of IOP were observed at 9 p.m. than at 3 p.m. in these animals, suggesting that antiglaucoma medication in cats should be considered for diurnal-nocturnal variations of IOP, in order to prevent the deleterious effect of the nocturnal peak of IOP.

In summary, these results indicate a daily rhythm of IOP in cats that persists in those subject to 48 h of constant darkness, suggesting some level of endogenous circadian control. In addition, daily variations of cat IOP seem to be independent of gender, age, or ocular disease. Furthermore, these

results indicate that ocular studies involving cats should recognize the 24-h pressure changes that can occur in IOP. As circadian variations in cat IOP seem to be independent of photoperiod, it could be expected that house cats and outdoor cats would have a similar rhythm of IOP. Experiments are now planned to address these issues. In addition, future studies will be performed in order to analyze the mechanisms involved in the circadian regulation of this parameter.

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