

Factors affecting intraocular pressure in lions

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Accepted 4 April 2007

Abstract

The aim of this study was to conduct a detailed analysis of the relationship between age and intraocular pressure (IOP) in lions. Tonometry was conducted in 33 lions aged 5 days to 80 months. Age was significantly associated with IOP ($P < 0.005$). Mean IOP was $12.8 \pm$ and 23.9 ± 4.1 mmHg in lions ≤ 1 year old and > 1 year old, respectively. IOP linearly rose with age during the first 20 months of life, plateaued until approximately 40 months, and then gradually declined ($r = 0.85$). Age-related changes in IOP were highly correlated with ultrasonographic measurements of intraocular dimensions ($r \geq 0.72$), and may be a determinant factor in developmental ocular growth. The dramatic rise in IOP of young lions is similar to that observed in children, but has not been previously demonstrated in animals. Significant IOP differences between lion sub-species were also demonstrated.

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Keywords: Age; Development; Intraocular pressure; Lion; Tonometry

Introduction

Intraocular pressure (IOP) results from equilibrium between production of aqueous humor in the ciliary processes of the eye and its drainage through the iridocorneal angle and unconventional pathways. Elevation of IOP, caused by decreased drainage, is a major risk factor in the pathogenesis of glaucoma, a leading cause of blindness both in humans and in animals (Gelatt and Brooks, 1999).

Although abnormal elevation of IOP is pathological, the pressure may also be affected by numerous physiological factors. Short-term fluctuations in IOP have been associated with variables such as blood pressure (Wu et al., 2006), the diurnal cycle (Gelatt et al., 1981), posture (Setogawa and Kawai, 1998; Komaromy et al., 2006), and blood biochemistry (Klein et al., 1992). Long-term variables, such

as obesity (Mori et al., 2000), season (Giuffre et al., 1995) and the reproductive cycle (Ofri et al., 2002), may also affect IOP. Finally, IOP may also be affected by the patient's signalment. Significant inter-species differences have been reported, even between closely-related species such as the Arabian oryx and the scimitar-horned oryx (Ofri, 2002). Gender may also have a significant effect on IOP in some species, including humans (Wu et al., 2006) and lions (Ofri et al., 1998).

Age is another variable closely correlated with IOP in numerous species, including humans (Sihota et al., 2006), dogs (Ekestén and Narfström, 1991; Gelatt and MacKay, 1998) and domestic cats (Kroll et al., 2001; Stadtbaumer et al., 2002). The relationship between age and IOP may be of particular relevance in young subjects. In species as varied as the chicken (Schmid et al., 2003) and the marmoset (Nickla et al., 2002) it has been suggested that age-related changes in IOP of the developing eye serve as the driving force for the elongation and expansion of the eye.

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Consequently, lowering IOP during developmental stages leads to the development of a small eye in chickens (Neath et al., 1991), although not in rabbits (Nastri et al., 1985). Conversely, in human infants, abnormal elevation of IOP results in excessive eye enlargement, or buphthalmos (Kiskis et al., 1985).

However, despite the impact of IOP on glaucoma, ocular physiology and eye development, there are few reports of IOP in young subjects in the veterinary literature (Stadtbaumer et al., 2002; Plummer et al., 2003; Mughannam et al., 2004). None of these offers a detailed analysis of IOP during the early, developmental period. The aim of this study was to conduct a detailed survey of IOP in a wildlife species, and to assess its relationship to age, intraocular dimensions and sub-species.

Materials and methods

Study populations

The study was conducted on two groups of lions in two countries (Table 1). A group of 11 (5 females, 6 males) Angola lions (*Panthera leo bleyenberghi*) was examined in Germany (Steinmetz et al., 2006). The lions ranged in age between 5 days and 80 months (median 6 months; average age \pm standard deviation 17.2 ± 21.6 months). Four of the lions were examined only once, while seven were examined at intervals that ranged between 3 and 16 months, resulting in a total of 26 examinations.

A second group, consisting of 22 (11 females, 11 males) African lions (*Panthera leo*) was examined in Israel (Ofri et al., 1998, 1999). At the first examination, the age of the lions ranged between 13 and 36 months (median 18.5 months; average 21.3 ± 5.8 months). All but three of the lions were re-examined 1–1.5 years later, resulting in a total of 41 examinations. At the time of the second examination the age of the lions ranged between 28 and 49 months (median 35.0 months; average 36.1 ± 5.9 months).

In both countries, studies were approved by the respective Institutional Animal Care and Use Committees. The study protocols conformed to the International Guiding Principles for Biomedical Research Involving Animals as issued by the Council for the International Organizations of Medical Sciences.

Anesthesia

In Germany, lions examined at age ≤ 2 months were unsedated. Lions aged 2–6 months were examined following intramuscular (IM) sedation with ketamine (1 mg/kg) and medetomidine (0.04 mg/kg). Lions older than 6 months of age were anesthetized with IM ketamine (2 mg/kg) and medetomidine (0.04–0.05 mg/kg). While we are not aware of any studies

documenting the effects of these anesthetic protocols on IOP in lions, intravenous (IV) medetomidine has been shown to have no significant effect on canine IOP (Verbruggen et al., 2000). Topical administration of the drug in both rabbits and cats, however, caused a significant reduction in IOP (Jin et al., 1991).

In Israel, the first examination was conducted using either IM xylazine (1 mg/kg), atropine (0.02 mg/kg) and ketamine (10 mg/kg) or IM ketamine (20 mg/kg) followed by IV ketamine (5 mg/kg) and diazepam (0.5 mg/kg). In the second examination, conducted 2 years later, lions were randomly assigned to one of four anesthetic groups, which are described in detail elsewhere (Ofri et al., 1999; Epstein et al., 2002). The effect on IOP of the various anesthetic protocols used to restrain the lions in Israel was analyzed at length in two previous reports and was demonstrated to be insignificant (Ofri et al., 1998, 1999).

Ophthalmic examination

In both countries, the lions underwent a complete ophthalmic examination, including slit lamp biomicroscopy, tonometry and indirect ophthalmoscopy. No ophthalmic abnormalities were noted in any of the African lions examined in Israel. In the Angola lions examined in Germany several ocular abnormalities were noted, mostly various stages of cataractous lenticular opacities, as described elsewhere (Steinmetz et al., 2006). There was no sign of glaucoma, uveitis or any other ocular disease which could affect IOP in these lions.

Tonometry was conducted using a Tono-Pen XL applanation tonometer. This instrument takes several IOP readings, and electronically calculates the mean pressure and the statistical variance. Only readings with variance $\leq 10\%$ were recorded for the purpose of this study. Three to five such averaged readings were taken in each eye of each lion. All IOP measurements were conducted by two experienced veterinary ophthalmologists (RO, AS), following application of topical anesthetic (0.4% oxybuprocaine). Instrument calibration was checked at the beginning of each workday.

In Germany, several of the lions were also examined using gonioscopy and electroretinography. Results of these examinations are reported elsewhere (Steinmetz et al., 2006). In addition, in 14/26 examinations, the eye was evaluated ultrasonographically (B-mode, 15-Mhz-linear-scan, Sequoia 512, Accuson, or 10-MHz-linear-scan, Oculus CS 9100, Hitachi). These examinations were conducted in 10/11 lions, ranging in age from 1 to 66 months. The following parameters were measured, in mm, by a single investigator (AS): axial length of the eye, depth of the anterior chamber, axial length of the lens and axial length of the vitreous.

Statistical analysis

Student's *t* test was used to compare mean IOP between adult (age > 12 months) lions of the two sub-species; a *P*-value < 0.05 was considered statistically significant. As noted previously, all of the African lions and several of the Angola lions were studied at least twice. The intervals between repeat examinations in the African lions ranged between 11 and 17 months (mean = 15 months) after the initial IOP reading. The intervals between repeat examinations in the Angola lions ranged between 3 and 16 months (mean = 12 months) after the initial reading. Due to the availability of only a small number of lions, these replicates were statistically treated as independent observations because these time intervals between measurements were judged to be large relative to the within-lion dependency at a particular age. However, violations of the assumption of independence can lead to *P*-values from statistical tests that are too low.

The relationship between age and mean IOP was evaluated both nonparametrically using locally weighted scatterplot smoother (loess) with a bandwidth of 0.8, and parametrically using a linear model with IOP as the dependent variable and fractional polynomials of age as well as sub-species as the independent variables. The relationship between ultrasound measurements and mean IOP was evaluated by calculating Pearson

Table 1
Study populations

	Number of animals	Number of IOP readings	Age
Angola lions	11	26	Range: 5 days–80 months Mean \pm SD (months): 17.2 ± 21.6
African lions	22	41	Range: 13–49 months Mean \pm SD (months): 28.1 ± 9.4

correlation coefficients (r) following visual verification of a linear relationship on scatterplots.

Results

The tonometry findings are summarized in Table 2. Age was significantly associated with mean IOP ($P < 0.005$). Mean IOP in lions ≤ 1 year of age was 12.8 ± 3.5 mmHg (a total of 17 measurements in six individuals). Mean IOP in lions > 1 year of age was 23.9 ± 4.1 mmHg (a total of 50 measurements in 27 individuals). The relationship between age and IOP is presented in Fig. 1, which shows a scatterplot and the loess smoother of the relationship between age and IOP for the entire study population ($r = 0.85$). IOP linearly rose with age during the first 20 months of life, where it plateaued until approximately 40 months, and then showed evidence of a gradual decline.

We also analyzed potential differences in IOP between the two sub-species. The mean IOP of adult African lions (> 1 year of age) was 24.2 ± 4.0 mmHg, and the mean IOP in the adult Angola lions was 20.6 ± 3.9 mmHg; this difference was significant ($P = 0.0035$). Although, the mean age of adult African lions was 28.1 ± 9.4 months, and the mean age of adult Angola lions was 40.3 ± 20.8 months, a linear model that controlled for age using linear, qua-

Table 2
Tonometry results

	Mean IOP \pm SD (mmHg)
Angola lions	Lions ≤ 1 year of age: 12.8 ± 3.5 Lions > 1 year of age: 20.6 ± 3.9
African lions	24.2 ± 4.0

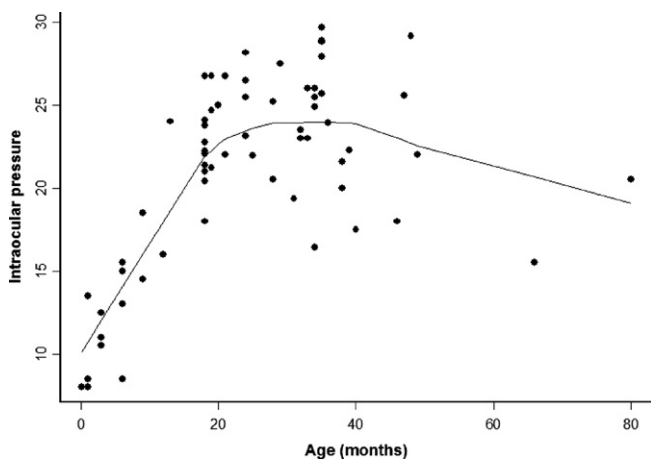


Fig. 1. Sixty-seven measurements of IOP were undertaken in 33 lions ranging in age from 5 days to 80 months. The relationship between age and IOP is presented as a scatterplot and includes a loess smoother ($r = 0.85$). Age was significantly associated with mean IOP ($P < 0.005$). Mean IOP in lions ≤ 1 year of age was 12.8 ± 3.5 mmHg (a total of 17 measurements in six individuals). Mean IOP in lions > 1 year of age was 23.9 ± 4.1 mmHg (a total of 50 measurements in 27 individuals).

dratic, and cubic terms still showed a significant difference between sub-species ($P = 0.0019$).

Ocular ultrasonography was conducted in 14 of the examinations of the Angola lions. These included eight examinations of five young individuals, and six examinations of five adult lions. The relationship between IOP and the intraocular dimensions is depicted in Fig. 2. The correlation coefficients for the relationships between IOP and axial length of the vitreous, anterior chamber depth, axial length of eye and axial length of the lens were 0.72, 0.73, 0.75 and 0.80, respectively.

Discussion

The most striking result of our study is the relationship between age and IOP depicted in Fig. 1. In lions, IOP dramatically rose during the first 20 months of life, plateaued between 20 and 40 months of age, and then began a gradual decline. To the best of our knowledge, this is the first detailed report of a significant increase in IOP in early life in animals. Previous studies in horses (Plummer et al., 2003) and dogs (Mughannam et al., 2004) have failed to find a significant difference in IOP between young and adult animals, while in cats IOP has been shown to decrease after the first year of life (Stadtbaumer et al., 2002). On the other hand, in young lions mean IOP was an average of 11.1 mmHg, or nearly 50%, lower than in lions > 1 year of age. These changes are remarkably similar to those reported in humans, as mean IOP in infants is an average of 7.3 mmHg, or 45%, lower than in adults (Jaafar and Kazi, 1993); IOP of children reaches human adult values only at 12 years of age (Jaafar and Kazi, 1993; Sihota et al., 2006).

Previously, we have reported that in lions IOP is not significantly affected by age (Ofri et al., 1998). The effect was noticed only when additional data were collected and our measurements pooled, demonstrating the important role that sample size has in analysis of results. We propose that additional studies be conducted in young animals of various species, to test whether findings in lions and humans are applicable in other species. Besides their contribution to our understanding of ocular physiology, such studies may also hold clinical relevance. If similar findings are documented in other species (e.g., the closely-related domestic cat), it would mean that baseline IOP values in pediatric patients such as kittens are significantly lower than those of adult patients. Therefore, it is possible that some cases of pediatric glaucoma in these species are not correctly diagnosed, as clinicians may not be aware that normal IOP of young patients is significantly lower than that of adults.

On the other hand, a negative correlation between age and IOP, similar to that we observed in adult lions > 40 months of age, has been demonstrated in adult animals in a number of domesticated and wildlife species. Ekesten and Narfström (1991) performed tonometry in 420 eyes of Samoyed dogs, and showed a gradual decline

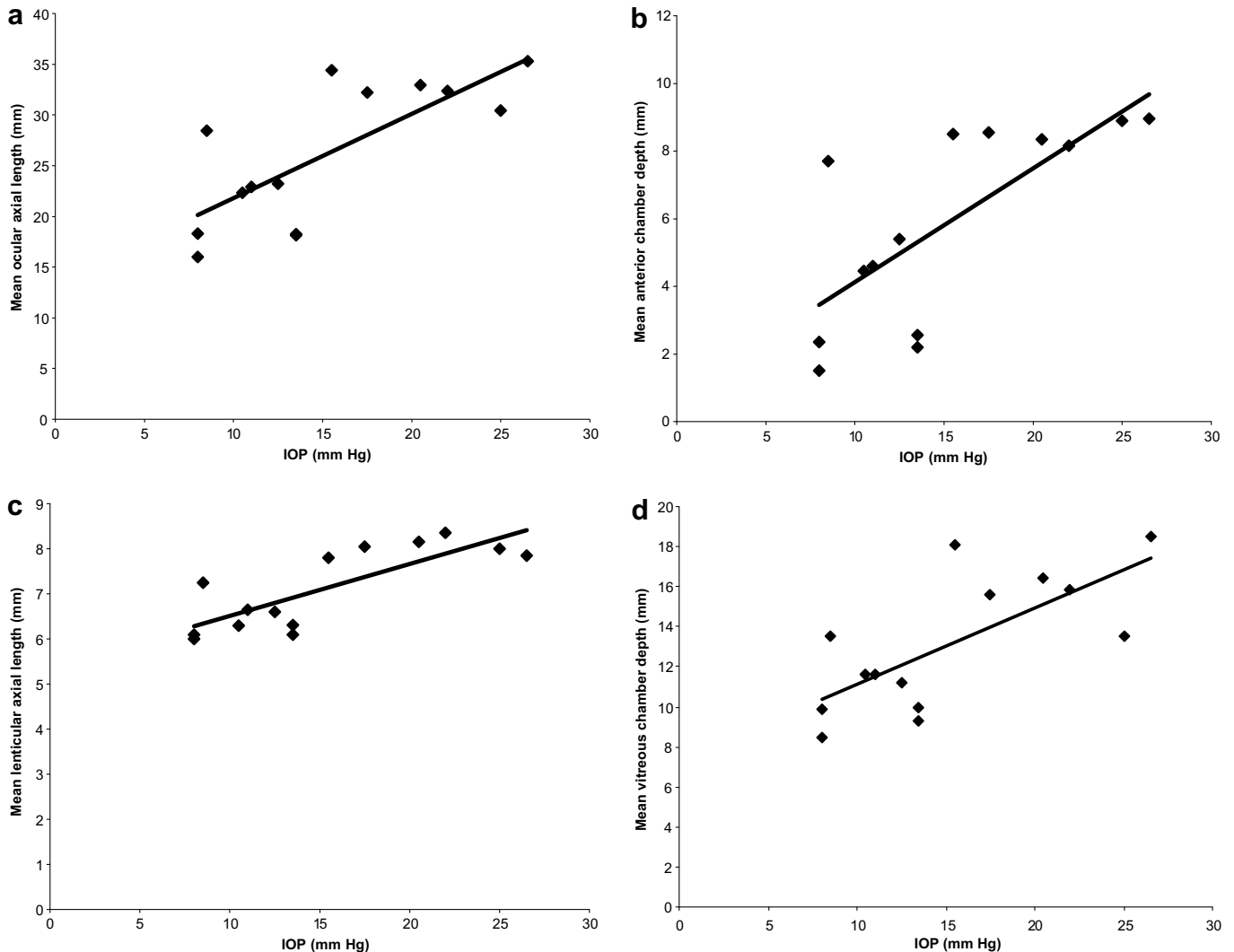


Fig. 2. B-mode ultrasonography was conducted in 10 lions, ranging in age from 1 to 66 months. Four lions were examined more than once, resulting in 14 measurements of intraocular dimensions (in mm). Scatterplots depicting the relationship between mean IOP (mmHg) and ocular axial length (a), anterior chamber depth (b), axial length of the lens (c) and vitreous chamber depth (d). The Pearson correlation coefficients (r) for these relationships were 0.75, 0.73, 0.80 and 0.72, respectively.

in pressure with age, with a significant difference between dogs <1 year of age and dogs >7 years old. Similar findings have been reported by Gelatt and MacKay (1998), who demonstrated a significant, 2–4 mmHg, IOP decline between dogs <1 year of age and dogs >6 years of age. In cats older than 7 years that underwent tonometry more than once, follow-up measurements were significantly lower than initial measurements (Kroll et al., 2001). Another study in cats compared IOP in three age groups (animals <1 year of age, animals 1–4 years old, and animals >4 years of age), and reported a decline in IOP with age (Stadtbaumer et al., 2002). In infant rhesus monkey, average IOP is 5.1 mmHg higher than in adults (De Rousseau and Bito, 1981). Similar findings have also been demonstrated in non-mammalian species, with IOP reportedly being inversely related to body length, an indicator of age, in the American alligator (Whittaker et al., 1995).

Numerous factors have been suggested as playing a role in the effect of age on IOP. Some of these, such as refractive error, corneal curvature and corneal thickness, were not assessed in the present study. On the other hand, we did measure the axial length of the eye, which is frequently cited as a factor that influences human IOP. However, it is rather surprising to note that the human pediatric literature frequently reports conflicting findings regarding the effects of these factors on tonometry. IOP in children has been reported to increase with myopia (Quinn et al., 1995), to increase with hyperopia (Sihota et al., 2006), or to be unaffected by refractive error (Lee et al., 2004). Similarly, IOP in children has been reported to increase with axial length (Youn et al., 1990), to decrease with axial length (Sihota et al., 2006), or to be unrelated to axial length (Lee et al., 2004). In the present study we found a strong correlation between IOP and all intraocular dimensions, including axial length, in lions (Fig. 2). In experimental

studies where a positive correlation was demonstrated between IOP and axial length, it has been suggested that IOP may exert a modulatory effect on ocular elongation and expansion (Nickla et al., 2002; Schmid et al., 2003), and it is possible that IOP may have a similar role in ocular development in the lion.

In this context it is interesting to note in both the Samoyed dog (Ekesten and Torrang, 1995) and the miniature horse (Plummer et al., 2003) intraocular dimensions including the axial length of the eye, anterior chamber depth, axial length of the lens and vitreous axial length all increase dramatically in early life, just as they did in our lions. However, as noted, in neither the Samoyed dog (Ekesten and Narfström, 1991) nor the miniature horse (Plummer et al., 2003) have these changes been correlated with corresponding, age-related changes in IOP similar to those that we observed in the lions. It is possible, however, that in both studies the number of young animals in which tonometry was conducted was too small to establish such a correlation. Ekesten and Narfström (1991) studied IOP in 43 Samoyeds <1 year of age, but provided no breakdown or distribution of their results in this age category. Plummer et al. (2003) similarly provided no data regarding the age distribution of the animals, but careful inspection of Fig. 2 in their paper reveals only 10 IOP measurements in horses <2 years of age. However, it is also possible that while IOP is correlated with axial length in lions, such a relationship does not exist in other species. As noted, pharmacological reduction of IOP in juvenile rabbits had no significant effect on globe growth (Nastri et al., 1985).

Studies in humans report conflicting results regarding the factors that affect the relationship between age and IOP. A likely explanation is the fact that in humans, IOP is reportedly affected by ethnicity and by geography. In Japan, IOP has been shown to decrease in people older than 40 or 50 years of age (Okada et al., 2003). A similar decrease has been shown in Portuguese people older than 60 years of age (Gonzalez-Mejome et al., 2006). On the other hand, IOP has been shown to increase with age in Iran (Hashemi et al., 2005), Barbados (Wu et al., 2006) and the USA (Klein et al., 1992). Factors such as blood pressure, iris color, refractive errors and corneal curvature have been proposed as explanations for these differences. Therefore, it is not surprising that we documented a significant difference in IOP between our two study populations. These differences could stem from the fact that the two populations live in different countries, or that they represent two different sub-species. In this context, it is noteworthy that Gelatt and MacKay (1998) did not find significant IOP differences between dog breeds. However, the taxonomic distance between sub-species of lions is larger than the distance between dog breeds.

Conclusions

In lions, IOP rises dramatically in the first 20 months of life, and decreases gradually from age 40 months. The

rapid increase in IOP of juvenile lions is similar to that observed in children, but has not been previously reported in other animal species. If similar patterns can be demonstrated in other species, it would have implications for the diagnosis of glaucoma in young patients. The changes we observed in IOP of the lions may be related to changes in intraocular dimensions and to sub-species.

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