Effect of Anesthesia on Intraocular Pressure Measured With Continuous Wireless Telemetry in Nonhuman Primates

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Purpose. To compare the effects of both injectable anesthesia (ketamine/dexmedetomidine versus ketamine/xylazine) and inhalant anesthesia (isoflurane) on IOP using continuous, bilateral IOP telemetry in nonhuman primates (NHP).

Methods. Bilateral IOP was recorded continuously using a proven implantable telemetry system in five different sessions at least 2 weeks apart in four male rhesus macaques under two conditions: ketamine (3 mg/kg) with dexmedetomidine (50 μg/kg) or ketamine with xylazine (0.5 mg/kg) for induction, both followed by isoflurane for maintenance. IOP transducers were calibrated via anterior chamber manometry. Bilateral IOP was averaged over 2 minutes after injectable anesthetic induction and again after isoflurane inhalant had stabilized the anesthetic plane, then compared to baseline IOP measurements acquired immediately prior to anesthesia (both before and after initial human contact).

Results. When compared to pre-contact baseline measurements, ketamine/dexmedetomidine injectable anesthesia lowers IOP by 1.5 mm Hg on average ($P < 0.05$), but IOP did not change with ketamine/xylazine anesthesia. IOP returned to baseline levels shortly after isoflurane gas anesthesia was initiated. However, injectable anesthesia lowered IOP by an average of 5.4 mm Hg when compared to that measured after initial human contact ($P < 0.01$).

Conclusions. Anesthetic effects on IOP are generally small when compared to precontact baseline but much larger when compared to IOP measures taken after human contact, indicating that IOP is temporarily elevated due to acute stress (similar to a "white coat effect") and then decreased with anesthetic relaxation. Anesthetic induction with ketamine/xylazine and maintenance with isoflurane gas should be used when IOP is measured postanesthesia.

Keywords: intraocular pressure, Anesthesia, Telemetry

General anesthesia is common in both animal studies and human patient procedures, but the effects of injectable and inhalant anesthesia on IOP have not been fully characterized. IOP is the only known treatable risk factor for glaucoma; therefore, the effects of anesthesia on IOP are important to know, especially for glaucoma studies involving IOP measurement under anesthesia. IOP is one of the primary modifiable variables in many research studies, and IOP is often experimentally elevated in research animals to induce experimental glaucoma for the study of downstream effects. Hence, accurately quantifying IOP in the research setting is extremely important, as artifacts due to anesthesia or animal handling could confound reported results. In particular, nonhuman primates (NHPs) are considered an important animal model in glaucoma studies and IOP measurements are difficult to obtain in awake, behaving animals, requiring most researchers to assume that IOP measurements in anesthetized NHPs accurately reflect the true IOP.

The effects of anesthesia on IOP have been studied in both animal models and human patients using single time-point (snapshot) IOP measurements, but comparisons were not made to true naïve baseline IOP since only postcontact and/or postanesthesia IOP measurements were obtained. Studies have shown that contact with a clinician or human animal handler can acutely elevate IOP.[1–7] Ketamine is an NMDA receptor antagonist anesthetic that is a commonly used in animal studies and in ophthalmic procedures involving children and uncooperative patients. Dexmedetomidine and xylazine are commonly used in conjunction with ketamine as an injectable anesthetic, and both are known to lower IOP.[8–13] Dexmedetomidine is a synthetic alpha2-adrenoreceptor agonist with sedative and analgesic properties, and xylazine is an analogue of clonidine and an alpha2 adrenergic receptor agonist. Isoflurane is a halogenated ether used as an inhalation anesthesia, commonly after induction with injectables such as ketamine along with either dexmedetomidine or xylazine.

Human studies have reported both increases and decreases in IOP following ketamine injection alone, along with a dependence on dosage,[14–17] so there is some confusion in the literature as to the effects of ketamine on IOP. The most common animal models in which the effects of anesthesia on IOP have been studied are rodents, sheep, and NHPs; other

Table 1. Time Course of Data Collection

Event	Data Collection Trigger	Duration of Measurement, s
Precontact baseline	5-10 min before entering room, prior to any human contact	120
Preinjection baseline	Immediately upon entering room but prior to anesthetic injection	30
Postinjection	After the injectable anesthetic had taken effect	120
Preisoflurane	Immediately after intubation but prior to isoflurane administration	30
Postisoflurane	60–90 s after anesthetic plane achieved with inhalant anesthesia	120

studies have also included rabbits, cows, pigs, dogs, and cats.[18–22] Raposo et al. reported the effect of four different anesthetics on capuchin monkeys, which included ketamine-xylazine and ketamine-dexmedetomidine.[23] In their study, IOP was measured at four different time points after anesthetic induction with a contact tonometer (Tono-Pen; Reichert, Depew, New York, USA); importantly, a baseline IOP was not obtained prior to injection. Similarly, Bunch et al. examined the effect of ketamine on IOP in cynomolgus monkeys hourly over a 6-hour period with measurements taken with a Goldmann tonometer, but again, preanesthesia baseline IOP was not measured. Compared to postanesthesia baseline IOP, results showed a 2 to 6 mm Hg reduction in IOP over consecutive days of ketamine anesthesia and the reduction of IOP increased over more days that the animals were anesthetized.[19]

Continuous IOP telemetry allows us to obtain IOP readings in awake, unrestrained NHPs without human contact, thereby establishing a true baseline IOP and quantifying second-to-second IOP changes that may be missed by single-time-point measurements. In this study, we used continuous IOP telemetry to quantify true baseline IOP in awake, behaving NHPs prior to human contact, after human interaction but prior to anesthetic induction, after induction with common injectable anesthetics (ketamine with dexmedetomidine or ketamine with xylazine), and after anesthetic plane was achieved with inhalant anesthesia. We report the effect of the different types of anesthesia on IOP in NHPs, which is especially important for glaucoma researchers that employ the NHP model of glaucoma. IOP is generally measured in NHPs after anesthetic induction, potentially confounding analyses of the effects of IOP on research outcomes. Hence, the effect of injectable and inhalant anesthesia on IOP is important in clinical assessment of mean IOP and research studies that rely upon experimental perturbations in IOP measured with snapshot devices.

Methods

Animals

All animals were treated in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research under a protocol approved and monitored by the UAB Institutional Animal Care and Use Committee. Four adult male rhesus macaques (4–6 years) with no ocular abnormalities were used for anesthesia data collection as a part of a larger NIH-funded study aimed at determining the contributions of IOP fluctuations to glaucoma pathophysiology. All animals were kept on a 6 AM to 6 PM light-dark cycle and fed at approximately 6 AM and 2 PM daily. All animals received water ad libitum through a continuous feed. Food and water intake were not measured for this study. NHP 9028 had the IOP telemetry system functioning only in the left eye (OS); therefore, data were only collected in the left eye for this animal. All animals were intubated postinjection and prior to isoflurane initiation. Standard intubation technique was used, with no topical anesthetic spray.

IOP Telemetry System

We have developed and validated an implantable telemetry system (Konigsberg Instruments, Inc., Pasadena, CA, USA) that allows continuous monitoring of IOP and aortic blood pressure and records 500 measurements of IOP per second for up to 2.5 years.[1,24] IOP transducers were calibrated biweekly via anterior chamber manometry from 5 to 30 mm Hg in 5 mm Hg steps, and all data were corrected for signal drift assuming a linear drift between calibration tests. An aortic BP transducer was placed directly in the vessel lumen at the aortic arch via thoracotomy in each NHP. Pressure transducers generally drift less than 1 mm Hg/week, and are linear and accurate to $\pm$0.2 mm Hg from 0 to 500 mm Hg. Barometric pressure compensation occurred in real time.

Data Collection and Analysis

Bilateral IOP, aortic blood pressure and time-synchronized video were recorded continuously during the entire time course of the experiment, from well before precontact baseline to well after isoflurane had stabilized the anesthetic plane. Data were acquired in five sessions per animal, at least 2 weeks apart, for each anesthetic (ketamine [3 mg/kg]/dexmedetomidine [50 μg/kg] or ketamine/xylazine [0.5 mg/kg], and isoflurane inhalant [0.5%–2% in oxygen]). Only unilateral IOP data were acquired (OS) in NHP 9028 due to transducer failure in the right eye. We chose the precontact baseline to be the period ~20 minutes prior to the technician entering the room to minimize acute stress and concomitant IOP, BP, and HR changes associated with the NHPs hearing the technicians preparing to enter the room.[1] The preinjection baseline was the 30-second period immediately after the technician entered the room, but before touching the cage to squeeze the animal for injection. The time between the technician entering the room and squeezing the animal in its cage for induction injection was limited to the extent possible to minimize stress on the animals, consistent with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Hence, the preinjection baseline measurement time was limited to 30 seconds, which was the maximum amount of time available across all sessions. The postinjection period was defined as 120 seconds of data immediately after the animals were immobilized and therefore able to be safely removed from their cage. The preisoflurane period was defined as the 30-second period immediately following intubation but before isoflurane gas anesthesia was initiated. The postisoflurane period was defined as ~10 minutes after isoflurane was initiated and IOP had stabilized. Continuous video recordings, time-synchronized to the telemetry data, were acquired in the data acquisition software along with the telemetry signals. A single observer (JVJ) then used the time-synchronized video in conjunction with the IOP, BP, and HR telemetry data to identify the appropriate time periods for analyses consistently across sessions as shown in Table 1. A single technician (LH) performed all anesthetic injections, intubations, and isoflurane anesthesia operations.

Paired *t*-tests were used to compare post-anesthesia means to their respective baseline values, with an alpha level of

Table 2. Mean ± Standard Deviation of IOP, MAP, and HR

	Baseline	Preinjection	Postinjection	Preisoflurane	Postisoflurane
Ketamine/Dexmedetomidine					
IOP-OD (mm Hg)	14.6 ± 1.7	18.8 ± 2.1*	13.1 ± 1.8†	13.9 ± 3.4	14.4 ± 0.5
IOP-OS (mm Hg)	14.1 ± 1.6	18.9 ± 1.8†	12.9 ± 1.6*	13.5 ± 2.4	14.4 ± 0.5
MAP (mm Hg)	108 ± 20	137 ± 26†	138 ± 23†	124 ± 26*	111 ± 24
HR (BPM)	128 ± 21	175 ± 36†	86 ± 13†	74 ± 14†	79 ± 14†
Ketamine/Xylazine					
IOP-OD (mm Hg)	13.3 ± 1.8	18 ± 0.7†	12.9 ± 1.9	12.7 ± 0.7	12.3 ± 0.9
IOP-OS (mm Hg)	11.8 ± 1.7	16.4 ± 2.2†	11.5 ± 1.5	11.6 ± 0.7	11.8 ± 0.8
MAP (mm Hg)	119 ± 22	150 ± 25†	133 ± 24†	118 ± 25	113 ± 26*
HR (BPM)	117 ± 14	171 ± 24†	110 ± 27	80 ± 22†	81 ± 20†

Measurements taken at baseline, preinjection, postinjection, preisoflurane timepoints for ketamine/dexmedetomidine or ketamine/xylazine, and post-isoflurane across all 4 NHPs and sessions.

* $P < 0.05$ indicate significant change relative to precontact baseline.

† $P < 0.01$.

$P < 0.05$ indicating a significant change. A comparison of the use of intramuscular injectable anesthesia, ketamine with xylazine or ketamine with dexmedetomidine was investigated for the change in IOP in the four NHPs.

Results

Table 2 shows the mean response of IOP, MAP, and HR to both forms of injectable anesthesia followed by inhalant anesthesia compared to baseline values acquired before human contact (baseline), as well as the period just prior to injection when staff were in the room with the NHPs (preinjection). Results show that IOP increases by an average of 4.6 mm Hg just prior to anesthetic injections (preinjection) compared to precontact baseline in both conditions and all eyes ($P < 0.05$), and significantly decreases by 5.4 mm Hg immediately after the animals are immobilized by injectable anesthetics ($P < 0.01$). Compared to precontact baseline, however, IOP was significantly lower by only 1.5 mm Hg after ketamine/dexmedetomidine anesthetic induction ($P < 0.05$), with no significant IOP change occurring with either ketamine/xylazine injectable anesthesia or isoflurane inhalant anesthesia. There was no significant difference between the postinjection and preisoflurane IOP for either injectable anesthetic, indicating that IOP did not change significantly in the postinjection period once the animals were immobilized after induction. However, there was considerably more variability in the IOP measurements at the preisoflurane timepoint in the ketamine/dexmedetomidine sessions, so the preisoflurane IOP was not significantly different from baseline, whereas the postinjection IOPs were significantly lower than baseline. MAP and HR are significantly higher just prior to anesthetic injections and after induction with injectable anesthesia when compared to precontact baseline ($P < 0.01$), but MAP generally returns to near baseline levels after inhalant anesthesia is initiated; HR was significantly lower than baseline after inhalant anesthetic plane is reached ($P < 0.01$).

The Figure shows the responses of IOP, MAP, and HR relative to precontact baseline in each NHP by session; results show that the changes are animal and session specific, although they follow the general trends shown in Table 2. Interanimal and intereye analyses were not performed due to the limited sample size, although fellow eyes within animals followed a very similar pattern within individual sessions (Figure). In general, intersession and interanimal variability was higher than variability between fellow eyes within animals.

Discussion

Results show that changes in IOP with injectable and inhalant anesthesia relative to precontact baseline are generally small, which bodes well for clinical and animal research activities that rely on postanesthesia IOP measurements. Both this study and a recent study from our group show that acute stress associated with human contact significantly elevates IOP, MAP, and HR in NHPs, demonstrating the importance of measuring IOP using telemetry that doesn't require human contact.[1] Anesthesia did lower IOP significantly when compared to IOP measured when the NHPs are in contact with staff (mean decrease of 5.4 mm Hg), but this is likely to be due to the relaxation of the animals from a stressful state and not the pharmacologic effects of the anesthesia itself, as postulated in prior NHP and human studies.[1,15] Previous studies have shown that changes in IOP can be modulated through relaxation of the extraocular muscles, which could be the mechanism through which anesthesia acutely lowers IOP when the subject is stressed and IOP is acutely elevated as a result.[25] Continuous IOP measurement via implanted transducers also has the advantage of avoiding ocular contact for IOP measurement that may affect IOP. In previous studies, IOP measurements were obtained with tonometers that rely on corneal applanation. Tonometers were used to measure IOP only a few minutes apart in some studies, and repeated tonometry readings have been shown to reduce IOP.[26,27]

The results of this study show that ketamine/dexmedetomidine injectable anesthesia lowers IOP by 1.5 mm Hg compared to baseline, but IOP returned to baseline levels shortly after isoflurane gas anesthesia was initiated. Although the reported effects are generally small and vary by animal and session, IOP changes with ketamine/dexmedetomidine anesthesia should be considered when IOP or its effects are important, especially when IOP is measured immediately after the animals are immobilized. Ketamine/xylazine did not significantly affect IOP in NHPs compared to preanesthesia baseline, and therefore should be considered as a preferred method of induction for NHP glaucoma research studies where IOP is measured immediately after induction. Also, isoflurane did not alter IOP irrespective of the injectable anesthesia used, so it remains a good option for studies in which IOP is measured after inhalant anesthesia has stabilized both the anesthetic plane and IOP. The MAP and HR data presented are consistent with previous reports, which shows an overall decrease in HR with the use of injectable and inhalant anesthesia. The MAP increased with the use of the injectable anesthesia and returned to near baseline levels with inhalant anesthesia.

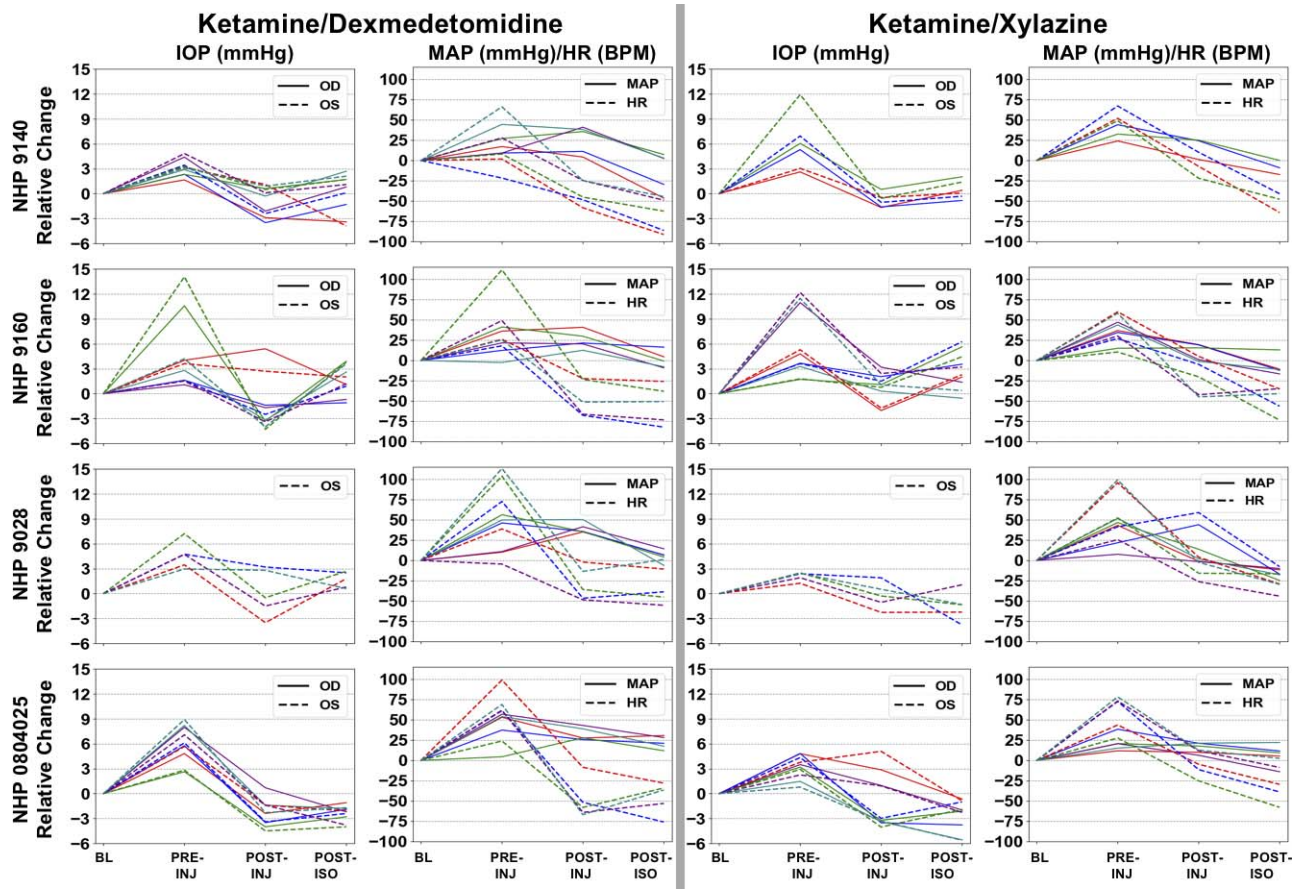

Figure. Relative Change from baseline (BL) in IOP, MAP, and HR during the pre-injection (PRE-INJ), post-injection (POST-INJ), and post-isoflurane (POST-ISO) periods by animal and session with (*left*) ketamine/dexmedetomidine and (*right*) ketamine/xylazine. Each session is denoted by a unique color.

The study is subject to the following limitations. First, we used ketamine with dexmedetomidine or xylazine, followed by isoflurane, instead of ketamine or inhalant anesthesia alone for induction as is most common in human patients. However, NHP studies commonly employ the anesthetics tested; therefore, the results are directly comparable to those studies. Second, the sample size was limited, although results were consistent and significant differences were found even with a relatively small effect size of 1.5 mm Hg; increasing the sample size would be unlikely to yield different results from those reported herein. That said, the results may not reflect the response of the full population of NHPs, and may not translate directly to human patients. Leveraging continuous IOP telemetry to obtain true precontact baseline IOP in an animal model that is similar to humans both anatomically and pharmacokinetically, provides unique insight into the true effects of anesthesia on IOP.

Overall, IOP changes due to injectable and inhalant anesthesia were generally small when compared to precontact baseline measurements. However, there was a significant anesthesia-related decrease in IOP of 5.4 mm Hg when compared to that measured after human contact was initiated, indicating that IOP was temporarily elevated due to acute stress (similar to a "white coat effect") and then decreased with anesthetic relaxation. This is consistent with a prior report[1] and should be considered in both experiments and clinical practice when consideration of IOP or its effects is important.

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References

1. Turner DC, Miranda M, Morris JS, Girkin CA, Downs JC. Acute stress increases intraocular pressure (IOP) in nonhuman primates. *Ophthalmol Glaucoma*. 2019;2:210–214.
2. Miyazaki Y, Matsuo T, Kurabayashi Y. Immobilization stress induces elevation of intraocular pressure in rabbits. *Ophthalmic Res*. 2000;32:270–277.
3. Jiménez R, Vera J. Effect of examination stress on intraocular pressure in university students. *Appl Ergon*. 2018;67:252–258.
4. Méndez-Ulrich JL, Sanz A, Feliu-Soler A, Álvarez M, Borràs X. Could white coat ocular hypertension affect to the accuracy of the diagnosis of glaucoma? relationships between anxiety and intraocular pressure in a simulated clinical setting. *Appl Psychophysiol Biofeedback*. 2018;43:49–56.

5. Brody S, Erb C, Veit R, Rau H. Intraocular pressure changes: the influence of psychological stress and the Valsalva maneuver. *Biol Psychol*. 1999;51:43–57.
6. Kaluza G, Strempel I, Maurer H. Stress reactivity of intraocular pressure after relaxation training in open-angle glaucoma patients. *J Behav Med*. 1996;19:587–598.
7. Sauerborn G, Schmitz M, Franzen U, Florin I. Stress and intraocular pressure in myopes. *Psychol Health*. 1992;6:61–68.
8. Jaakola ML, Ali-melkkilä T, Kanto J, Kallio A, Scheinin H, Scheinin M. Dexmedetomidine reduces intraocular pressure, intubation reponses and anaesthetic requirements in patients undergoing ophthalmic surgery. *Br J Anaesth*. 1992;68:570–575.
9. Zhou C, Zhu Y, Liu Z, Ruan L. The effects of intravenous dexmedetomidine injections on iop in general anesthesia intubation: a meta-analysis. *Biomed Res Int*. 2017;2017:1–6.
10. Abdalla MIM, Al Mansouri F, Bener A. Dexmedetomidine during local anesthesia. *J Anesth*. 2006;20:54–56.
11. Mowafi HA, Aldossary N, Ismail SA, Alqahtani J. Effect of dexmedetomidine premedication on the intraocular pressure changes after succinylcholine and intubation. *Br J Anaesth*. 2008;100:485–489.
12. Burke JA, Potter DE. The ocular effects of xylazine in rabbits, cats, and monkeys. *J Ocul Pharmacol*. 1986;2:9–21.
13. Ding C, Wang P, Tian N. Effect of general anesthetics on IOP in elevated IOP mouse model. *Exp Eye Res*. 2011;92:512–520.
14. Nagdeve NG, Yaddanapudi S, Pandav SS. The effect of different doses of ketamine on intraocular pressure in anesthetized children. *J Pediatr Ophthalmol Strabismus*. 2006:43:219–223.
15. Ausinsch B, Rayburn RL, Munson ES, Levy NS. Ketamine and intraocular pressure in children. *Anesth Analg*. 1976;55:773–775.
16. Drayna PC, Estrada C, Wang W, Saville BR, Arnold DH. Ketamine sedation is not associated with clinically meaningful elevation of intraocular pressure. *Am J Emerg Med*. 2012;30:1215–1218.
17. Halstead SM, Deakyne SJ, Bajaj L, Enzenauer R, Roosevelt GE. The effect of ketamine on intraocular pressure in pediatric patients during procedural sedation. *Acad Emerg Med*. 2012;19:1145–1150.
18. Millar JC, Pang IH. Non-continuous measurement of intraocular pressure in laboratory animals. *Exp Eye Res*. 2014;141:74–90.
19. Bunch BS TJ, Tian B, Seeman DVM JL, et al. Effect of Daily Prolonged Ketamine Anesthesia on Intraocular Pressure in Monkeys. *Curr Eye Res*. 2008;33:11–12.
20. Camras LJ, Sufficool KE, Camras CB, Fan S, Liu H, Toris CB. Duration of anesthesia affects intraocular pressure, but not outflow facility in mice. *Curr Eye Res*. 2010;35:819–827.
21. Gatson BJ, Pablo L, Plummer CE, Granone TD. Effects of premedication with sustained-release buprenorphine hydrochloride and anesthetic induction with ketamine hydrochloride or propofol in combination with diazepam on intraocular pressure in healthy sheep. *Am J Vet Res*. 2015;76:771–779.
22. Johnson TV, Fan S, Toris CB. Rebound tonometry in conscious, conditioned mice avoids the acute and profound effects of anesthesia on intraocular pressure. *J Ocul Pharmacol Ther*. 2008;24:175–185.
23. Raposo ACS, Ofri R, Schaffer DPH, et al. Evaluation of ophthalmic and hemodynamic parameters in capuchin monkeys (Sapajus sp.) submitted to dissociative anesthetic protocols. *J Med Primatol*. 2015;44:381–389
24. Downs JC, Burgoyne CF, Seigfreid WP, Reynaud JF, Strouthidis NG, Sallee V. 24-hour IOP telemetry in the nonhuman primate: implant system performance and initial characterization of IOP at multiple timescales. *Invest Ophthalmol Vis Sci*. 2011;52:7365–7375.
25. Kornblueth W, Aladjemoff L, Magora F, Gabbay A. Influence of general anesthesia on intraocular pressure in man; the effect of diethyl ether, cyclopropane, vinyl ether, and thiopental sodium. *AMA Arch Ophthalmol*. 1959;61:84–87.
26. Moses RA, Liu CH. Repeated applanation tonometry. *Am J Ophthalmol*. 1968;66:89–91.
27. Wilke K. Effects of repeated tonometry: genuine and sham measurements. *Acta Ophthalmol*. 1972;50:574–582.

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