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Article

Posture-Dependent 24-Hour Intraocular Pressure Fluctuation Patterns in an Intraocular Hypertension Monkey Model

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Purpose: We investigate 24-hour intraocular pressure (IOP) fluctuation patterns and the influence of body position on IOP in a chronic ocular hypertension (COHT) monkey model.

Methods: We recorded 24-hour IOPs (nine time points) in the different body positions in 10 eyes with normal and eight with high IOP (with random selection of one eye of each monkey) using a Tonopen. The IOPs at various time points and in different body positions were compared.

Results: The average 24-hour IOPs in the immediate-supine, 10-minute supine, 10-minute seated, and immediate-seated positions in the COHT models were 28.64 ± 9.82, 25.42 ± 7.62, 23.49 ± 7.67, and 20.53 ± 7.80 mmHg, respectively. The diurnal-to-nocturnal IOP changes were 8.51 ± 2.93, 5.81 ± 3.67, 5.48 ± 2.97, and 3.59 ± 2.74 mmHg, respectively. The sudden shift between the supine and seated positions bring greater IOP variations (8.11 ± 2.85 mmHg) in the COHT monkeys, and the IOP fluctuations reached 14 to 38 mmHg when considering body position and the measurement time points.

Conclusions: The measurement time and body position influenced IOP. More elevated IOP occurred in the immediate-supine position and during the transient shift between the seated and supine positions. Maintaining a fixed position for sufficient time before measurement is important.

Translational Relevance: Glaucoma patients should focus on the importance of IOP measurements in the clinic occurring after an adequate amount of time in a fixed body position.

Introduction

Pathologic ocular hypertension is universally acknowledged as the most important risk factor for the development and progression of glaucoma.[1,2] The role of intraocular pressure (IOP) fluctuations requires investigation because snapshot IOP measurements may be inadequate for capturing the true dynamic character of IOP. Some studies have reported that IOP changed sharply at the transition between light and dark, and IOP has a diurnal rhythm with variations in healthy individuals and a greater range of fluctuation in glaucoma patients.[3,4] Additionally, the magnitude of posture-induced IOP changes in patients has been observed in many studies.[5–7] Higher readings were found in the supine position compared to those observed in the upright position in patients with glaucoma.[8,9] The 24-hour IOP is regarded as one of the most important indicators for determining peak IOP and setting the target IOP.

Nonhuman primates have been ideal animal models to evaluate IOP-reducing drugs because they can closely mimic human glaucoma.[10–12] Accurate assessment of IOP is considered essential before using an animal model for glaucoma research, especially for evaluations of IOP-reducing drugs. Turner et al.[13] demonstrated that body position had a significant

effect on IOP and that changes persisted over time in nonhuman primates. Downs et al.[14] reported that IOP fluctuates as much as 10 mmHg day-to-day and hour-to-hour in unrestrained nonhuman primates by monitoring anterior chamber IOP with an implantable telemetric pressure transducer system. To our knowledge, no reports in the literature discuss posture-induced 24-hour IOP fluctuations in glaucoma monkey models. The IOP fluctuation pattern of nonhuman primates remains unclear, and clarifying posture-dependent 24-hour IOP fluctuation patterns in monkeys with chronic ocular hypertension (COHT) may be especially helpful.

This study was designed to establish a COHT monkey model and compare 24-hour IOP fluctuations in different body positions. Its purpose was to characterize IOP fluctuation patterns and investigate the influence of body position on IOP to improve the experimental animal model used in glaucoma research.

Material and Methods

Animals and Anesthesia

The study procedure was performed according to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Twenty adult rhesus monkeys (males, ages 4–6 years, weighing 4–8 kg) purchased from Landao Biotechnology Co., Ltd. (Guangdong, China) were used to investigate 24-hour IOP fluctuation patterns and the influence of body position on IOP. The monkeys were housed in standard animal rooms with sufficient food and water. The animal rooms were illuminated under a 12-hour light-dark cycle with a daytime light intensity of approximately 200 lux. The room was maintained under a controlled humidity (50%–55%) and temperature (24°C–25°C). The monkeys' health was monitored daily by the animal care staff and veterinary personnel. All procedures were performed under deep general anesthesia via intramuscular injection of ketamine hydrochloride (5 mg/kg, Ketalar 50; GuTian Pharmaceuticals Ltd, Fujian, China) plus chlorpromazine hydrochloride (2.5 mg/kg, chlorpromazine 50; JiaoZuo Pharmaceuticals Ltd, Tianjin, China).

Establishment of the Monkey COHT Model

Ten monkeys randomly selected from 20 healthy monkeys were regarded as the healthy control group (we randomly selected one eye from each animal). Another 10 monkeys were assigned to the COHT monkey model group. COHT was induced successfully in eight monkeys (we randomly selected one eye from each animal), while COHT induction failed in two monkeys. The primary steps in the procedure were as follows: IOP and slit-lamp examination before laser photocoagulation were performed to exclude any existing ocular disease. Pupils were sufficiently contracted (1 mm) with 1% pilocarpine eye drops (Pilocarpine; Zhongshan Ophthalmic Center, Guangdong, China). The entire circumference of the trabecular meshwork (TM) was ablated by VISULAS Trion (Carl Zeiss Meditec, Jena, Germany) using the slit-lamp delivery system and a laser gonioscope as described previously.[15,16] The laser parameters were slightly modulated as follows: 50-µm spot size, 0.5-second duration, 1000-mw laser power and 150 to 250 spots. Laser treatments were repeated for consistently high IOPs according to previous research.[17] Care was taken to photocoagulate the middle TM. Effective ablation in the TM always was confirmed by formation of a vapor bubble. Tobramycin dexamethasone (TobraDex; Alcon, Inc., Vilvoorde, Belgium) and tropicamide-phenylephrine ophthalmic solution (Mydrin; Santen Pharmaceutical, Osaka, Japan) were used to alleviate noninfectious inflammation during the immediate postlaser photocoagulation period. If the IOP was not consistently higher than 21 mmHg, additional laser photocoagulation was performed again at 3-week intervals until a stable high IOP was achieved.

Identification of the Monkey COHT Model

Color Photography

Color fundus photographs captured at 35° were performed on anesthetized animals using a retinal camera (TRC-50DX Retinal Camera; Topcon, Tokyo, Japan) with a Nikon 200 D digital camera. Pupils were sufficiently dilated (8 mm) with 0.25% tropicamide eye drops (Mydrin, Santen Pharmaceutical) and an ocular lubricating agent (Artificial Tears; Zhongshan Ophthalmic Center) was applied to preserve corneal clarity during the examination. The narrowed neuroretinal rim and enlarged optic cup were observed in the animal model.

Optical Coherence Tomography (OCT) Measurements of Retinal Nerve Fiber Layer (RNFL) Thickness

Pupils were sufficiently dilated, and corneal clarity was maintained during the examination using the same methods as those used for the color photogra-

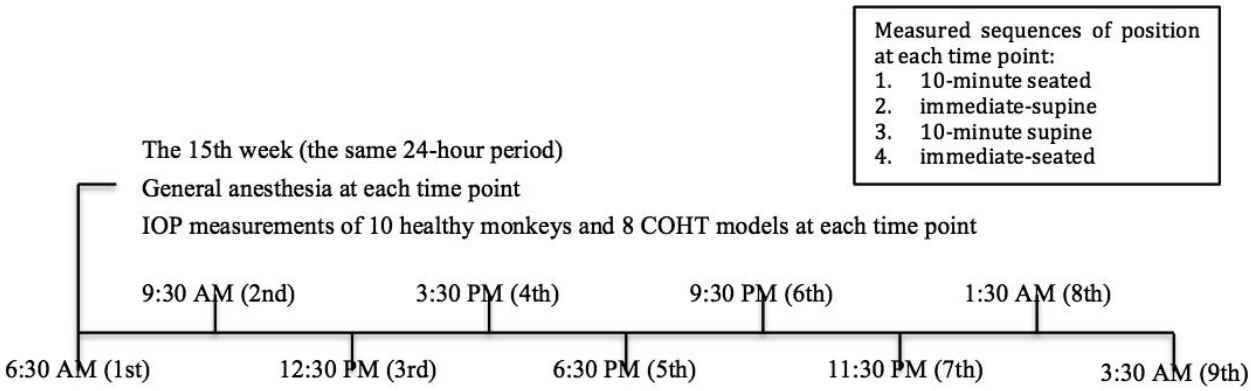

Figure 1. A brief diagram of the study design/IOP measurement.

phy measurements. Cross-sectional images of the RNFL were scanned with the circular scan (3.4-mm diameter) procedure using the STRATUS OCT Instrument (Model 3000; Carl Zeiss Meditec). The damaged RNFL thickness was examined in the animal model.

Central Corneal Thickness (CCT) Assessment

Anterior segment OCT (AS-OCT; Fourier OCT, Carl Zeiss Meditec) was used to measure CCT before the first laser photocoagulation procedure to exclude the effect of the corneal thickness of the animals on IOP measurements. A procedure using the four-line scan model of the cornea was applied. The line was centered on the corneal vertex based on horizontal, vertical, 45°, and 135° scans. The animals' eye positions and the scan lines were carefully observed through the central cornea.

Twenty-Four-Hour IOP Measurements

The 24-hour IOP measurements in different body positions (Fig. 1) were conducted at week 15 after the first photocoagulation procedure, using the Tonopen XL (Reichert, Depew, NY) tonometer in anesthetized animals according to the manufacturer's recommended procedures. According to our previous study,[17] the monkeys' high IOP was sustained for 3 to 6 weeks, and some problems, such as transient IOP increases and corneal edema, were observed in the early period after photocoagulation. To reduce the measurement bias from these problems as much as possible, 24-hour IOPs were measured when the ocular condition stabilized with a high IOP. To maintain high IOPs, every monkey received multiple laser treatments, and some monkeys experienced severe IOP spikes. Additional laser photocoagulation was not performed in the COHT animal models once stable high IOPs were achieved and laser-induced ocular noninfectious inflammation and corneal edema had gradually disappeared. The fifth week after the first photocoagulation procedure was selected as the IOP measurement time point. At that time, the IOP gradually decreased to approximately 21 mmHg. Different IOPs were observed in the 24-hour period because of the animal models' IOP fluctuations.[14]

Considering that the IOPs of the animals were measured under deep general anesthesia, the time points over 24 hours were adjusted.[18] For the diurnal measurements, IOPs were measured every 3 hours at 6:30 and 9:30 AM, and 12:30, 3:30, 6:30, and 9:30 PM (Beijing time). For the nocturnal measurements, IOPs were measured every 2 hours at 11:30 PM, and 1:30 and 3:30 AM. Light intensity was maintained at 500 to 1000 lux in the daytime, and lights were turned off at 11:00 PM. The room light was maintained at less than 10 lux when only nocturnal IOPs were measured.

The position sequence for IOP measurements was as follows: 10 minute-seated, immediate-supine, 10-minute supine, and immediate-seated. The seated posture of the animals was maintained by seating the animals in a custom-designed chair with the bodies gently restrained, while the supine posture with the face up was maintained by laying the animals on a wide table. The IOP was measured by another operator.

The healthy control and COHT groups were maintained on a daily 8-hour sleep routine before the IOP measurements. All IOPs were measured without topical anesthesia. An experienced operator completed all IOP measurements in this experiment, and the Tonopen was calibrated before each measurement. Ten consecutive IOP readings using the Tonopen tonometer for each measurement were acquired, and the average IOP value was calculated

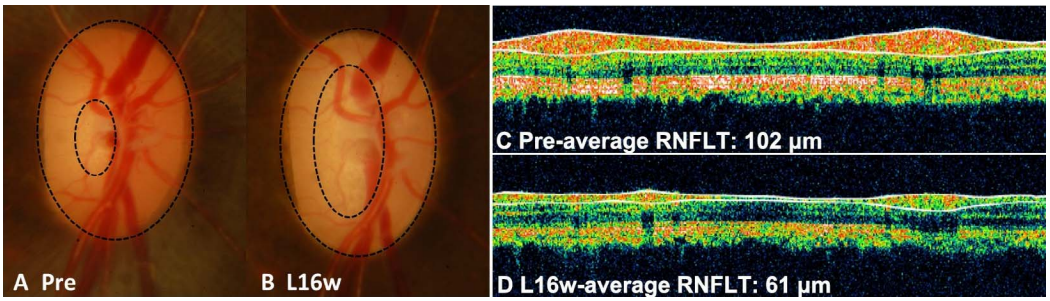

Figure 2. COHT monkey model. (A) The optic cup before laser treatment. (B) The enlarged optic cup after laser treatment (16th week). (C) Average RNFL thickness before laser treatment. (D) Average damaged RNFL thickness after laser treatment (16th week).

automatically. Only consecutive readings with minimal variation (<3 mmHg) at one time point were regarded as valid measurements.

Statistical Analysis

Statistical analyses were performed using SPSS software (Version 13.0; SPSS, Inc., Chicago, IL). Pearson's r coefficient of correlation was used to evaluate CCT and IOP measurements. Comparisons of IOP values at various time points and in different body positions between the healthy monkeys and COHT models were tested with 2-tailed paired Student's t-tests. Deviation was considered significant at $P \leq 0.05$. Data are expressed as mean ± standard deviation (SD). All figures were generated by GraphPad Prism 5.0 (Prism 5.0; GraphPad Software, Inc., San Diego, CA).

Results

Average IOP and CCT values of 20 monkey eyes were 13.35 ± 3.01 mmHg and 487.50 ± 25.93 μm, respectively. The correlation coefficient (r^2) between CCT and IOP was 0.402 ($P = 0.079$; $Y = -9.45 + 0.05X$; $r^2 = 1.16$; $P > 0.05$). No significant correlation was found between CCT and average IOP in this study. Eight eyes from 10 animals were established successfully as COHT monkey models with a dramatically increased cup-to-disc ratio and damaged RNFL thickness (Fig. 2). The 24-hour IOP fluctuations of the eight animal models and 10 eyes of the healthy control group were measured and analyzed.

Figure 3 shows the 24-hour IOP patterns in different body positions for both groups. The IOP peaks occurred at 3:30 PM, and the troughs occurred between 11:30 PM and 1:30 AM. The IOPs at all time points in the immediate-supine position were the highest, followed by the 10-minute supine, 10-minute seated, and immediate-seated positions. In the healthy

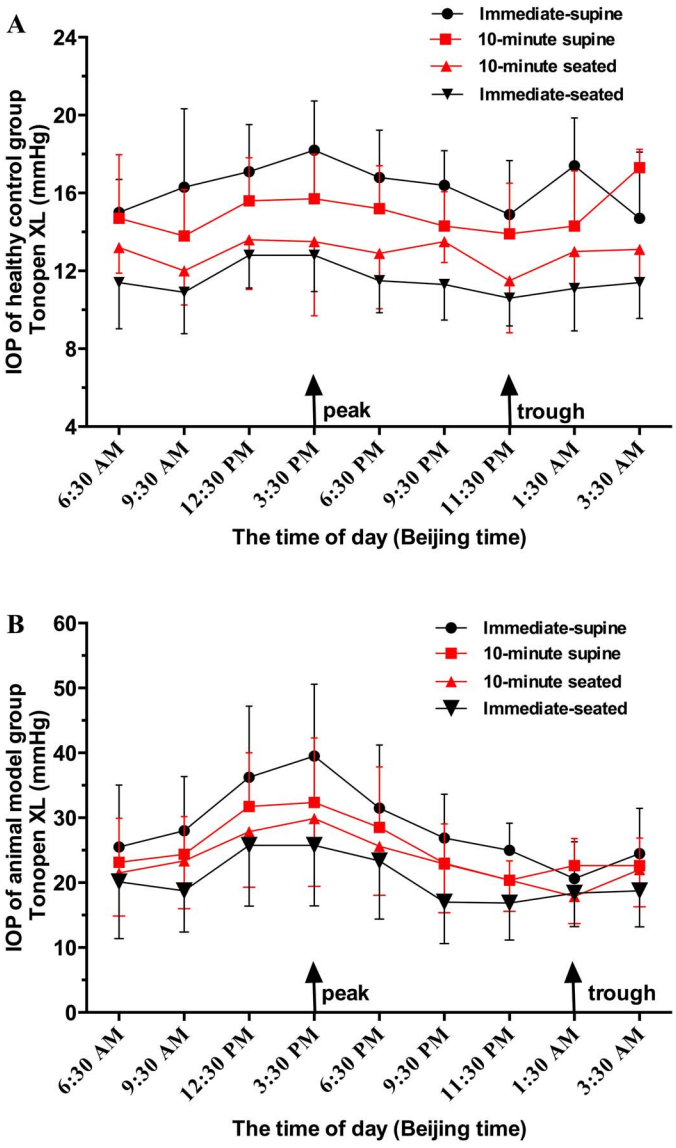

Figure 3. The 24-hour IOP fluctuation curves of different body positions. (A) healthy monkey. (B) Monkey models with COHT.

Table 1. Peak-to-Trough Changes in IOP

Group	Body Position/IOP, mmHg	3:30 PM	11:30 PM/1:30 AM	Change[a]	*t*	*P*
Healthy control	Immediate-supine	18.20 ± 2.53	14.90 ± 2.77	3.30 ± 4.13	2.52	0.033
	10-minute supine	15.70 ± 2.31	13.90 ± 2.60	1.80 ± 2.49	2.29	0.048
	10-minute seated	13.50 ± 3.81	11.50 ± 2.68	2.00 ± 5.14	1.23	0.250
	Immediate-seated	12.80 ± 1.87	10.60 ± 1.43	2.20 ± 2.30	3.03	0.014
Animal model	Immediate-supine	39.50 ± 11.07	20.63 ± 5.68	18.88 ± 8.06	6.62	0.000
	10-minute supine	32.38 ± 9.97	22.63 ± 4.17	9.75 ± 6.71	4.11	0.005
	10-minute seated	29.88 ± 10.47	17.88 ± 4.16	12.00 ± 7.46	4.55	0.003
	Immediate-seated	25.75 ± 9.32	18.38 ± 5.18	7.38 ± 5.01	4.16	0.004

Data are expressed as mean ± SD.
[a] Change, IOP (3:30 PM minus 11:30 PM/1:30 AM).

control group, the average 24-hour IOPs in the immediate-supine, 10-minute supine, 10-minute seated, and immediate-seated positions were 16.31 ± 2.82, 14.98 ± 2.50, 12.92 ± 2.31, and 11.53 ± 1.96 mmHg, respectively, and the corresponding average 24-hour IOPs in the COHT monkey group were 28.64 ± 9.82, 25.42 ± 7.62, 23.49 ± 7.67, and 20.53 ± 7.80 mmHg, respectively.

The peak-to-trough changes in IOP are summarized in Table 1. The changes in the animal model group were significantly greater than those in the healthy control group. The IOP change was greatest in the immediate-supine position, followed by 10-minute seated, 10-minute supine, and then immediate-seated positions. IOP fluctuations became larger as the IOP increased.

Mean diurnal and nocturnal IOPs for both groups are summarized in Table 2. Mean diurnal and nocturnal IOPs were significantly higher in the COHT model group than those in the healthy control group. The average value was slightly higher in the immediate-supine position than in the other three body positions in both groups. Diurnal IOPs were higher than nocturnal IOPs in all four body positions in both groups. No statistically significant difference was found between the diurnal-to-nocturnal IOP changes in the four body positions in the healthy control group, while the changes in the COHT animal models in the immediate-supine, 10-minute supine, 10-minute seated, and immediate-seated positions were 8.51 ± 2.93, 5.81 ± 3.67, 5.48 ± 2.97, and 3.59 ± 2.74 mmHg, respectively.

Table 3 summarizes the changes in IOP upon awakening and before sleep (6:30 AM and 9:30 PM). No obvious differences were observed in the four body positions in both groups (–0.30–3.13 mmHg).

Tables 4 to 6 compare the effects of body positions on IOP in both groups. No obvious differences were found in the average IOP of the healthy control group when the body position changed over time (1.33–2.06 mmHg). Slightly higher IOP was observed in the COHT model group when the body position changed from immediate-supine to 10-minute supine (3.22 mmHg) or from immediate-seated to 10-minute

Table 2. Mean Diurnal and Nocturnal IOP

Group	Body Position/IOP, mmHg	Diurnal, 7 AM–11 PM	Nocturnal, 11 PM–7 AM	Change[a]	*t*	*P*
Healthy control	Immediate-supine	16.96 ± 2.72	15.50 ± 2.78	1.46 ± 1.48	3.13	0.012
	10-minute supine	14.92 ± 2.23	15.05 ± 2.81	−0.13 ± 1.76	−0.23	0.821
	10-minute seated	13.10 ± 2.55	12.70 ± 1.99	0.40 ± 1.76	0.72	0.491
	Immediate-seated	11.86 ± 1.94	11.13 ± 1.94	0.74 ± 1.33	1.75	0.114
Animal model	Immediate-supine	32.43 ± 10.26	23.91 ± 6.84	8.51 ± 2.93	8.22	0.000
	10-minute supine	28.00 ± 8.55	22.19 ± 4.65	5.81 ± 3.67	4.48	0.003
	10-minute seated	25.93 ± 8.38	20.44 ± 5.41	5.48 ± 2.97	5.23	0.001
	Immediate-seated	22.13 ± 8.59	18.53 ± 6.25	3.59 ± 2.74	3.71	0.008

Data are expressed as mean ± SD.
[a] Change, IOP (diurnal minus nocturnal).

Table 3. Changes in IOP upon Awakening and Before Sleep

Group	Body Position/IOP, mmHg	6:30 AM	9:30 PM	Change[a]	*t*	*P*
Healthy control	Immediate-supine	15.00 ± 1.70	13.05 ± 1.08	1.50 ± 2.64	1.80	0.105
	10-minute supine	14.70 ± 3.27	14.30 ± 1.77	0.40 ± 2.12	0.60	0.565
	10-minute seated	13.20 ± 1.32	13.50 ± 1.08	−0.30 ± 1.49	−0.64	0.541
	Immediate-seated	11.40 ± 2.37	11.30 ± 1.83	0.10 ± 2.02	0.16	0.879
Animal model	Immediate-supine	25.50 ± 9.56	26.88 ± 6.77	−1.38 ± 6.59	−0.59	0.574
	10-minute supine	23.13 ± 6.79	23.00 ± 6.05	0.13 ± 4.76	0.07	0.943
	10-minute seated	21.50 ± 6.65	22.87 ± 7.51	−1.38 ± 4.07	−0.96	0.371
	Immediate-seated	20.13 ± 8.76	17.00 ± 6.39	3.13 ± 3.72	2.38	0.049

Data are expressed as mean ± SD.
[a] Change, IOP (6:30 AM minus 9:30 PM).

seated (2.96 mmHg). Greater IOP variations (8.11 ± 2.85 mmHg) were observed in the animal models when the body position changed suddenly (the shift from immediate-supine to immediate-seated positions), which were obviously higher than those in the healthy control group. However, slight IOP variations (1.93 ± 1.98 mmHg) were observed when the animal models' body position changed between 10-minute supine and 10-minute seated.

Figure 4 shows the greatest fluctuation values considering the measurement time points and body position in both groups. The IOP deviation was 4 to 14 mmHg for the healthy control group and 14 to 38 mmHg for the animal model group.

Discussion

To our knowledge, this is the first study reporting 24-hour IOP fluctuations in different body positions in a COHT monkey model. Its purpose was to characterize the 24-hour IOP fluctuation patterns and investigate the influence of body position on IOP to improve this experimental animal model for use in glaucoma research.

Yu et al.[19] reported that the lowest IOP values occurred at noon and 6:00 PM, while the IOP peaked at 3:00 and 9:00 PM in normotensive eyes of monkeys, and 24-hour IOP fluctuations showed only a small difference (1.2 mmHg). Other studies also showed that monkeys' peak IOPs occurred between 2:00 and 4:00 PM.[20,21] During a previous 6-hour study (from 7:00 AM to 1:00 PM), the IOP variation in nonhuman primate models with laser-induced ocular hypertension was significantly greater than that in normotensive eyes.[22] Our study found similar results in the peak (3:30 PM) and trough (between 11:30 PM and 1:30 AM) IOP. The average 24-hour IOPs (16.31 ± 2.82, 14.98 ± 2.50, 12.92 ± 2.31, and 11.53 ± 1.96 mmHg for the immediate-supine, 10-minute supine, 10-minute seated, and immediate-seated positions, respectively) were determined in the healthy monkeys, and higher values (28.64 ± 9.82, 25.42 ± 7.62, 23.49 ± 7.67, and 20.53 ± 7.80 mmHg, respectively) were observed in the COHT monkey models. Other clinical studies also have reported this finding. Grippo et al.[23] investigated the peak IOP time points (OHT patients, 3:30 PM [supine], 1:30–3:30 AM [seated]; healthy control and glaucoma patients, awaking [supine and seated]) and the trough IOP that occurred at 9:30 PM in all three groups. They also reported that seated and supine IOPs at all time points were higher in the OHT than in the healthy control and glaucoma groups. Cheng et al.[24] reported

Table 4. The Difference in Average IOP (Body Position Change for 10 Minutes)

Group	Body Position/IOP, mmHg	Average IOP	Change[a]	*t*	*P*
Healthy control	10-minute supine	14.98 ± 1.51	2.06 ± 1.98	3.28	0.009
	10-minute seated	12.92 ± 1.13			
Animal model	10-minute supine	25.42 ± 5.65	1.93 ± 1.98	2.76	0.028
	10-minute seated	23.49 ± 6.51			

Data are expressed as mean ± SD.
[a] Change, IOP (10-minute supine minus 10-minute seated).

Table 5. The Difference in Average IOP (the Same Body Position Changed Suddenly)

Group	Body Position/IOP, mmHg	Average IOP	Change[a]	*t*	*P*
Healthy control	Immediate-supine	16.31 ± 1.51	1.33 ± 1.26	3.35	0.009
	10-minute supine	14.98 ± 1.51			
	10-minute seated	12.92 ± 1.13	1.39 ± 1.54	2.85	0.019
	Immediate-seated	11.53 ± 1.17			
Animal model	Immediate-supine	28.64 ± 7.26	3.22 ± 1.78	5.13	0.001
	10-minute supine	25.42 ± 5.65			
	10-minute seated	23.49 ± 6.51	2.96 ± 0.88	9.47	0.000
	Immediate-seated	20.53 ± 6.79			

Data are expressed as mean ± SD.
[a] Change, IOP (immediate-supine minus 10-minute supine); IOP (10-minute seated minus immediate-seated).

that IOP decreased during the diurnal period and increased progressively during the nocturnal period, with the peak IOP occurring from 2:00 to 10:00 AM. They also reported that the IOP parameters (mean, peak, and trough IOP, and IOP fluctuations) were significantly higher in hypertension glaucoma subjects ($P < 0.001$) than those in normotensive glaucoma subjects. Liu et al.[25] also reported that mean diurnal IOPs (seated and supine) were significantly higher in the glaucoma than in the control groups. Though these published studies have different estimations of IOP peaks/troughs in healthy control/ocular hypertension/glaucoma patients, the findings indicated that in glaucoma patients, some IOP parameters (diurnal IOP, IOP fluctuation, and so forth.) are significantly higher than those in normal controls. The 24-hour IOP fluctuations in nonhuman primates and COHT animal models in our experiment showed many similarities to those of glaucoma patients, which not only is beneficial for glaucoma animal experimental research, but also provides a basis for guiding clinical practice.

The greatest novelty in this study appears to be the investigation of 24-hour IOP fluctuations in four body positions in COHT monkey models. Previous studies have reported 24-hour IOP fluctuations in nonhuman primates and orthostatic IOP changes. Turner et al.[13] reported that IOP in the standing and seated positions of healthy nonhuman primates decreased by 1.5 and 2.2 mmHg, respectively, compared to that in the supine position, reflecting the first report of IOP changes in different body positions using continuous IOP measurement techniques. Downs et al.[14] reported that IOP fluctuates as much as 10 mmHg day-to-day and hour-to-hour in nonhuman primates using an implantable telemetric pressure transducer system. Continuous IOP monitoring techniques and equipment were used in both studies, but to our knowledge no studies have examined the effects of body position and various measurement time points on IOP. Additionally, most previous research investigated IOP changes in healthy nonhuman primates rather than glaucoma animal models. In our study, the peak-to-trough

Table 6. The Difference in Average IOP (the Different Body Positions Changed Suddenly)

Group	Body Position/IOP, mmHg	Average IOP	Change[a]	*t*	*P*
Healthy control	Immediate-supine	16.31 ± 1.51	4.78 ± 1.38	10.95	0.000
	Immediate-seated	11.53 ± 1.17			
	10-minute supine	14.98 ± 1.51	2.06 ± 1.98	3.28	0.009
	10-minute seated	12.92 ± 1.13			
Animal model	Immediate-supine	28.64 ± 7.26	8.11 ± 2.85	8.04	0.000
	Immediate-seated	20.53 ± 6.79			
	10-minute supine	25.42 ± 5.65	1.93 ± 1.98	2.76	0.028
	10-minute seated	23.49 ± 6.51			

Data are expressed as mean ± SD.
[a] Change, IOP (immediate-supine minus immediate-seated); IOP (10-minute supine minus 10-minute seated).

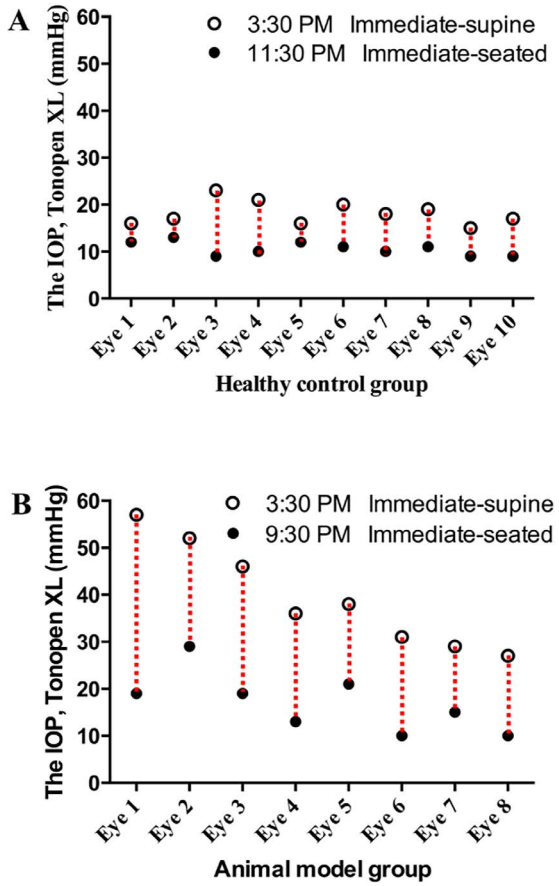

Figure 4. The largest IOP fluctuation values considering the measured time point and body position. (A) Healthy monkey. (B) Monkey models with chronic ocular hypertension.

changes in IOP, diurnal IOP, nocturnal IOP, and diurnal-nocturnal changes in IOP were significantly higher in the immediate-supine body position, especially in the animal model. Figure 4 shows that the IOP fluctuation reached 14 to 38 mmHg for the animal model group when considering the factors of body position and measurement time points. Therefore, the influence of IOP measurement time points and body positions should be considered. IOP should be measured at a fixed time point (especially not the peak or trough) when using the COHT model for experiments. Additionally, the immediate-supine position yielded greater standard deviations in both groups, and when the body position was changed for a sufficient amount of time (10-minute supine and 10-minute seated), the IOP values were more stable. Therefore, maintaining a fixed position for a sufficient amount of time before measurement is helpful to obtain a more accurate IOP in animal experiments.

Some clinical studies[26,27] reported an elevated IOP when the body position switched from seated to supine in healthy volunteers. Greater differences in IOP were observed in an inverted body position in glaucoma patients and patients with suspected glaucoma, but not in normal subjects.[28] Prata et al.[28] reported a wide range of IOP differences (1.6–8.6 mmHg) when changing from a seated/upright to a horizontal position. Kim et al.[29] determined that the IOP of the worse eye was significantly higher than that of the better eye in the supine position (16.8 ± 3.0 vs. 15.1 ± 1.8 mmHg; $P < 0.001$). Lee et al.[30] demonstrated that the postural change from the supine to the lateral decubitus position may increase the IOP of the dependent eye in patients with open-angle glaucoma. Similar to published literature, our results further found that changing the body position led to greater differences in IOP, especially in the COHT models whose positions suddenly were changed. The transient shift between supine and seated positions in the animal model caused an IOP change of 8.11 ± 2.85 mmHg, which is obviously higher than that in the healthy control group. Additionally, only a mild IOP variation of 1.93 ± 1.98 mmHg occurred during a body position change from 10-minute supine to 10-minute seated. A clinically significant increase in IOP can be found when suddenly moving from an upright to a horizontal or inverted body position. A few case reports have documented a significant disease progression in patients who routinely had practiced the Sirsasana yoga posture for several years.[31,32] However, this finding is limited to clinical case reports and has not been appropriately confirmed. This finding reminded us of another type of popular shaping exercise in China known as the "sit-up." Whether sit-ups, with repeated lying down and sitting up, can lead to IOP changes and glaucoma disease progression in glaucoma patients requires further investigation. It is recommended that glaucoma patients should focus on the importance of IOP measurement in the clinic occurring after an adequate period of fixed body position, which is conducive to monitoring and follow-up of glaucoma disease progression.

The use of anesthetized animals as experimental subjects is a flaw of this study. In the clinic, IOP is likely to be influenced by anesthetic drugs, with the possible exception of ketamine.[33–35] However, ketamine sedation and ketamine-pentobarbital anesthesia caused elevated IOP in rabbits/cats/Syrian hamsters.[36–38] Currently, no reference has been found regarding how anesthesia acts on the IOP of

nonhuman primates. The role of ketamine in IOP in human surgery and animal anesthesia remains controversial. Anesthesia is difficult to avoid in animal research. In this study, IOP measurements were performed in anesthetized monkeys (an intramuscular injection of ketamine hydrochloride plus chlorpromazine hydrochloride), without topical anesthesia. The animals were re-anesthetized before each IOP measurement in the study. Thus, all IOP measurements were affected by anesthesia, but the effect of anesthesia on IOP may have little impact on the conclusions of this study.

Conclusions

In summary, measurement time points and body position influence IOP. The animal models had greater IOP fluctuations compared to healthy monkeys. More pronounced IOP elevation occurred in the immediate-supine position and during the transient change between seated and supine positions. Keeping a fixed position for a sufficient amount of time before measurements is helpful to obtain a more accurate IOP for that specific position. Glaucoma patients should focus on the importance of IOP measurement in the clinic occurring after an adequate period of fixed body position.

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