

Observation seasonal variation of intraocular pressure in young healthy volunteers

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Abstract

• **AIM:** To investigate fluctuation of intraocular pressure (IOP) and seasonal variation of 24-hour IOP during one year in healthy participants

• **METHODS:** Totally 13 young healthy volunteers participated in this study. IOP was measured with Canon TX-20 at about 8:00-9:00 a.m. from Monday to Friday every week for a whole year. They also underwent 24-hour IOP examination every three months. Blood pressure, heart rate, temperature, humidity, atmosphere pressure, sunshine duration and other environment parameters were recorded.

• **RESULTS:** The yearly fluctuation curve showed IOP in the summer months were lower than other seasons. In the multivariable generalized estimating equation analysis, IOP had a negative correlation with both temperature and sunshine duration ($P < 0.05$). There also was a seasonal effect on 24-hour IOP. However, all intraclass correlation coefficients values of minimum, maximum and average of the 24-hour IOP and each individual IOP were less than 0.30.

• **CONCLUSION:** IOP is trend to be higher in cold days than warm days. IOP have negative association with both environmental temperature and duration of sunshine. On a season-to-season basis, 24-hour IOP is not highly reproducible in healthy volunteers.

• **KEYWORDS:** intraocular pressure; season; temperature; sunshine duration

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INTRODUCTION

It is recognized that intraocular pressure (IOP) measurements play an important role in diagnosis and management of some ocular diseases, especially those related to IOP elevation. Considering the factor that IOP does not have a constant value, many glaucoma researchers have conducted studies to characterize its short/long-term variations in order to better understand the mechanisms of glaucomatous damage and its potential contributory factors^[1-2]. Previous reports demonstrated that IOP was not strictly consistent during one day and tended to peak early in the morning and decline over time^[3]. The instability of 24-hour IOP fluctuations in young healthy subjects were also confirmed in a previous study^[4]. Moreover, fluctuations in diurnal IOP were considered as independent risk factors for the progression of glaucoma^[5-6]. There are some studies focus on the variations of IOP through a whole year, however, lack of consecutive recording IOP for a long time other than that from each month during the year^[7]. Yearly IOP distribution depends on many internal and environmental factors. Nevertheless, there is still some debate as to the risk factors associated IOP, such as blood pressure^[8-9]. The objective of this study was to evaluate the daily fluctuation of IOP, potential associated factors and the variations of 24-hour IOP during each season.

SUBJECTS AND METHODS

Ethical Approval The prospective study was approved by the Institutional Review Board of Wenzhou Medical University and in accordance with the tenets of the Declaration of Helsinki. All participants enrolled in the study signed written informed consents.

Thirteen healthy volunteers (7 females and 6 males) were recruited. Each subject received a comprehensive ophthalmic examination including slit-lamp and ophthalmoscopy examination, and no participant demonstrated any signs of ophthalmic and/or systemic diseases or had a family history of glaucoma. Central corneal thickness and axial

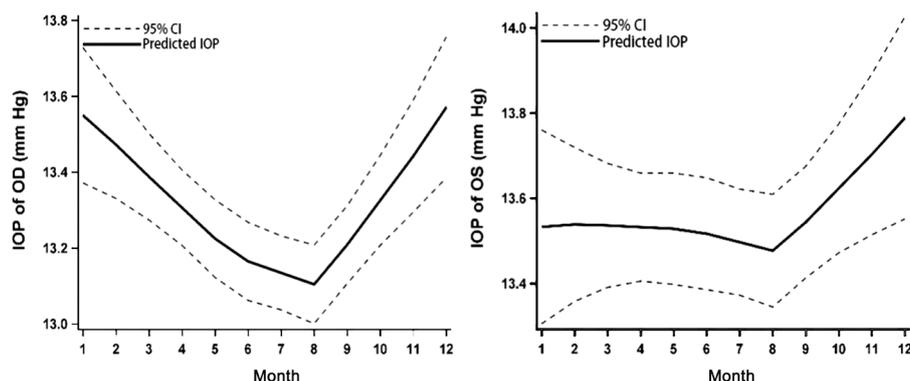


Figure 1 Fluctuation of predicted IOP with time during a whole year.

length were evaluated using Lenstar LS 900 (Haag Streit, Koeniz, Switzerland). Blood pressure was measured using electronic sphygmomanometer (HEM-8102A, Omron, China). Sphygmus, respiration and heart rate were also recorded before IOP evaluations. Additionally, to determine IOP patterns in the participants' daily lives, they were not hospitalized and their sleep cycles were not controlled. Subjects were allowed to continue with their lives as normal and maintained their regular eating habits. The spring term was from 4th February to 4th May, summer from 5th May to 6th August, autumn from 7th August to 6th November and winter from 7th November to 3rd February.

Intraocular Pressure Measure Procedures The IOP measurements were taken with Cannon TX-20 tonometer (Canon Inc., Tokyo, Japan) at a fixed time from 8:00 *a.m.* to 9:00 *a.m.* to minimize the effect of diurnal variations. IOP was measured after subject had been seated for at least 5 min. The measurement procedure was automated by default and only done manually if there was any difficulty achieving results. During each visit, three measurement series within a maximum range of 3 mm Hg were obtained and the mean corrected IOPs were documented. The 24-hour IOP measurements were taken every 4h over a 24-hour period (2:00 *a.m.*, 6:00 *a.m.*, 10:00 *a.m.*, 2:00 *p.m.*, 6:00 *p.m.*, 10:00 *p.m.*) one day out of each season. Four parameters of maximum, minimum, average and daily fluctuations were determined for IOP each day of the 24-hour IOPs. Daily fluctuation was defined as the difference between the maximum and minimum measurements in the study period. Meanwhile temperature, humidity, atmosphere pressure, sunshine duration and other environment parameters were recorded. They were in accordance with the WenZhou Bureau of Meteorology report^[10]. To avoid bias, clinicians had no knowledge of prior IOP values.

Statistical Analysis Stata 15.1 (StataCorp College Station, Texas 77845 USA) was used for the data management, data analysis and figure drawing. Principle component analysis was applied to reduce the dimension of the data and avoid potential collinearities among confounding factors. Multiple locally

weighted scatterplot smoothing models were first performed to assess the relationship between IOP and the month when data were collected. Then the multivariable generalized estimating equation (GEE) models were conducted to evaluate the association between the IOP and internal/environmental factors since it is a typical repeated measure designed study. Besides, intra-class correlation coefficients (ICCs) were also calculated to individually assess the reproducibility of the 24-hour IOP (maximum, minimum, average, daily fluctuation). All the above-mentioned hypothesis tests were two-sided and the significant level was set as 0.05.

RESULTS

Thirteen healthy young Chinese volunteers were enrolled in this study. The characters of these participants are shown in Table 1. This survey began in 30th December, 2013 and lasted until 9th January, 2015. The lowest IOP was obtained during summer and the deviation between the lowest and highest IOP was an average of 0.4-0.5 mm Hg. Figure 1 shows both eyes' fitting curves yearly IOP fluctuation. It demonstrates that the winter months IOP (7th November to 3rd February) are higher than those in the spring (4th February to 4th May), summer (5th May to 6th August), and autumn months (7th August to 6th November).

The principle component analysis revealed that the combination of the former principle components (Z_1 =age, Z_2 =pulse, Z_3 =gender, Z_4 =breathe, and Z_5 =humidity) had contributed 84.33% variances of the potential confounders. Thus, we adjusted for these five principle components in the following multivariable regression models. In this typical repeated measure designed study, we performed a GEE analysis using IOP yearly fluctuation to evaluate the relationship between IOP and individual/environmental factors (systolic blood pressure, diastolic blood pressure, pulse rate, breathe, temperature, wind, atmosphere, visibility, daily rain, humidity and sunshine duration). IOP had a negative correlation with temperature and sunshine duration (Table 2). There was no significant relationship with other individual/environmental confounding factors. When evaluating temperature, IOP was significantly

Table 1 Demographics of participants

Parameters	Total	Spring	Summer	Autumn	mean±SD
					Winter
<i>n</i>	13	-	-	-	-
Age (y)	24.1±2.9	-	-	-	-
Gender (M/F)	7/6	-	-	-	-
CCT_OD (μm)	525.8±39.2	-	-	-	-
CCT_OS (μm)	526.8±39.3	-	-	-	-
AL_OD (mm)	24.5±1.4	-	-	-	-
AL_OS (mm)	24.5±1.4	-	-	-	-
Refraction, OD (D)	-2.4±2.0	-	-	-	-
Refraction, OS (D)	-2.6±2.1	-	-	-	-
Adjusted IOP, OD (mm Hg)	14.1±1.9	13.5±2.0	12.9±1.9	13.3±2.1	13.5±2.3
Adjusted IOP, OS (mm Hg)	14.0±3.4	13.7±2.6	13.3±2.6	13.5±2.6	13.6±2.9
Sbp (mm Hg)	111.8±10.0	106.4±11.0	103.8±9.6	105.1±9.1	106.5±9.1
Dbp (mm Hg)	68.2±5.8	62.9±7.5	61.6±7.2	63.5±23.7	66.0±20.0
Breath (breaths/min)	14.2±2.0	12.1±1.8	11.8±1.5	11.6±1.7	12.4±2.0
Pulse (beats/min)	83.8±12.4	79.9±9.3	78.6±8.6	77.9±9.3	80.6±10.4
Temperature (°C)	6.1±1.9	15.7±4.1	25.7±2.1	19.2±4.7	6.8±3.7
Humidity (%)	71.7±15.3	86.1±9.0	86.0±12.5	79.2±9.7	74.3±16.5
Atmosphere (MPa)	1018.2±2.6	1012.8±5.8	1003.2±3.7	1015.4±5.7	1022.5±4.7
Wind scale (0-17)	3.2±1.9	4.8±2.9	5.4±2.6	4.8±2.4	4.6±2.5
Visibility (m)	45.3±27.7	38.6±39.7	64.2±61.9	69.9±55.6	86.4±80.1
Daily rain (mm)	0.5±1.2	0.3±1.0	0.1±0.4	0.0±0.1	0.0±0.0

CCT: Central corneal thickness; AL: Axial length; IOP: Intraocular pressure; Sbp: Systolic blood pressure; Dbp: Diastolic blood pressure.

Table 2 Generalized estimating equation model analysis of correlated factors with intraocular pressure (OD)

Variable	<i>n</i>	Mean±SD	Crude			Adjusted		
			β	SE	<i>P</i>	β	SE	<i>P</i>
Temperature								
-0.4°C-11.6°C	663	13.5±2.3	0.0	0.0		0.0	0.0	
11.7°C-17.0°C	649	13.4±2.1	-0.1	0.2	0.532	-0.3	0.2	0.180
17.1°C-23.9°C	649	13.2±2.0	-0.4	0.2	0.121	-0.7	0.3	0.018
24.0°C-29.7°C	657	13.0±1.9	-0.5	0.3	0.058	-0.9	0.4	0.012
Trend test					<0.001			<0.001
Sunshine duration								
37324.0-39673.0s	649	13.6±2.2	0	0.0		0.0	0.0	
39674.0-44229.0s	649	13.2±2.2	-0.4	0.2	0.036	-0.2	0.2	0.305
44230.0-48241.0s	651	13.4±2.0	-0.2	0.2	0.338	-0.0	0.2	0.983
48242.0-050110.0s	654	13.0±2.0	-0.6	0.2	0.006	-0.5	0.2	0.038
Trend test					<0.001			0.003

Adjusted for: Z₁ (age), Z₂ (pulse), Z₃ (gender), Z₄ (breathe), and Z₅ (humidity), which indicated the five principle components.

lower on hotter days ($\beta=-0.9$, $P=0.012$, temperature $>24^{\circ}\text{C}$). The calculated β -value is rising with increasing of the sunshine duration, it gets to -0.5 when day length is above 48242.0s (about 13.5h). Moreover, the trend tests show statistically significant findings in temperature and sunshine duration.

The mean maximum/minimum/average/fluctuation values of IOP and IOP of every time point were described in Figures 2 and 3. There also was a seasonal effect on 24-hour IOP, the minimum, maximum, and average IOP measurements during the summer months (May 5th to August 6th) were

significantly lower than those during the winter months (November 7th to February 3rd). Descriptive data and ICCs of the 24-hour IOP measurements were summarized in Table 3. All ICC values were below 0.30.

DISCUSSION

To our knowledge, this is the first time to address the seasonal IOP change with one year-long daily IOP measurement and that greatly demonstrated that IOP is lowest in summer.

There are many studies related to the effects of climatic changes on IOP, whether in normal or in glaucoma patients^[7,11]. Such

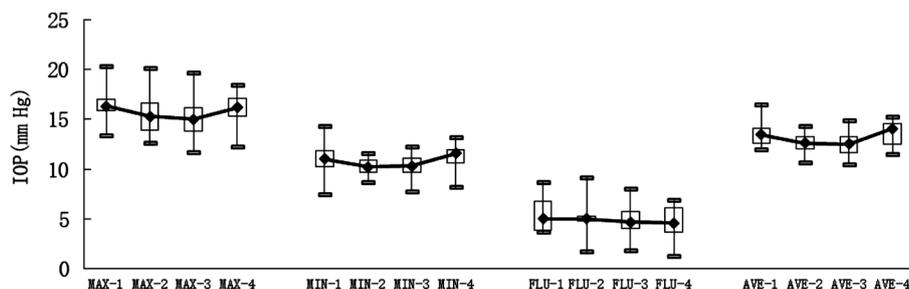


Figure 2 The maximum/minimum/fluctuation/average values of IOP MAX: Maximum; MIN: Minimum; FLU: Fluctuation; AVE: Average; 1: Spring; 2: Summer; 3: Autumn; 4: Winter.

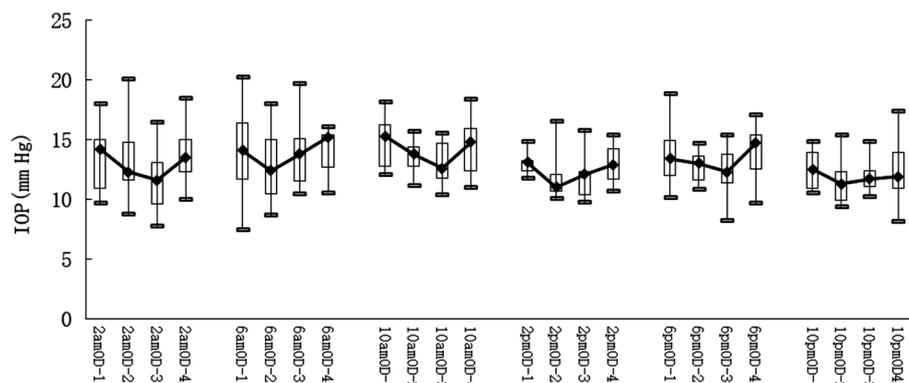


Figure 3 Every time point values of IOP 1: Spring; 2: Summer; 3: Autumn; 4: Winter.

Table 3 Intraclass correlation coefficients for comparison of intraocular pressure parameters for seasons among healthy young individuals *n*=13

Parameters	IOP for each individual (mm Hg)	ICC values	<i>P</i>
Maximum	11.7 to 20.3	0.152 (-0.07 to 0.501)	0.104
Minimum	7.5 to 14.3	0.224 (-0.019 to 0.570)	0.038
Average	10.5 to 16.5	0.263 (0.011 to 0.604)	0.002
Fluctuation ^a	1.3 to 9.2	0.016 (-0.157 to 0.345)	0.471
2 a.m.	7.8 to 20.1	0.126 (-0.088 to 0.474)	0.143
6 a.m.	7.5 to 20.3	0.159 (-0.065 to 0.509)	0.094
10 a.m.	10.4 to 18.4	0.094 (-0.109 to 0.440)	0.204
2 p.m.	9.8 to 16.6	0.109 (-0.099 to 0.457)	0.173
6 p.m.	8.3 to 18.9	0.174 (-0.055 to 0.265)	0.078
10 p.m.	8.2 to 17.4	-0.017 (-0.176 to 0.302)	0.525

^aDifference between the maximum and minimum IOP values observed in a single day. IOP: Intraocular pressure; ICC: Intraclass correlation coefficients.

as Qureshi *et al*^[7] who used a Goldmann applanation tonometer (GAT) to measure IOP in 103 healthy male Chinese volunteers over a 14mo period. It was found that IOP was highest during the winter and lowest in summer, and that the discrepancy was 1.4±0.7 mm Hg. There were several possible reasons for the fluctuation of IOP in a whole year. The fluctuations reached their peak during the month of December and were possibly affected by the decrease in hours of daylight. It was

implied that the IOP fluctuations are correlated to the amount of sunlight exposure. It was supported by our report, especially the sunshine duration was more than 13.5h. Qureshi *et al*^[7] hypothesized that the winter month’s decreased levels of sunlight and the amount of certain chemicals secreted by the pineal gland increased which induced IOP raise. According to this hypothesis, prolonged sunlight affects certain secretions from pineal gland, causing reduced IOP in summer, especially during the nocturnal sleeping periods. The Pineal gland is considered as the “biological clock” with melatonin as its main secretion. The chemicals would result in an increase in the secretion of progesterone and estrogen, which have been reported to reduce IOP values by increasing aqueous outflow^[12]. Moreover, Stoupe *et al*^[13] reported that levels of daily geomagnetic and extreme yearly solar activity can affect IOP. The possible reason was that geomagnetic activity influenced human physiology (plasma viscosity increased, leucocyte aggregation and drop of growth hormone) and caused a decreasing in IOP. Another possible cause was temperature. The temperature in Wenzhou was highest in June to September. The GEE model revealed that warm temperature to be correlated with lower IOP. Findikoglu *et al*^[14] and his colleagues found that IOP and arterial pressure decreased and showed statistically significant differences after head-out hot-water immersion. It is speculated that the warm weather caused vasodilation and up-regulation of metabolic processes. This reflected the dynamic role they had in aqueous production,

which was mediated by ciliary blood flow and ciliary oxygen delivery, as well as in regulating aqueous outflow by their effects on episcleral venous pressure and pulse-dependent motion of the trabecular meshwork^[15]. Further studies are needed to confirm these hypotheses and mechanisms.

However, the internal factors, such as blood pressure, pulse rate, breathe had no effects on the IOP. Some previous reports demonstrated blood pressure maybe a possible influence factor. Based on the Beaver Dam Eye Study, there was a 0.21 mm Hg and 0.43 mm Hg increase in IOP for a 10 mm Hg increase in systolic and diastolic blood pressure respectively^[16]. The present study was failed to find the relationship between blood pressure and IOP. It was speculated that it might be due to all participants in the study were normal healthy subjects. Sehi *et al*^[17] reported that diastolic blood pressure significantly influenced IOP over the course of a day in glaucoma patients but not in normal subjects. Although the dynamic role of blood pressure has in aqueous production and aqueous outflow regulation by their effects on episcleral venous pressure and pulse dependent motion of the trabecular meshwork. While in healthy subjects participated in this study, the blood pressures were all in normal range. Moreover, the IOP regulation capacity in healthy participants was better than glaucoma patients. These were the possible reasons why could not detect any correlation between IOP and blood pressure in normal subjects.

In our study, 24-hour IOPs were not reproducible on a seasonal basis, even in healthy young subjects. Realini *et al*^[18] investigated diurnal IOP patterns in the eyes of 40 healthy subjects without glaucoma and revealed that diurnal IOP patterns were not replicated in the short term. Another prospective, cross-sectional survey found that apart from the IOP fluctuations, the maximum/minimum values of IOP and blood pressure were in excellent agreement^[4]. In the current study, all the IOP parameters consistent with that Realini *et al*'s^[18] study were not reproducible. Moreover, our seasonal ICC values over showed that IOP fluctuations were worse than those found in previous reports. As compared to previous studies, this showed how over longer periods of time there was less replicability. Another possible reason was that the daily lives of participants were not controlled during the study. Generally, 24-hour IOP was taken when participants were hospitalized with regular sleep cycles, restrain of their fluid and food intake and carefully monitored their physical activities. However, this was not their true daily life pattern. Mottet *et al*^[19] strictly controlled environment (light cycle, temperature, fluid intake, meals) which included the monitoring of subjects sleep while in a sleep laboratory for 24h. The results also revealed that intra-subject homogeneity of distribution over time of the acrophase and bathyphase was significant. This

was same as our findings, in which acrophase and bathyphase distributions varied greatly. In our study, the ICC values of IOP showed poor agreement. However, the curve showed that in the spring and winter the maximum, minimum and average as well as each time point of IOPs higher than other seasons in most of the volunteers, while the fluctuation remained relatively stable. These seasonal differences in 24-hour IOP was consistent with previous study in Shanghai, China^[1]. Cheng *et al*^[1] reported that the 24-hour IOP curve was significantly higher, and peak IOP observed in winter (February) than in summer (August). Similarly in the present study, they also found that these differences might be related to temperature and sunlight time.

There are some limitations of this survey. Previous studies have shown that the IOP level can vary depending on the measuring devices^[20]. Although GAT is regarded as the gold standard for IOP measuring, the inherent flaw of contact tonometer is that it requires corneal anesthesia and fluorescein staining. Considering the high frequency measurements of IOP, GAT could not be tolerated by volunteers every day. Therefore, non-contact tonometer was used in this study. However, previous report found that there was consistence between GAT and non-contact tonometer in healthy eye^[21]. Meanwhile 3 repeated IOP measurements would also reduce measurement bias. Moreover, the main purpose of this study was to investigate the IOP fluctuation over time. As long as the device had good repeatability, it was sufficient to complete the study. Hence, the more comfortable and easily used device—the Canon TX-20 Tonometer was the ideal choice, although not including other IOP measuring devices as comparison was still a deficiency of this study. Besides the examination technique, the environmental factors recorded in these reports were all from the Meteorological Bureau in Wenzhou, which were not completely consistent with the participants' real life. Meanwhile, no restriction of participants' living habit (eating preferences, sleeping habits, *etc.*) and some individual characteristic parameters (weight, height, *etc.*) in this study may also affect the observational results. The other limitation was the small sample size, while the research was the first documented report referred to consecutive IOP measurements that lasted for a whole year. The number of times each person was evaluated was more crucial than the number of subjects that were evaluated. It was well known that ethnicity demonstrated to be effective on many ocular parameters, such as IOP^[22-23]. The participants involved in this report were all from Asian, not including other races which was another limitation not to be neglected.

Besides potentially contributing to the increasing risk for glaucoma events during the colder seasons, yearly IOP variations can influence results of clinical trials and epidemiological surveys. The current results, least in parts, were supported by

IOP yearly fluctuation and some possible mechanisms. These results in normal eyes did not diminish the value of assessing diurnal IOP patterns of individuals with suspected or diagnosed glaucoma. However, it implied that fully characterizing diurnal IOP variability in such individuals may require more than a single 24-hour diurnal IOP testing session.

In conclusion, IOP showed a yearly fluctuation which tended to be lower in warm seasons, while the exact physiological mechanism variation of IOP was still unknown. The 24-hour IOP was not highly reproducible in healthy young volunteers, which implies that a single 24-hour IOP assessment may not be sufficient to evaluate the daily IOP fluctuations.

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