• Investigation •

Effect of body position on the pathogenesis of asymmetric primary open angle glaucoma

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Abstract

● AIM: To explore the pathogenesis of asymmetric primary open angle glaucoma (POAG) in both eyes by comparing the intraocular pressure (IOP) of patients who sleep in different positions and to investigate the relationship between IOP variations and sleep positions.

● METHODS: One hundred and thirty-one patients with asymmetric POAG and forty-six healthy volunteers were enrolled. All participants completed a questionnaire that provided information about their sleep laterality. The cup disc ratio (C/D) and visual field defect established binocular asymmetry. The IOP of both eyes was measured using iCare parameters after the patients were asked to change body position. The "worse" and "better" eyes were identified according to the diagnosis, whereas the "dependent" and "independent" eyes were defined according to the lateral position.

● RESULTS: No significant difference in sleep laterality was observed between healthy people and patients with POAG (F=3.195, P=0.362). Among the enrolled patients, the IOP of the dependent eye was always greater than that of the independent eye in the lateral position (P<0.05). In the patients with binocular asymmetric POAG, the questionnaire clearly showed that 85.7% of left side preferences were found their left eyes to be the worse eyes and the right eyes of 71.4% patients with a right side preference were the more serious. When the asymmetric C/D ratio was greater than or equal to 0.2, the worse eye of patients with POAG and a preferred sleeping position was the dependent eye (χ^2=16.762, P=0.001).

● CONCLUSION: A higher IOP was measured in the dependent eye in the lateral position. The long-term tendency to choose a lateral sleeping position might lead the dependent eye to manifest more severe symptoms than the independent eye. Thus, the lateral sleeping position might be one cause of asymmetric POAG.

● **KEYWORDS:** asymmetric primary open angle glaucoma; intraocular pressure; body position

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INTRODUCTION

Glaucoma is an important cause of blindness worldwide. In 2013, 64.3 million patients had glaucoma, and this number will reach 111.8 million in 2040 according to WHO estimates[1]. Primary angle opened glaucoma (POAG) is the most common type of glaucoma[2]. Intraocular pressure (IOP) is the critical modifiable factor that can prevent POAG progression using therapeutic interventions[3-4]. However, for some patients with POAG, disease progression continues even if the IOP is controlled to normal levels because IOP fluctuations area risk factor for POAG progression[5-6]. IOP readings involve many kinds of tonometries, such as Goldmann applanation tonometry or non-contact tonometry, which are obtained in a seated posture at a hospital clinic. The IOP is typically assessed every two hours for one day, but nocturnal measurements in the seated position may not reflect the full range of IOP rhythms, which change with sleep posture, body posture and physical activity[7]. The IOP has been shown increase by more than 6 mm Hg between the seated and the supine position[8], and large fluctuations in IOP have negative effects on patients with glaucoma[9]. When a substantial difference in IOP between eyes is observed, the prognosis for each eye may be different. Asymmetric eye damage is common in patients with glaucoma[10]. The exact same situation is rarely observed in both eyes of patients with POAG, and one eye is almost always worse than the other eye in patients with glaucoma. Thus, studies exploring why and how asymmetric damage occurs in patients with POAG are important.

Humans spend approximately 8h sleeping per day; therefore, we hypothesized that nearly one-third of the lives of patients with glaucoma is affected by the patients' sleeping behaviors. According to some studies, sleeping position may be a disease mechanism because it results in fluctuations in IOP[11], and Kaplowitz *et al*[12] suggests that the side of the worse eye is related to the preferred sleeping position. Nevertheless, precise evidence proving the role of life style in glaucoma progression is insufficient[13].

The current study attempted to investigate the differences in sleep laterality between patients with POAG and healthy people and to explore the most appropriate sleep position for patients with asymmetric POAG according to IOP variations measured in different sleeping positions. If changes in IOP following a change in body position are correlated with sleep laterality, then the relationship may explain the pathogenesis of asymmetric POAG.

SUBJECTS AND METHODS

Subjects Selection This prospective, observational study was performed in the Department of Ophthalmology, West China Hospital, Sichuan University. All procedures reported in this study were performed in accordance with the principles of the Declaration of Helsinki, and ethical permission was obtained from Chinese Clinical Trial Registry (ChiCTR-ROC-16010264). The patients were diagnosed by an experienced glaucoma specialist (Chen XM) based on slit lamp microscope and ophthalmoscope exams as well as a visual field test (OCTOPUS 101; HAAG-STREIT AG Company, Switzerland) and optic nerve analysis (Cirrus HD OCT; Carl Zeiss Meditec, CA, USA).

Clear inclusion criteria were utilized. Patients were required to have normal open angles on gonioscopy, significant optic disc changes in the form of focal or diffuse neuroretinal rim thinning, and visual field defects corresponding to a retinal nerve fiber layer defect. Patients were diagnosed asymmetric POAG if the difference in the binocular C/D ratio was greater than 0.2. Patients with a binocular C/D ratio of less than 0.2 were diagnoses with relatively symmetric POAG. Healthy volunteers were observed in this study to compare the differences in sleeping positions between patients with POAG and healthy people. Participants with other ocular diseases such as a history of trauma, ocular tremor that cannot be corrected, ocular infection, optical neuropathy not resulting from glaucoma, or other systematic diseases, were excluded. A few individuals who could not report their sleep position were also excluded.

Measurements All measures were performed by a single operator between 9 a.m. and 11 a.m. A single iCare rebound tonometer (Care Pro; TiolatOy, Finland) was used to measure the IOP of both eyes in each posture. First, participants were guided into a quiet, dimly lit room and then allowed to rest for five minutes in a chair. During that time, the operator checked most of the basic information and sleep habits. Then, the subjects were asked to maintain their IOP by changing positions: sitting, supine, and lying on the right and left sides. Measurements were collected in each posture at five-minute intervals. A built-in incline sensor in the iCare system measures the supine IOP. During the examination, a pillow was used to support the patient's neck and head in the supine position (Figure 1). The subject was asked to look straight ahead, and the IOP was measured in the center of the cornea using a touching transducer. The left eye was always checked after the right eye. Each eye was measured five times, and the average value was used for the statistical analysis.

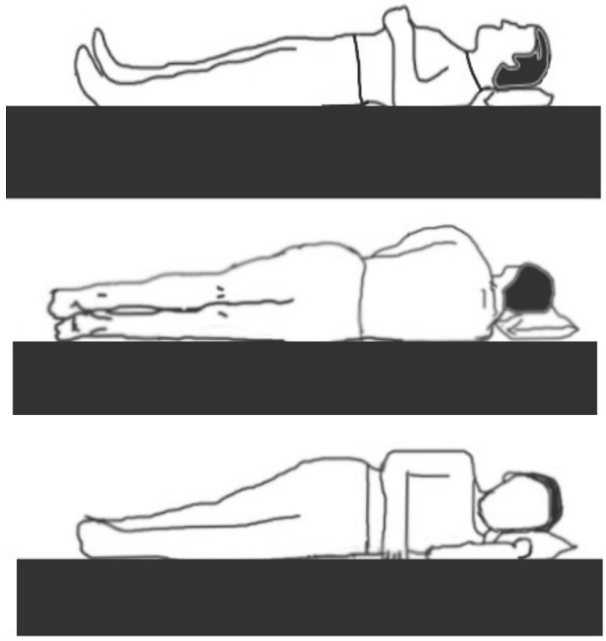

Figure 1 Sleeping position included supine, right lateral decubitus posture and left lateral decubitus posture When the participant face to right side, the right eye was the dependent eye and left eye was the independent eye, while reversely when he/she faces to left side.

When the participants were lying in the lateral decubitus posture, the lower eye was defined as the dependent eye, and the other eye was the independent eye. The better and worse eyes were defined by the C/D ratio and visual field analysis.

Statistical Analysis The statistical analysis was performed using SPSS Version19.0 (SPSS Inc., Chicago, Illinois, USA). Figures were created in Origin (Origin Lab Corporation, USA). The sample size was calculated using the following formula:

$$N=\left[\frac{(Z_{\alpha/2}+Z_{\beta})\sigma}{\delta}\right]^2\left(Q_1^{-1}+Q_2^{-1}\right)$$, α=0.05, β=0.1, δ=0.05, $Q_1=n_1/N$, and $Q_2=n_2/N$, where $n_1=n_2$ and $Q_1=Q_2=1$. Seventy-five patients were calculated as the minimum sample size. All values are presented as mean±standard deviations. The independent-sample *t*-test was used to compare the mean values of the data, and a paired *t*-test was used to compare values obtained from each eye. Percentages were used to describe the results of the questionnaire, and the relationship between the worse eye and the predominant sleeping position was determined using a Chi-square test. A *P* value less than 0.05 was considered to represent a significant difference.

RESULTS

Analysis of Sleep Laterality Forty-six volunteers and 131 patients with POAG were included in this study. The average age of the healthy population was 56.8±17.93y and included 29 males (63%) and 17 females (37%), where as the average age of patients with POAG was 44.8±16.69y and included 83 males (63%) and 48 females (37%).

All 177 participants completed a survey to assess their predominant sleep position. Most healthy individuals (45.65%) preferred the right lateral decubitus (RLD) posture. Approximately 21.74% preferred the supine posture, and nearly 13.04% preferred the left lateral decubitus (LLD) posture and lateral decubitus posture, respectively. Only 3 people claimed no preference (non-fixed; Figure 2). Most patients with POAG (48.09%) preferred the RLD, followed by the LLD (20.61%), non-fixed (12.98%), supine (12.21%), and lateral decubitus postures (6.11%; Figure 3). The greatest proportions of patients with POAG and healthy volunteers preferred the RLD posture (48.09% and 45.65%); the non-fixed posture was not the least common posture when bilateral alternative sleeping positions and non-fixed sleeping positions were included in this group. The sleep laterality of patients with POAG was not significantly different from the healthy population (Table 1).

Effect of the Sleeping Position on Intraocular Pressure Variations

Ipsilateral intraocular pressure of all patients with primary open angle glaucoma As shown in Table 2, the difference in IOP between eyes between any two positions was statistically significant. For the right eye, the IOP was highest when the patient laid in the RLD position, followed by the LLD and supine positions, and the lowest IOP was measured in the seated position. The IOP of the left eye was similar across individuals because the highest IOP was detected in the LLD position. Based on these results, the dependent eye always had the higher IOP.

Compared to the IOP in sitting position, that of the right eye in the RLD position was increased to 7.44±4.72 mm Hg, and the maximum variation was 25 mm Hg, whereas the left eye increased to 5.64±4.42 mm Hg, for a maximum value of 18 mm Hg. In the left lateral position, the IOP of the right eye increased to 5.77±5.04 mm Hg, and the IOP of the left eye increased to 7.34±4.93 mm Hg; the maximum values were 20 mm Hg and 27 mm Hg, respectively. All these values were obviously greater than the IOP ranges measured in the supine position, which were 2.80±4.34 mm Hg for the right eye and 2.89±3.99 mm Hg for the left eye, with maximum values of no more than 20 mm Hg. Hence, IOP exhibited the least variation in the supine position, and the independent eye always experienced a greater IOP fluctuation during the transition into the lateral position.

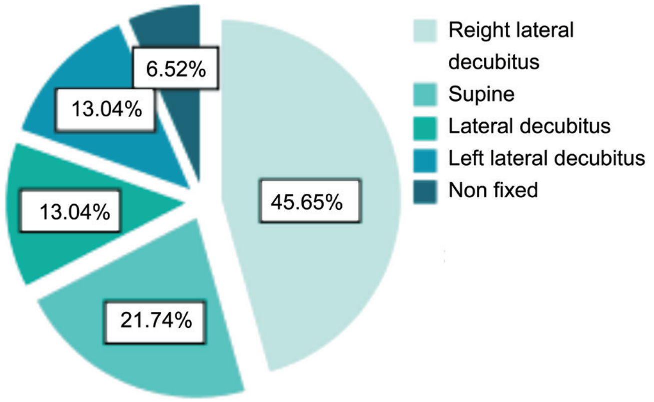

Figure 2 The sleep laterality of normal population.

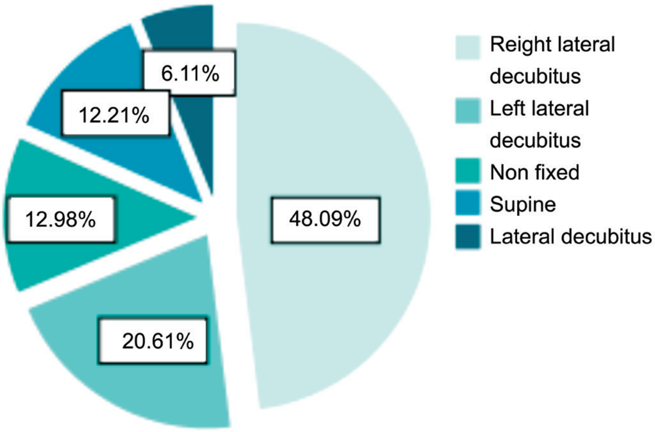

Figure 3 The sleep laterality of POAG patients.

Table 1 Comparison of sleep laterality between normal population and POAG patients

Sleep laterality	Participant		*F*	*P*
	POAG	Normal		
LLD	27	6		
RLD	63	21		
Supine	16	10	3.195	0.362
Non-fixed	25	9		
Sum	131	46		

Because small sample size of no fixed and lateral decubitus posture, it was combined into a set of statistics; POAG: Primary open angle glaucoma; LLD: Left lateral decubitus posture; RLD: Right lateral decubitus posture.

When the patients assumed the RLD position, the IOP of the right eye was 1.40±5.70 mm Hg higher than that of the left eye, and in the LLD position, the IOP of the left eye was 1.96±6.58 mm Hg higher than that of the right eye. A significant difference in the IOP between the right and left eyes was observed when patients were lying in the lateral decubitus posture (Figure 4; RLD: P=0.006; LLD: P=0.001). The IOP of the dependent eye always increased to a greater extent than the IOP of the independent eye. The IOP was significantly elevated in the dependent eye when the patients were lying in the lateral decubitus posture.

Table 2 The IOP of right/left eye on different position mean±SD; mm Hg

Parameters	Position	Number	Right eye	*t*	*P*	Left eye	*t*	*P*
Compare 1	Sitting	131	17.44±4.83			17.84±5.49		
	Supine	131	20.24±4.96	-7.385	<0.001	20.73±6.30	-8.286	<0.001
Compare 2	Sitting	131	17.44±4.83			17.84±5.49		
	RLD	131	24.88±6.66	-18.041	<0.001	23.48±6.50	-14.578	<0.001
Compare 3	Sitting	131	17.44±4.83			17.84±5.49		
	LLD	131	23.21±6.52	-13.126	<0.001	25.18±7.31	-17.016	<0.001
Compare 4	RLD	131	24.88±6.66			23.48±6.50		
	Supine	131	20.24±4.96	10.65	<0.001	20.73±6.30	7.564	<0.001
Compare 5	Supine	131	20.24±4.96			20.73±6.30		
	LLD	131	23.21±6.52	-6.999	<0.001	25.18±7.31	-9.568	<0.001
Compare 6	RLD	131	24.88±6.66			23.48±6.50		
	LLD	131	23.21±6.52	4.061	<0.001	25.18±7.31	-3.631	<0.001

RLD: Right lateral decubitus posture; LLD: Left lateral decubitus posture.

Table 3 Description of right eye IOP in POAG patients with RLD mean±SD; mm Hg

Position	Object	Number	IOP (right eye)	*t*	*P*
Baseline IOP	RLD preference	63	17.86±5.56		
	Others	68	17.04±4.05	0.962	0.338
RLD	RLD preference	63	24.95±7.41		
	Others	68	24.81±5.93	0.123	0.902
Supine	RLD preference	63	20.22±5.13		
	Others	68	20.25±4.85	-0.032	0.975
LLD	RLD preference	63	22.95±6.97		
	Others	68	23.46±6.11	-0.44	0.66

POAG: Primary open angle glaucoma; LLD: Left lateral decubitus posture; RLD: Right lateral decubitus posture.

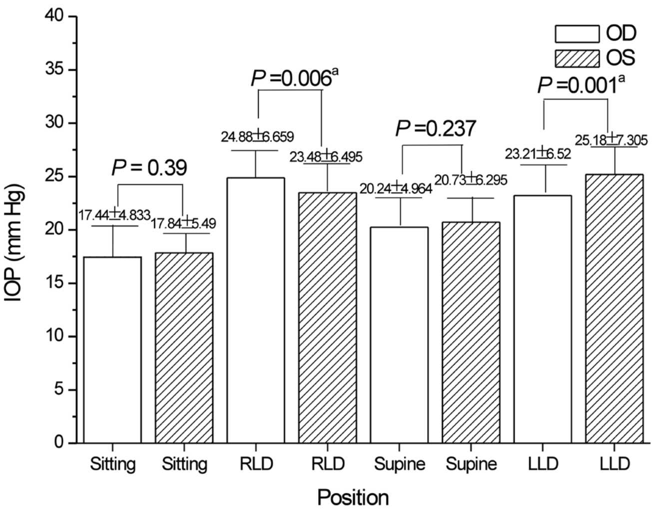

Figure 4 Comparison of the binocular IOP in the POAG patients at different positions [a]Statistical significance. POAG: Primary open angle glaucoma; LLD: Left lateral decubitus posture; RLD: Right lateral decubitus posture.

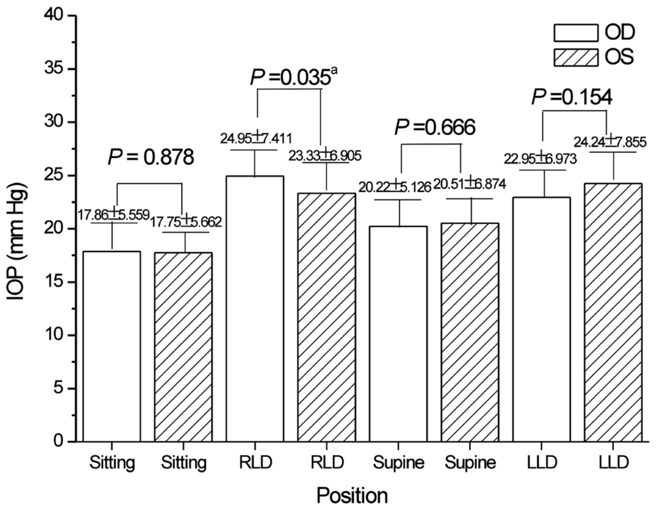

Figure 5 Comparison of binocular IOP in RLD preferences of POAG patients [a]Statistical significance. LLD: Left lateral decubitus posture; RLD: Right lateral decubitus posture.

Ipsilateral intraocular pressure of patients with primary open angle glaucoma and a preferred sleep position The IOP of individuals who expressed a preference for the RLD position was not significantly different from individuals who preferred other positions (Table 3). The results for patients who preferred the LLD position were similar (Table 4). Based on these results, it appears that unilateral IOP and preferred sleep position are not significantly associated.

Regarding the RLD preference, a significant difference in the bilateral IOP was observed only when patients slept facing right (Figure 5); similar results were observed for patients lying in their preferred LLD position (Figure 6). The IOP of the right eye is greater than the IOP of the left

Table 4 Description of left eye IOP in POAG patients with LLD mean±SD; mm Hg

Position	Object	Number	IOP (left eye)	*t*	*P*
Baseline IOP	LLD preference	27	16.26±3.50		
	Others	104	17.74±5.09	-1.425	0.157
RLD	LLD preference	27	23.96±6.30		
	Others	104	25.12±6.76	-0.8	0.425
Supine	LLD preference	27	20.04±4.80		
	Others	104	20.29±5.03	-0.234	0.816
LLD	LLD preference	27	22.59±5.71		
	Others	104	23.38±6.73	-0.554	0.58

LLD: Left lateral decubitus posture; RLD: Right lateral decubitus posture.

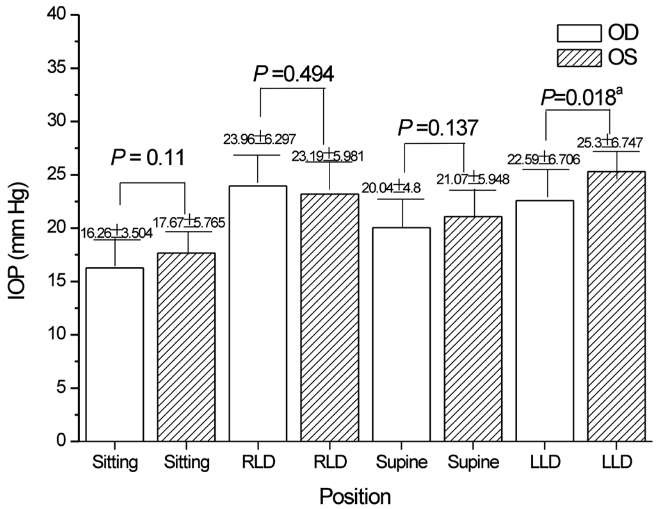

Figure 6 Comparison of binocular IOP in LLD preferences of POAG patients [a]Statistical significance. LLD: Left lateral decubitus posture; RLD: Right lateral decubitus posture.

eye in patients with POAG who prefer the RLD position, and similar results were observed in patients with POAG who preferred the LLD position. This result was primarily observed in the same subject. Hence, the variation in the IOP due to changes in sleeping position mainly existed in the same individual difference between preoperative and postoperative measurement, with no specificity in the overall sample.

Relationship Between Lateral Sleep Position Tendency and Asymmetric Severity in Primary Open Angle Glaucoma POAG patients with a C/D ratio greater than or equal to 0.2 and with a difference in binocular visual field MD more than 5 dB were classified as the standard for bilateral asymmetric POAG. In these patients, the ipsilateral eye with the larger C/D ratio and greater visual field defect was the worst of both eyes. In the patients with binocular asymmetric POAG (Table 5), the questionnaire clearly showed a lateral sleep position tendency for 42 people, of whom 14 tended to lie on the left side and 28 on the right side. The left eyes of 12 patients with a left side preference (85.7%, 52.2% in overall patients) were found to be the worse eyes. Similarly, the right eyes of 20 patients with a right side preference (71.4%, 62.6% in overall patients) were the more serious. There was no such pattern for the supine or non-fixed position. Hence, when the C/D ratio was greater than or equal to 0.2, the worse eye was significantly associated with sleep laterality (χ^2=16.762, *P*=0.001).

Table 5 Distribution of sleeping laterality in asymmetric group

Position	Sum	Left eye		Right eye	
		Number	CR (%)	Number	CR (%)
LLD	14	12	52.2[a]	2	6.3
RLD	28	8	34.8	20	62.5[a]
Supine	5	0	0.0	5	15.6
Non fixed	8	3	13.0	5	15.6
Sum	55	23	100.0	32	100.0

CR: Constituent ratio; LLD: Left lateral decubitus posture; RLD: Right lateral decubitus posture. χ^2=16.762, *P*=0.001. [a]Statistical significance.

Table 6 Distribution of sleeping laterality in relative symmetric group

Position	Sum	Left eye		Right eye	
		Number	CR (%)	Number	CR (%)
LLD	13	5	15.2	8	18.6
RLD	35	14	42.4	21	48.8
Supine	11	6	18.2	5	11.6
Non fixed	17	8	24.2	9	20.9
Sum	76	33	100.0	43	100.0

CR: Constituent ratio; LLD: Left lateral decubitus posture; RLD: Right lateral decubitus posture. χ^2=0.943, *P*=0.815.

By contrast, this situation was not found for the POAG patients with a binocular C/D ratio less than 0.2, and the worse eye was not significantly associated with sleeping laterality (χ^2=0.943, *P*=0.815) in these subjects (Table 6).

DISCUSSION

This study confirmed the findings of previous studies showing that the lateral decubitus posture induced POAG progression[14-15], though other investigators concluded this effect was not obvious[16]. However, most of these studies examining risk factors used only visual field loss as an indicator of progression, which may be insufficient to elucidate a relationship between sleep posture and POAG severity, particularly in patients with asymmetric POAG, since changing the sleep position has a proven effect on patients with asymmetric POAG. We analyzed the relationship between differences in sleeping laterality and variations in IOP and further speculated on the effect of the independent eye on patients with asymmetric POAG, which may provide new insights into the pathogenesis of asymmetric glaucoma.

Moreover, the greatest mean IOP variation across different positions was approximately 2 mm Hg in healthy people and more than 7 mm Hg in patients with POAG. The peak value always appeared in the LLD or RLD position. Even when the IOP is controlled, some patients with glaucoma continue to progress[17], possibly because of pathologically significant fluctuations in their IOPs during sleep[18]. Kaplowitz *et al*[12] used an initial sleep laboratory video to analyze patients' continuous sleep positions and observed a significant association (77%) between the objective primary sleep position and the self-reported sleep position (P=0.03), which led us to believe that sleep data obtained from a questionnaire are reasonable. Based on the study by Kaplowitz *et al*[12], people tend to prefer the RLD posture compared with other positions, which was also observed in the patients with POAG in our study. When the IOP of the right eye was compared across positions, the peak value (24.88 mm Hg) appeared in the RLD posture, whereas the highest IOP of the left eye (25.18 mm Hg) was measured in the LLD posture. Similarly, adjustments to the pillow height may affect the increase in IOP[16]. The IOP may fluctuate as the elevation of the eye changes, regardless of whether it is measured in the right or left eye. Elevation may play an important role related to Schlemm's canal area[19], in which case the lateral decubitus posture should have more influence on IOP fluctuations than the supine position because changes in the 24-hour bilateral IOP between diurnal sitting and the nocturnal supine position are similar[20].

According to previous investigations, postural changes induce an increase in IOP. However, in other studies, the difference in the IOP of patients with POAG between the sitting and supine postures was greater in the worse eye than that in the better eye[14-15,21-23]. However, in contrast to previous findings, the sleep laterality of patients with POAG was not different from healthy individuals in the present study. In the analysis of the ipsilateral eye, the IOP of patients with POAG and laterality preferences was not significantly different from patients without such a preference, suggesting that sleep laterality preferences in patients with POAG were not correlated with the overall IOP because an obvious difference between these patients and those with other preferences was not observed. Moreover, the dependent eye was significantly more likely to be the worse eye when the asymmetry of the C/D ratio was ≥0.2. Sleep laterality is likely related to the asymmetry in severity between eyes. We concluded that a laterality preference does not dispose patients to an overall high IOP. The tendency to spend a long time sleeping in a certain position is related only to an increase in baseline IOP in patients with POAG but not in the general population. Therefore, the sleeping position has no long-term effect. With a suitable sleeping position, such as lying supine with an elevated pillow, patients may exhibit a relatively lower IOP during sleep.

The maximum IOP fluctuations always occurred in the dependent eye when the patient was sleeping in a lateral position. We assumed that IOP fluctuations were related to the sleeping position. Thus, the long-term adoption of a lateral sleeping position by patients with POAG may increase the IOP in the dependent eye, which might affect the progression of POAG and asymmetric pathogenesis. Thus, the relationship between the asymmetric IOP and sleeping position may play a role in the pathogenesis of glaucoma.

Although this case-control study utilized a standard protocol for diagnosis and the inclusion criteria, some limitations need to be recognized. First, the age of the participants ranged from 18 to 80. Age, sex and systematic disease are associated with the IOP[24]; the formation of the aqueous humor is sensitive to pressure, and the outflow of aqueous humor decreases with age in patients with glaucoma[25]. The study reflects the total population studied and did not stratify subjects by age. Next, we tested the IOPs in patients lying in different positions at a fixed time of day, which is not the habitual sleep time. This protocol likely resulted in lower measured IOP values, as the IOP is higher at night than during the day[26]. Although some devices for continuous IOP monitoring *via* an integrated pressure sensor have been developed and are available for commercial or scientific use[26], truly continuous IOP monitoring in individual patients is not yet available.

In conclusion, the IOP of the dependent eye might be higher than that of the independent eye when patients are lying in a lateral sleeping position. The long-term tendency to sleep on the right or left side may cause the dependent eye to be more severely affected than the independent eye. Based on these findings, an unsuitable sleeping position may accelerate the progression of POAG, and a lateral sleeping position might be one cause of asymmetric POAG. Therefore, we conclude that the adoption of the supine position may benefit patients with glaucoma.

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Conflicts of Interest: Tang J, None; **Li N,** None; **Deng YP,** None; **Qiu LM,** None; **Chen XM,** None.

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