



# 24-h intraocular pressure patterns measured by Icare PRO rebound in habitual position of open-angle glaucoma eyes

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## Abstract

**Purpose** To measure the 24-h intraocular pressure (IOP) by Icare PRO rebound in healthy and primary open-angle glaucoma (POAG) eyes and compare it with non-contact tonometry (NCT).

**Methods** Thirty POAG patients, who were under IOP-lowering treatment, and 30 healthy subjects were included. Participants were hospitalized overnight for the 24-h IOP measurement. IOPs were measured by Icare PRO and NCT according to a standard protocol every 2 h during 24 h. The 24-h IOP curve and IOP-related parameters were compared between Icare PRO and NCT groups in POAG and healthy eyes.

**Results** The IOPs measured by Icare PRO in habitual position increased notably at 22:00 in the normal group and at 20:00 in the POAG group, reached peak at 0:00, stayed high until 4:00, and then decreased in both groups (all  $p < 0.05$ ). The POAG patients had higher mean 24-h IOP, peak IOP, IOP fluctuation, and greater IOP change from supine to sitting position in the nocturnal period than those in the normal subjects even after adjusting for eyes, age, gender, CCT, and axial length (all  $p < 0.05$ ).

**Conclusions** The Icare PRO provides a well-tolerated approach for 24-h IOP monitoring in habitual position. Twenty-four-hour IOP in habitual position is more sensitive for detecting high nocturnal IOP peaks and greater IOP fluctuation for POAG patients.

**Keywords** Icare PRO rebound tonometry · Non-contact tonometry · 24-h intraocular pressure pattern · Primary open-angle glaucoma · Body position

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### Key messages

- Twenty-four-hour IOP measurement is important for understanding the IOP fluctuation of POAG, and various devices are used for 24-hour IOP measurement.
- The Icare PRO provides a well-tolerated approach for 24-hour IOP monitoring in habitual position.
- Twenty-four hour IOP in habitual position is more sensitive for detecting high nocturnal IOP peaks and greater IOP fluctuation for POAG patients. POAG patients had higher mean 24-hour IOP, peak IOP, IOP fluctuation, and greater IOP change from at supine to sitting position in the nocturnal period than normal people.

## Introduction

Elevated intraocular pressure (IOP) is a major risk factor for progression of primary open-angle glaucoma (POAG), and IOP reduction is the only evidenced-based therapy to control the progression of glaucomatous optic neuropathy [1]. However, it is not rare that the visual field still progresses despite well-controlled IOP [2]. Glaucoma patients usually have their IOP monitored with single time measurement during office hours. However, nearly two-thirds of POAG patients experience high IOPs outside regular clinic hours [3], with peak IOPs most frequently occurring at night detected by 24-h IOP measurement [4, 5]. Therefore, the 24-h IOP measurement can provide a complete picture of an individual's IOPs during a whole day, which is important for diagnosis and management of POAG.

Various devices are used for 24-h IOP measurement, such as Goldmann applanation tonometry (GAT), non-contact tonometry (NCT), and contact lens sensor (CLS). Although GAT is the gold standard for IOP measurement, multiple topical anesthesia and repeated applanation are needed for the procedure, which could potentially cause corneal abrasion. NCT is also a commonly used technique for 24-h IOP measurement [6–8]. However, it is taken in sitting position as well and fails to reflect the IOPs in natural body position over a 24-h period. The Triggerfish® (Sensimed AG, Lausanne, Switzerland) telemetric CLS is a technology for the continuous recording of IOP-related pattern with minimal disturbance to the wearer's daily routine and sleep cycle, while the direct association between CLS output and IOP has not been established [9, 10]. Recently, a new developed Icare PRO rebound tonometry has been available for clinical practice [11]. It can be used without topical anesthesia and is particularly useful for measuring IOP in children [12]. Additionally, the Icare PRO includes a built-in inclination sensor that permits IOP to be measured on the subjects in supine position [13]. Previous research showed that Icare PRO offers excellent intradevice repeatability and inter-device reproducibility in the measurement of IOP [11, 13]. Therefore, the Icare PRO is potentially a good approach to measure IOPs over 24 h in habitual position, which could reflect IOPs in natural position better.

The present study aimed to measure the 24-h intraocular pressure by Icare PRO rebound and compare it with NCT in healthy and POAG eyes to identify the circadian IOP fluctuation pattern.

## Methods

### Participants

This study was approved by the Ethical Review Committee of Shanghai Jing'an District Bei Zhan Hospital (Number: 20170607003) and it adhered to the Declaration of Helsinki for Research Involving Human Participants. Written informed consent was obtained from each participant enrolled in the study.

The diagnostic criteria for POAG included (1) presence of glaucomatous optic disc damage and retinal nerve fiber layer (RNFL) thinning; (2) visual field defects confirmed on at least two visual field examinations; (3) open anterior chamber angles under gonioscopic examination; and (4) no history of ocular or systemic diseases causing optic nerve atrophy. All patients were medically treated with prostaglandin analogues (PGA).

The inclusion criteria for the normal subjects were as follows: open anterior chamber angle, normal-appearing optic nerve head, intact retinal nerve fiber layer, normal standard automated perimetry, and no records of elevated IOP greater than 21 mmHg.

Participants who had (1) incisional surgeries in either eye, including cataract surgeries, glaucoma surgeries, vitreoretinal surgeries, et al., (2) histories of eye diseases, such as uveitis, keratitis, and scleritis, (3) histories of trauma, or (4) refractive error greater than 6.0 diopter or lower than −6.0 diopter were excluded.

Participants underwent a complete ophthalmic examination, including a review of their medical histories, measurements of best-corrected visual acuity (BCVA), refractive status, slit-lamp biomicroscopy, IOP (Goldmann applanation tonometry), funduscopy (Digital Retinal Camera CR-2 AF, Canon, Japan), gonioscopy, central corneal thickness (CCT) and axial length (Lenstar 900, HAAG-STREIT, AG, Swiss),

retinal nerve fiber layer and ganglion cell complex thickness (RTvue OCT; Optovue Inc., Toledo, OH), and visual field (Octopus perimeter 101, HAAG-STREIT, AG, Swiss).

## 24-h IOP measurement by Icare PRO and NCT

Subjects were hospitalized to undergo 24-h IOP monitoring with an Icare PRO (iCare Finland Oy, Vantaa, Finland) and a non-contact tonometer (Full Auto Tonometer TX-F, Canon, Japan). All the IOP measurements were taken by the same well-trained operator (Dr. Zhaobin Fang). The IOPs of both eyes were measured every 2 h from 8:00 AM to 6:00 AM of the next day, specifically, at 8:00, 10:00, 12:00, 14:00, 16:00, 18:00, 20:00, and 22:00 (diurnal period IOP), and at 00:00, 2:00, 4:00, and 6:00 (nocturnal period IOP). Each subject was firstly measured IOP by Icare PRO followed by NCT from 6:00 to 22:00. During 0:00 to 4:00 time points, the IOPs were firstly measured in supine position by Icare PRO, then in sitting position by Icare PRO and NCT. For each time point, six consecutive measurements were performed for Icare PRO. The built-in software automatically discarded the highest and the lowest values, and the average IOP was calculated from the remaining four values. Three repeated measurements of NCT were taken at each time point and the average value was recorded. Measurements of different devices were separated by a 5-min interval.

Twenty-four-hour IOP curves were generated by using the IOP values at each time point. Mean IOP was calculated for the entire day, and separately for the diurnal period and the nocturnal period. Peak IOP and trough IOP were noted as the highest and lowest values among the 12 IOP values of the 24-h IOP records. IOP fluctuation was calculated by subtracting the trough IOP from the peak IOP.

## Statistical analysis

All analyses were performed using SAS version 9.4 for Windows (SAS Institute) and R 3.4.3 (<http://www.R-project.org>). Numerical variables were shown as mean  $\pm$  standard deviation. Reliability between Icare PRO and NCT was explored by intraclass correlation coefficient (ICC) and Bland-Altman plot. The differences between groups were analyzed by using mixed effect linear models for repeated measurements of two eyes and adjusted for age, sex, CCT, and AL. The exchangeable covariance structure was used to model the correlation of responses of two eyes from the same patients. Bonferroni test was used to do the post hoc analyses. Piecewise linear regression models and likelihood ratio tests were used to analyze the differences of changes at different time points.  $p < 0.05$  was considered to be statistically significant.

## Results

A total of 60 eyes of 30 POAG patients and 60 eyes of 30 healthy subjects were enrolled in this study (S1. file). All the POAG patients were under IOP-lowering treatment (11 patients were treated with travoprost, 8 patients with bimatoprost, 7 patients with latanoprost, and 4 patients with tafluprost). The clinical characteristics of the two groups are shown in Table 1. The POAG group had longer axial length ( $p = 0.010$ ) and thinner RNFL and GCC thickness (both  $p < 0.001$ ) compared to healthy subjects. There were no statistically significant differences in gender ( $p = 0.796$ ), age ( $p = 0.064$ ), and CCT ( $p = 0.523$ ) between two groups.

The inter-device agreement analysis was used to compare the consistence of the IOP values measured by Icare PRO and those by NCT. The intraclass correlation coefficient was 0.776 (95% confidence interval, CI: 0.738–0.810,  $p < 0.001$ ) which was based on the measurements from 60 eyes in the normal group in sitting position at the diurnal time points. Additionally, the Bland-Altman analysis with linear regression was also assessed for the normal group and presented in Fig. 1. The diurnal IOP curve had no significant difference between NCT and Icare PRO in healthy subjects by piecewise linear regression model and likelihood ratio tests ( $p = 0.136$ ). All those results showed good agreement between Icare PRO and NCT in sitting position during the diurnal period.

The 24-h IOP measurements of Icare PRO in habitual position and NCT in sitting position in normal and POAG groups are listed in Table 2 and the 24-h IOP curves are presented in Fig. 2. We statistically analyzed the differences of IOPs between Icare PRO and NCT in normal group, and found that the differences of IOPs at 25%, 50%, 75% percentiles were 0.1 mmHg, 1 mmHg, and 2.1 mmHg. In both groups of normal and POAG subjects, the mean differences of the IOPs (95% confidence interval) between Icare PRO in

**Table 1** Clinical characteristics of the study subjects

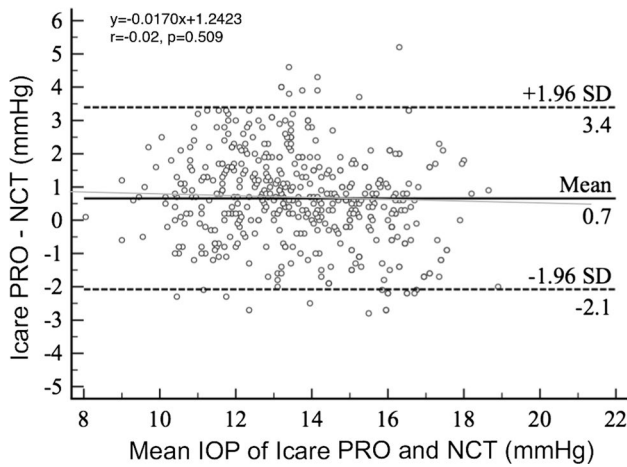
Characteristics	Normal	POAG	<i>p</i> value
Gender (male:female), <i>N</i> = 30	15:15	16:14	0.796 <sup>a</sup>
Age (yrs), <i>N</i> = 30	46.9 $\pm$ 13.7	53.3 $\pm$ 12.3	0.064 <sup>b</sup>
CCT ( $\mu$ m), <i>N</i> = 60	535.9 $\pm$ 26.6	531.1 $\pm$ 32.3	0.523 <sup>c</sup>
Axial length (mm), <i>N</i> = 60	23.34 $\pm$ 0.89	24.10 $\pm$ 1.38	0.010 <sup>c</sup>
RNFL thickness ( $\mu$ m), <i>N</i> = 60	110.6 $\pm$ 8.8	81.2 $\pm$ 10.4	<0.001 <sup>c</sup>
GCC thickness ( $\mu$ m), <i>N</i> = 60	95.6 $\pm$ 5.4	73.0 $\pm$ 9.0	<0.001 <sup>c</sup>

POAG, primary open-angle glaucoma; CCT, central corneal thickness; RNFL, retinal nerve fiber layer; GCC, ganglion cell complex

<sup>a</sup>Gender was compared between two groups by chi-square test

<sup>b</sup>Age was compared between two groups by independent-samples *T* test

<sup>c</sup>These *p* values were calculated by a mixed effect linear model



**Fig. 1** The Bland-Altman analysis with linear regression for the Icare PRO and NCT in the healthy subjects

supine position and NCT in sitting position were more than 2.1 mmHg from 0:00 to 4:00 (Fig. 2 and Table 2).

The 24-h IOP curves of normal and POAG groups by Icare PRO are shown in Fig. 3. The IOPs increased notably

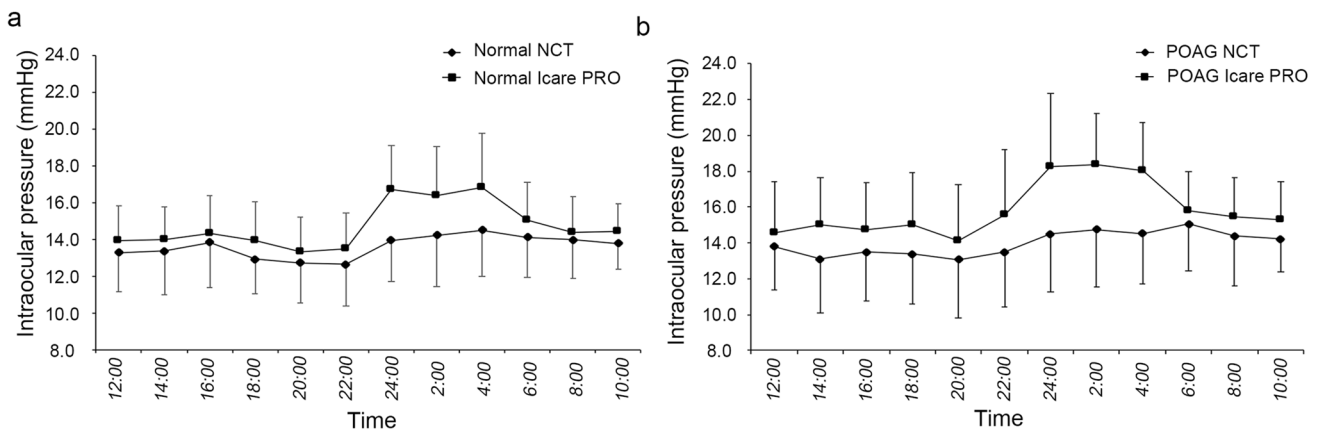
at night from 22:00 in the normal group [1.62 (1.30, 1.94),  $p < 0.001$ ] and 20:00 in the POAG group [1.06 (0.77, 1.35),  $p < 0.001$ ], reached peaks at 0:00 in both groups, stayed high until 4:00 in the morning [normal: 0.02 (− 0.21, 0.25),  $p < 0.001$ ; glaucoma: 0.00 (− 0.29, 0.29),  $p < 0.001$ ], and then decreased [normal: − 0.38 (− 0.51, − 0.25),  $p = 0.024$ ; POAG: − 0.45 (− 0.61, − 0.30),  $p = 0.035$ ]. The 24-h mean IOP ( $p = 0.034$ ), nocturnal mean IOP ( $p = 0.028$ ), peak IOP ( $p = 0.028$ ), diurnal peak IOP ( $p = 0.004$ ), nocturnal peak IOP ( $p = 0.042$ ), 24-h IOP fluctuation ( $p = 0.014$ ), and diurnal IOP fluctuation ( $p = 0.010$ ) were all significantly higher in the glaucoma group compared with those in the normal group, after adjusting for eyes, age, gender, CCT, and axial length. No significant difference was found in other parameters (Table 3).

The changes of IOPs from supine to sitting position measured by Icare PRO were greater in the POAG group than those in the normal group at 0:00 ( $2.63 \pm 2.23$  mmHg in POAG vs.  $1.92 \pm 1.20$  in normal,  $p = 0.042$ ) and 2:00 ( $2.53 \pm 1.52$  mmHg in POAG vs.  $1.76 \pm 1.17$  mmHg in normal,  $p = 0.001$ ) after adjusting for eyes, age, gender, CCT, and axial length (Fig. 4 and

**Table 2** Intraocular pressure at each point by Icare PRO and non-contact tonometry in normal and primary open-angle glaucoma participants

Variables	Icare PRO tonometry	Non-contact tonometry	Mean difference (95%CI)
<b>Normal</b>			
8:00	14.37 ± 1.99	13.98 ± 2.13	0.40 (0.04, 0.75)
10:00	14.44 ± 1.52	13.78 ± 1.45	0.66 (0.35, 0.96)
12:00	13.94 ± 1.92	13.28 ± 2.19	0.66 (0.35, 0.97)
14:00	14.00 ± 1.79	13.36 ± 2.41	0.64 (0.24, 1.04)
16:00	14.31 ± 2.11	13.83 ± 2.51	0.49 (0.13, 0.84)
18:00	13.94 ± 2.13	12.92 ± 1.91	1.03 (0.69, 1.36)
20:00	13.31 ± 1.95	12.72 ± 2.24	0.59 (0.22, 0.96)
22:00	13.46 ± 1.99	12.64 ± 2.34	0.81 (0.39, 1.24)
0:00	16.73 ± 2.38	13.94 ± 2.24	2.80 (2.31, 3.28)
2:00	16.36 ± 2.71	14.23 ± 2.85	2.14 (1.79, 2.49)
4:00	16.81 ± 3.02	14.49 ± 2.53	2.32 (1.87, 2.77)
6:00	15.01 ± 2.13	14.11 ± 2.22	0.91 (0.52, 1.30)
<b>POAG</b>			
8:00	15.43 ± 2.23	14.39 ± 2.85	1.05 (0.43, 1.67)
10:00	15.31 ± 2.15	14.21 ± 1.85	1.10 (0.61, 1.58)
12:00	14.55 ± 2.89	13.80 ± 2.47	0.75 (0.09, 1.41)
14:00	15.01 ± 2.67	13.09 ± 3.07	1.93 (1.29, 2.56)
16:00	14.71 ± 2.71	13.48 ± 2.79	1.23 (0.74, 1.72)
18:00	15.02 ± 2.96	13.38 ± 2.82	1.64 (1.05, 2.22)
20:00	14.12 ± 3.18	13.06 ± 3.30	1.07 (0.51, 1.62)
22:00	15.55 ± 3.72	13.49 ± 3.11	2.06 (1.66, 2.45)
0:00	18.24 ± 4.15	14.48 ± 3.28	3.76 (3.04, 4.47)
2:00	18.35 ± 2.90	14.76 ± 3.25	3.60 (3.09, 4.11)
4:00	18.01 ± 2.76	14.52 ± 2.85	3.49 (3.06, 3.93)
6:00	15.79 ± 2.23	15.04 ± 2.64	0.75 (0.28, 1.21)

CI, confidence interval, POAG, primary open-angle glaucoma IOPs are displayed as mean ± standard deviation



**Fig. 2** The 24-h IOP curves by Icare PRO and NCT in normal and POAG groups. **a** The 24-h IOP curves by NCT in sitting position and Icare PRO in habitual position in the normal group. **b** The 24-h IOP

curves by NCT in sitting position and Icare PRO in habitual position in the POAG group

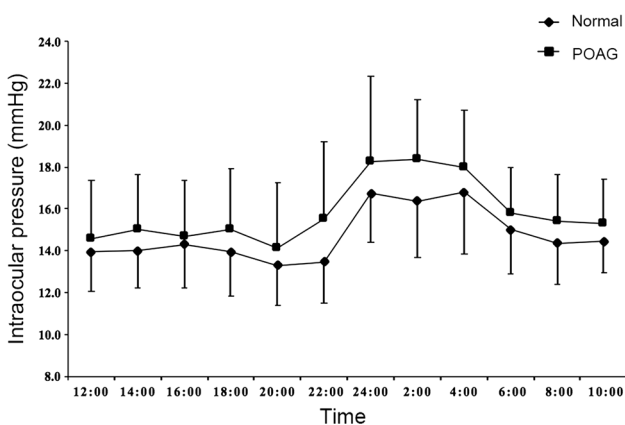
Table 4). No significant difference was found at 4:00 between two groups (all  $p > 0.05$ ).

**Discussion**

The present study investigated 24-h IOP patterns by Icare RPO in healthy subjects and POAG patients, and compared it with NCT. Our results showed that there was a very good inter-device agreement of IOP measurements from Icare RPO and NCT in sitting position. Both normal and POAG eyes had higher IOPs measured by Icare RPO than those by NCT during nocturnal period due to different body positions. Additionally, The POAG eyes had significantly higher 24-hIOP level, greater IOP fluctuation, earlier IOP elevation

in the nocturnal period in habitual position, and greater IOP change from supine to sitting position in the nocturnal period than those in the normal eyes even after adjusting for eyes, age, gender, CCT, and axial length.

It has been reported that Icare RPO has good inter-device agreement with other currently used devices [14–18]. Those studies demonstrated that there was good agreement among Icare PRO, Tonopen XL, NCT, and Goldmann applanation tonometer (GAT) in anesthetized children [14], in keratoconic eyes [15], and in healthy elder eyes [17, 18]. In our study, the agreement between Icare PRO and NCT was evaluated by ICC and Bland-Altman analysis with linear regression in sitting position during diurnal period. Additionally, the diurnal IOP curve measured by Icare PRO and NCT showed no significant difference in normal eyes by the piecewise linear regression model and likelihood ratio tests. These results were consistent with previous studies [13, 16–18].



**Fig. 3** The 24-h IOP curves in normal and POAG groups by Icare PRO. The IOP ascended notably at night from 20:00 in the POAG group ( $p < 0.001$ ) and from 22:00 in the normal group ( $p < 0.001$ ), reached peaks at 0:00 in both groups, stayed high until 4:00 (normal:  $p < 0.001$ ; glaucoma:  $p < 0.001$ ), and then descended (normal:  $p = 0.024$ ; POAG:  $p = 0.035$ )

Interestingly, the mean differences of IOPs between Icare PRO in supine position and NCT in sitting position were more than 2.1 mmHg from 0:00 to 4:00 for both normal and POAG groups. The results could be explained by the different body positions of two methods. The Icare PRO 24-h IOP curves were generated by measurements performed in habitual position, which was sitting position during the diurnal period and supine position during the nocturnal period. The NCT 24-h IOP curves were generated by measurements performed all in sitting position. Many studies had demonstrated that the IOP was higher in supine position compared to that in sitting position because of the elevated episcleral venous pressure [19–22]. Consistently, previous studies also reported that both POAG and normal-tension glaucoma (NTG) eyes showed a nocturnal acrophase pattern measured by a contact lens sensor [23]. Since Icare RPO is a position-independent rebound tonometer, it is able to be used to

**Table 3** Comparisons of IOP parameters in normal and POAG subjects by Icare PRO

Variables	Normal	POAG	Model 1		Model 2		Model 3	
			$\beta$ (95%CI)	<i>p</i> value	$\beta$ (95%CI)	<i>p</i> value	$\beta$ (95%CI)	<i>p</i> value
Mean	14.72 ± 1.69	15.84 ± 2.29	1.12 (0.13, 2.11)	<b>0.027</b>	1.16 (0.14, 2.18)	<b>0.026</b>	1.16 (0.09, 2.24)	<b>0.034</b>
Diurnal	13.97 ± 1.58	14.96 ± 2.34	0.99 (0.01, 1.98)	<b>0.049</b>	1.04 (0.03, 2.05)	<b>0.043</b>	1.03 (− 0.00, 2.06)	0.051
Nocturnal	16.23 ± 2.14	17.60 ± 2.66	1.37 (0.19, 2.55)	<b>0.023</b>	1.39 (0.16, 2.62)	<b>0.026</b>	1.47 (0.16, 2.78)	<b>0.028</b>
Change	2.26 ± 1.26	2.63 ± 1.87	0.38 (− 0.38, 1.14)	0.330	0.35 (− 0.44, 1.15)	0.382	0.44 (− 0.31, 1.18)	0.252
Max	18.35 ± 2.61	19.94 ± 3.47	1.58 (0.11, 3.05)	<b>0.035</b>	1.70 (0.15, 3.25)	<b>0.032</b>	1.81 (0.20, 3.42)	<b>0.028</b>
Diurnal	15.85 ± 1.55	17.50 ± 2.77	1.65 (0.58, 2.72)	<b>0.002</b>	1.61 (0.54, 2.69)	<b>0.003</b>	1.72 (0.55, 2.90)	<b>0.004</b>
Nocturnal	18.22 ± 2.71	19.75 ± 3.48	1.52 (0.04, 3.01)	<b>0.045</b>	1.67 (0.10, 3.24)	<b>0.038</b>	1.70 (0.06, 3.34)	<b>0.042</b>
Min	12.32 ± 1.85	12.67 ± 2.51	0.35 (− 0.72, 1.41)	0.521	0.44 (− 0.64, 1.52)	0.422	0.46 (− 0.66, 1.57)	0.421
Diurnal	12.34 ± 1.86	12.76 ± 2.53	0.42 (− 0.65, 1.48)	0.443	0.54 (− 0.54, 1.61)	0.326	0.54 (− 0.59, 1.67)	0.348
Nocturnal	14.53 ± 2.03	15.41 ± 2.15	0.88 (− 0.13, 1.88)	0.087	0.82 (− 0.22, 1.87)	0.120	0.93 (− 0.19, 2.05)	0.103
Fluctuation	6.03 ± 1.89	7.27 ± 2.59	1.23 (0.20, 2.27)	<b>0.019</b>	1.26 (0.17, 2.35)	<b>0.024</b>	1.34 (0.27, 2.40)	<b>0.014</b>
Diurnal	3.51 ± 1.27	4.75 ± 2.08	1.24 (0.51, 1.96)	<b>&lt;0.001</b>	1.08 (0.39, 1.77)	<b>0.002</b>	1.16 (0.28, 2.05)	<b>0.010</b>
Nocturnal	3.69 ± 1.81	4.34 ± 2.37	0.65 (− 0.29, 1.58)	0.174	0.84 (− 0.13, 1.82)	0.091	0.86 (− 0.13, 1.85)	0.090
Change	0.18 ± 2.08	− 0.41 ± 3.34	− 0.59 (− 1.75, 0.57)	0.321	− 0.23 (− 1.39, 0.92)	0.690	− 0.28 (− 1.51, 0.95)	0.650

POAG, primary open-angle glaucoma; CI, confidence interval

Statistical comparisons between normal and POAG groups were performed by using a mixed effect linear model

Numbers were displayed as mean ± standard deviation

Model 1, adjustment for eyes, Model 2, further adjustment for age and gender; Model 3, further adjustment for central corneal thickness and axial length

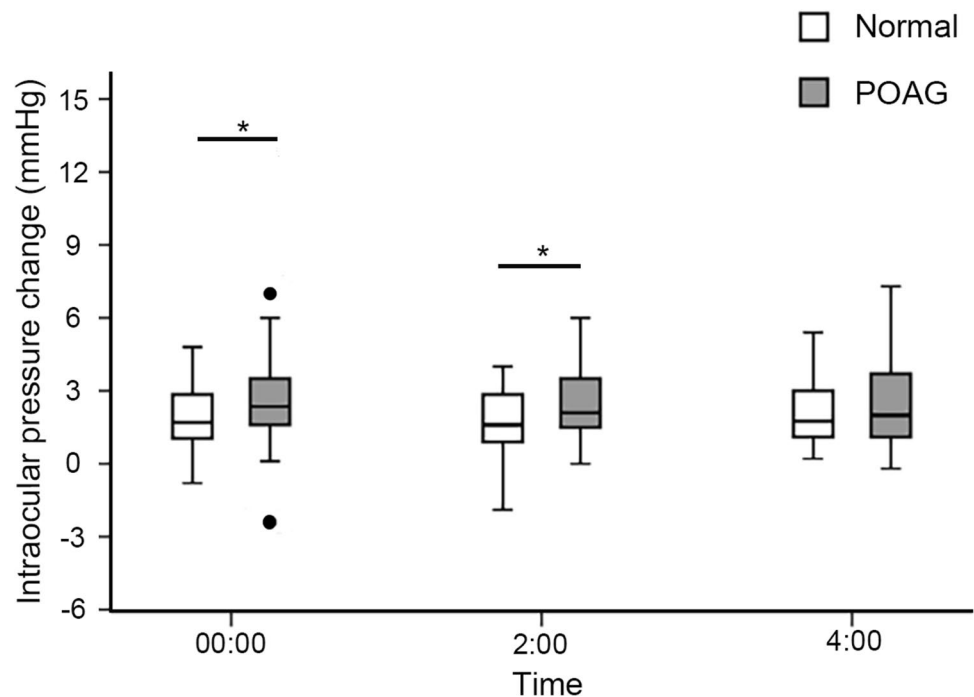
Statistically significant differences indicated for  $P < 0.05$  in bold

measure IOP in habitual position over 24 h, which reflects IOPs in patients' habitual position better and easier.

The Advanced Glaucoma Intervention Study (AGIS) showed that the most important predictors for glaucomatous optic neuropathy progression are higher mean IOP and

greater IOP fluctuation in the follow-up [24]. Besides, glaucomatous visual field progression has been demonstrated to be associated with nocturnal IOP elevation [25]. In our study, the POAG eyes, even under IOP-lowering treatment and with IOPs controlled within the normal range, had higher 24-h

**Fig. 4** The IOP changes from supine to sitting position by Icare PRO in normal and POAG groups by box plots. Box plots showed that IOP changes from supine to sitting position by Icare PRO in normal and POAG groups at the three time points of 0:00, 2:00, and 4:00. The minimum, the 25th percentile, the median, the 75th percentile, the maximum, and the outliers (•) of IOPs were presented. The changes of IOPs by Icare PRO were greater in the POAG group than those of the normal group at 0:00 and 2:00 after adjusting for eyes, age, gender, CCT, and axial length (both \*  $p < 0.05$ )



**Table 4** Changes of IOP from supine to sitting position in normal and POAG subjects by Icare PRO during nocturnal period

Time points	Normal	POAG	Model 1		Model 2		Model 3	
			$\beta$ (95%CI)	<i>p</i> value	$\beta$ (95%CI)	<i>p</i> value	$\beta$ (95%CI)	<i>p</i> value
0:00	1.92 ± 1.20	2.63 ± 2.23	0.71 (− 0.05, 1.47)	0.066	0.73 (− 0.05, 1.52)	0.067	0.80 (0.03, 1.57)	<b>0.042</b>
2:00	1.76 ± 1.17	2.53 ± 1.52	0.77 (0.26, 1.29)	<b>0.003</b>	0.73 (0.20, 1.27)	<b>0.007</b>	0.88 (0.36, 1.41)	<b>0.001</b>
4:00	2.03 ± 1.30	2.54 ± 1.76	0.51 (− 0.17, 1.19)	0.139	0.54 (− 0.18, 1.25)	0.143	0.58 (− 0.19, 1.36)	0.141

POAG, primary open-angle glaucoma; CI, confidence interval

Statistical comparisons between normal and POAG groups were performed using a mixed effect linear model

Numbers were displayed as mean ± standard deviation

Model 1, adjustment for eyes, Model 2, further adjustment for age and gender; Model 3, further adjustment for central corneal thickness and axial length

Statistically significant differences indicated for  $P < 0.05$  in bold

mean IOP and nocturnal mean IOP, greater IOP fluctuation, earlier IOP elevation in the nocturnal period in habitual position, and greater IOP change from supine to sitting position in the nocturnal period than those in normal eyes. These results were also in line with previous studies that used CLS for 24-h IOP-related parameters evaluation. Agnifili et al. and Tojo et al. reported greater 24-h IOP fluctuation in treated POAG and NTG eyes than in healthy controls [23, 26]. Mansouri et al. reported prolonged IOP peaks in 62.9–80% of POAG patients [27]. Furthermore, our results showed greater IOP variation in POAG eyes from supine to sitting position during nocturnal period compared with normal eyes, which was consistent with previous studies as well [28, 29]. Therefore, 24-h IOP in habitual position is more sensitive for detecting high nocturnal IOP peaks and large IOP fluctuation for POAG patients, which is potentially useful in the diagnosis, follow-up, and cause analysis for progression.

One of the limitations of this study was the small sample size, since the subjects had to be hospitalized overnight for every 2 h IOP measurement. Additionally, although GAT is the gold standard for IOP measurement, multiple topical anesthesia and repeated applanation are needed for GAT in 24-h IOP measurements, which could potentially cause corneal abrasion. Therefore, NCT was chosen in this study. Furthermore, although patients do not need to sit up at night, the biological rhythm would still be disturbed since they need to be awakened repeatedly, even if only Icare PRO is used for IOP measurement. A continuous IOP tonometer is probably an even better solution, which has the advantage in no sleep interruption [30]. Although the contact lens sensor is an option, it still has difficulties in data interpretation. Further effort is needed for a better continuous IOP tonometer, which could deal with the 24-h IOP measurement ideally in the future. At last, we did not investigate short-time variability of Icare PRO in this study, although six consecutive measurements were performed for Icare PRO at each time point. The built-in software automatically discarded the

highest and the lowest values, and the average IOP was calculated from the remaining four values according to the manufacturer's instruction. The short-time variability of Icare pro Tonometer needs to be investigated in further studies.

In conclusion, the results of the present study demonstrated the agreement between Icare PRO and NCT in sitting position. The Icare PRO has the advantage of being able to measure IOP in habitual position over 24 h. The POAG eyes, even if under IOP-lowering treatment, still have higher 24-h IOP level, earlier IOP peaks, and greater IOP change from supine to sitting position in the nocturnal period than those in the normal eyes. The current study highlighted the importance of detecting nocturnal elevation of IOP and emphasized the clinical use of 24-h habitual position IOP measurement in glaucoma patients.

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## Declarations

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Conflict of interest** The authors declare no competing interests.

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