Rhythm of 24-h Intraocular and Perfusion Pressure in Patients With Ocular Hypertension

Ran Xia  
Anhui No.2 Provincial People`s Hospital

Na Shu  
Anhui No.2 Provincial People`s Hospital

Huixian Cui  
Anhui No.2 Provincial People`s Hospital

JORGE AGUSTÍN TRUJILLO PERDOMO  
Instituto Cubano de Oftalmología Ramón Pando Ferrer: Instituto Cubano de Oftalmologia Ramon Pando Ferrer

Hong Zhang  
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology

Zhiqi Chen (✉ 66czq@163.com )  
Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology  
https://orcid.org/0000-0002-8322-9913

Research article

Keywords: 24-h, rhythm, intraocular pressure, intraocular perfusion pressure, ocular hypertension

DOI: https://doi.org/10.21203/rs.3.rs-125159/v1

License: ☒ This work is licensed under a Creative Commons Attribution 4.0 International License.  
Read Full License
Abstract

AIM

The aim of the present study was to characterize the rhythm of 24-h intraocular pressure (IOP) and ocular perfusion pressure (OPP) in patients with ocular hypertension (OHTN), in order to provide a reference for the clinical diagnosis and treatment of OHTN.

METHODS

According to the diagnostic criteria, 107 patients with OHTN were included, and an age- and sex-matched healthy control group (71 patients) was selected. The IOP and blood pressure (BP) of the OHTN and the healthy control groups were recorded every 2 h over a 24-h period. BP was measured using a digital automatic BP monitor, and IOP was measured using a non-contact tonometer.

RESULTS

The maximum, minimum and mean IOP were significantly higher in subjects with OHTN than in the healthy control group (P<0.05), and the maximum, minimum and mean MOPP were significantly lower in the OHTN group than in the healthy control group (P<0.05). The minimum and mean SOPP and DOPP values of the OHTN group were lower than those of the healthy control group (P<0.05), and the IOP, MOPP, SOPP and DOPP diurnal and nocturnal fluctuation values were significantly greater in the OHTN group than in the healthy control group (P<0.05). The peak and trough IOP times of the two groups coincided, which tended to be low during the day and higher at night. The peak and trough MOPP and SOPP times of the two groups also coincided, and were primarily higher during the day and lower at night. The 24-h DOPP in the healthy control group was generally higher during the daytime and lower at night, with peak values between 19:00-23:00 h, and trough values between 3:00-7:00 h. No obvious day-to-night fluctuations were observed in the OHTN group.

CONCLUSION

The OPP of patients with OHTN is lower, and the 24-h OPP fluctuates more than that of healthy control subjects. This may be an important blood flow factor for the progression to primary open angle glaucoma in patients with OHTN.

Introduction

The prevalence of ocular hypertension (OHTN) is between 1.37 and 5.40%, and the prevalence of OHTN among those > 40 years old is higher than in those with primary open angle glaucoma (POAG) [1−3]. The proportion of patients with untreated OHTN that progress to POAG is 0.5-2.0% each year [4,5]; a study reported that up to 25% of patients with OHTN developed POAG within a 10-year period [6], which resulted in irreversible blindness. The progression of OHTN is insidious, and identifying patients with OHTN who may progress to glaucoma is an important challenge in clinical diagnosis and treatment.
The blood flow theory is an important factor for the pathogenesis of POAG. Several epidemiological studies have confirmed that low systolic ocular perfusion pressure (SOPP) and/or diastolic ocular perfusion pressure (DOPP) are important risk factors for the development of glaucoma[7–9]. Furthermore, there are numerous studies reporting the 24-h IOP rhythm and OPP fluctuations of primary open-angle glaucoma (POAG). However, there are currently few reports on the rhythm of IOP and OPP fluctuations in those with OHTN.

The aim of the present study was to compare the characteristics of IOP and OPP fluctuations between patients with OHTN and healthy subjects, to highlight the OPP changes during patient follow-up, and to provide guidance for diagnosis, identification of high-risk individuals, and individualized preventive treatment. These observations aim to reduce the risk of disease, and provide a reference for the standardized, scientific diagnosis and treatment of OHTN.

**Patients And Methods**

The present study was approved by the Ethics Committee of Tongji Hospital (Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each subject prior to the start of the study.

*General information.* The OHTN group included 107 patients (107 eyes) diagnosed with OHTN in Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology between January 2016 and October 2019. The diagnostic criteria were based on the GDG (Guideline Development Group) guidelines[10] which include examinations of corneal thickness, IOP, visual field and fundus. As such, the inclusion criteria were as follows: i) The angle of the anterior chamber was checked under the anterior goniocope chamber, ensuring that it was open and with a wide angle; ii) central corneal thickness was measured, and the IOP measured using a Goldmann tonometer was > 21 mmHg at least twice in the first outpatient clinic visit without medication; iii) No obvious visual field defects, loss of optic nerve fiber layer, and/or change to the glaucoma optic papilla; and iv) no cataracts, ocular fundus lesions and/or other eye lesions, or a history of eye surgery. The control group included 71 healthy volunteers (71 eyes). The central corneal thickness was measured and the IOP corrected, and the IOP measurement was in the normal range. The anterior chamber angle was open and with a wide angle, and the optic disc structure and visual field detection were normal.

The exclusion criteria were as follows: i) History of eye surgery; ii) history of diabetes and/or heart disease; iii) history of hormone therapy; iv) presence of ocular conditions affecting ocular pressure measurement; and v) use of vasoactive drugs such as beta blockers.

The OHTN group (107 patients) including 53 males and 54 females, with an average age of 22.93 ± 12.40 years. The control group included 71 healthy volunteers (36 male and 35 female) with an average age of 22.79 ± 6.64 years. There were no significant differences in sex and age between the two groups.
**Methods.** All research subjects remained in hospital for 24-h IOP and blood pressure (BP) measurements. BP was determined using a blood pressure monitor (model, HEM-907; OMRON Corporation). After lying flat for 5 min, the patient was returned to the sitting position and BP was measured using the right arm; BP measurements were taken twice, 5 min apart, and the mean of the 2 readings was then considered as the BP of that individual. A third measurement was taken if the systolic BP (SBP) differed by > 10 mm Hg or if the diastolic BP (DBP) differed by > 5 mm Hg. The median of the 3 readings was then considered to be the BP of that individual. A non-contact tonometer (Nidek Co., Ltd.) was used to take IOP measurements. IOP and BP were recorded at 1:00, 3:00, 5:00, 7:00, 9:00, 11:00, 13:00, 15:00, 17:00, 19:00, 21:00 and 23:00 h. The IOP measurement was taken in a sitting position, the IOP value was taken from the right eye measurement value, and the average value of 3 readings was recorded. Mean arterial pressure (MAP) = diastolic BP + 1/3 (systolic BP - diastolic BP); mean ocular perfusion pressure (MOPP) = 2/3 MAP - IOP; systolic ocular perfusion pressure (SOPP) = systolic BP - IOP; diastolic ocular perfusion pressure (DOPP) = diastolic BP - IOP. All monitoring was performed by professionals in the inpatient Department of Ophthalmology.

**Observational indicators.** The following indicators were observed; i) IOP peak value, trough value, mean average value of 12 measurements, and fluctuation value (the difference between the peak and trough values from 12 measurements); ii) the maximum, minimum, mean and fluctuation mean arterial pressure (MAP) values of 12 measurements; and iii) the maximum, minimum, mean and fluctuation values for MOPP, SOPP and DOPP.

**Statistical Analysis.** Statistical analysis was performed using SPSS 22.0 (IBM, Corp). Continuous variables are expressed as the mean ± SD where appropriate, and were compared using the independent samples t-test. P < 0.05 was considered to indicate a statistically significant difference.

**Results**

*Comparison of 24-h IOP and OPP peak, trough, mean and fluctuation values between the OHTN and healthy control groups.* The mean 24-h IOP of the OHTN group (22.85 ± 2.82 mmHg) was higher than that of the healthy control group (15.81 ± 1.60 mmHg; t=-19.103; P < 0.01). The 24-h IOP diurnal and nocturnal fluctuation difference was higher in the OHTN group (8.91 ± 3.07 mmHg) than in the healthy control group (5.89 ± 0.86 mmHg; t=-8.085; P < 0.01) (Table 1).
Table 1 24-h IOP values

| Value       | OHTN group, mean ± SD | Control group, mean ± SD | t-value | P-value |
|-------------|------------------------|--------------------------|---------|---------|
| IOP peak    | 27.60 ± 3.80           | 18.97 ± 1.47             | -18.24  | < 0.001 |
| IOP trough  | 18.71 ± 2.91           | 13.08 ± 1.74             | -14.68  | < 0.001 |
| IOP mean    | 22.85 ± 2.82           | 15.81 ± 1.60             | -19.1   | < 0.001 |
| IOP fluctuation | 8.91 ± 3.07       | 5.89 ± 0.86              | -8.085  | < 0.001 |

OHTN, ocular hypertension; IOP, intraocular pressure.

The differences in MOPP, SOPP, DOPP and MAP between the OHTN and healthy control groups are displayed in Table 2. The maximum MAP values in the OHTN group were significantly higher than those in the healthy control group (P < 0.05), though there was no significant difference in the minimum and mean MAP values between the two groups. The maximum, minimum and mean MOPP values were significantly lower in subjects with OHTN than in the healthy controls (P < 0.05). There were no significant differences in the maximum SOPP and DOPP values between the OHTN and the healthy control group, and the minimum and mean SOPP and DOPP values in the OHTN group were lower than those in the healthy control group (P < 0.05). Regarding the fluctuation difference between the two sets of data, the IOP, MAP, MOPP, SOPP and DOPP diurnal and nocturnal fluctuation values were significantly larger in the OHTN group than in the healthy control group (P < 0.05).
| Variable | OHTN group, mean ± SD | Control group, mean ± SD | t-value | P-value |
|----------|-----------------------|--------------------------|---------|---------|
| MOPP     |                       |                          |         |         |
| Maximum  | 43.90 ± 7.62          | 46.89 ± 4.70             | 2.954   | 0.004   |
| Minimum  | 27.16 ± 6.21          | 35.46 ± 4.31             | 9.809   | < 0.001 |
| Mean     | 35.53 ± 6.36          | 41.15 ± 4.55             | 6.634   | < 0.001 |
| Fluctuation | 16.72 ± 5.64    | 11.43 ± 3.02             | -7.24   | < 0.001 |
| SOPP     |                       |                          |         |         |
| Maximum  | 107.51 ± 16.17        | 105.99 ± 8.75            | -0.724  | 0.470   |
| Minimum  | 77.07 ± 12.09         | 87.04 ± 7.50             | 6.2     | < 0.001 |
| Mean     | 91.57 ± 13.57         | 96.03 ± 8.30             | 2.478   | 0.014   |
| Fluctuation | 29.94 ± 100.05      | 18.95 ± 4.75             | -8.594  | < 0.001 |
| DOPP     |                       |                          |         |         |
| Maximum  | 62.87 ± 10.41         | 63.95 ± 6.82             | 0.767   | 0.444   |
| Minimum  | 390.01 ± 8.80         | 49.08 ± 6.43             | 8.292   | < 0.001 |
| Mean     | 50.48 ± 8.13          | 56.43 ± 6.47             | 5.169   | < 0.001 |
| Fluctuation | 23.86 ± 8.93      | 14.86 ± 4.14             | -7.943  | < 0.001 |
| MAP      |                       |                          |         |         |
| Maximum  | 98.46 ± 10.73         | 91.92 ± 7.04             | -4.528  | < 0.001 |
| Minimum  | 77.59 ± 9.17          | 79.49 ± 6.63             | 1.498   | 0.136   |
| Mean     | 87.51 ± 9.58          | 85.24 ± 6.82             | -1.726  | 0.086   |
| Fluctuation | 20.87 ± 7.89      | 12.27 ± 3.96             | -8.497  | < 0.001 |

OHTN, ocular hypertension; MOPP, mean ocular perfusion pressure; SOPP, systolic ocular perfusion pressure; DOPP, diastolic ocular perfusion pressure; MAP, mean arterial pressure.

**OHTN and healthy control group 24-h IOP, MOPP, SOPP and DOPP fluctuation curves.** The mean and standard deviation values for the IOP, MOPP, SOPP and DOPP of the two groups were plotted at 12 timepoints (Fig. 1–4). In the OHTN group, the peak IOP time was at 5:00–9:00 h, and the trough time was at 19:00–23:00 h; the peak IOP time in the healthy control group was at 5:00–9:00 h, and the trough time was between 17:00–23:00 h. The peak and trough IOP times of the two groups coincided. The peak MOPP time in the OHTN group was at 17:00–23:00 h, and the trough time was at 1:00–5:00 h. In the healthy control group, the peak MOPP time was at 19:00–23:00 h, while the trough time was between
3:00 and 7:00 h. Furthermore, the peak SOPP time of in the OHTN group was between 17:00 and 21:00 h, with a trough time at 1:00–5:00 h. The peak SOPP time in the healthy control group was at 17:00–23:00 h, and the trough time was between 3:00 and 7:00 h. The peak and trough MOPP and SOPP times of the two groups coincided, with a trend towards high day and low night values. The 24-h DOPP in the healthy control group tended to be higher in the day and lower at night, with peak values between 19:00–23:00 h and trough values between 3:00–7:00 h. No obvious changes in the day and night values were observed in the OHTN group.

**IOP peak, MOPP peak and MOPP trough frequency distribution between the OHTN and healthy control groups.** Within a 24-h period, peak IOP frequency distribution in the OHTN group was the highest at 1:00, 5:00 and 11:00 h, with a composition ratio of 15.89, 15.89 and 14.02%, respectively; these times were at 7:00, 3:00 and 5:00 h in the healthy control group, with a composition ratio of 18.31, 16.90 and 12.68%, respectively. The top three times with the highest frequency distribution of peak MOPP were 9:00, 19:00 and 17:00 h in the OHTN group (with a composition ratio of 13.08, 13.08 and 12.15%, respectively), and 21:00, 23:00 and 19:00 h in the healthy control group (with a ratio of 28.17, 21.13 and 18.31%, respectively). The three timepoints with the highest MOPP trough distribution frequency were 1:00, 3:00 and 5:00 h in the OHTN group (with a composition ratio of 17.76, 16.82 and 14.02%, respectively), and 3:00, 7:00 and 5:00 h in the healthy control group (the composition ratio of which was 22.54, 22.54 and 15.49%, respectively) (Fig. 5–7).

**Discussion**

The aim of the present study was to comprehensively observe the changes in IOP and OPP in patients with OHTN over a 24-h period. The maximum, minimum and mean IOP were significantly higher, and the maximum, minimum and mean MOPP were significantly lower in patients with OHTN than in healthy control subjects (P < 0.05). The minimum and mean SOPP and DOPP values in the OHTN group were lower than those in the healthy controls (P < 0.05). The IOP, MOPP, SOPP and DOPP diurnal and nocturnal fluctuation values were significantly larger in the OHTN group than in the healthy control group (P < 0.05). Furthermore, the peak and trough IOP timepoints were similar in both groups, with a trend towards low values during the day and higher values at night. The peak and trough MOPP and SOPP times for the two groups also overlapped, with higher daytime values which declined at night. The 24-h DOPP in the healthy control group tended to be high during the day and low at night, with peak values between 19:00 and 23:00 h and trough values between 3:00 and 7:00 h. No obvious changes were observed in the OHTN group from day to night. Over the 24-h timeframe, the top three times with the greatest frequency of peak IOP counts were 1:00, 5:00 and 11:00 h in the OHTN group, while those in the healthy control group were 7:00, 3:00 and 5:00 h. The top three times at which the highest frequency distribution of MOPP trough values occurred were 1:00, 3:00 and 5:00 h in the OHTN group, and 3:00, 7:00 and 5:00 h in the healthy control group.

There are various methods for conducting tonometry, including the use of, for example, the Schiotz tonometer, the Goldmann applanation tonometer, the Ton-Pen tonometer and the non-contact tonometer.
Each tonometer has its own advantages and disadvantages. The Goldmann applanation tonometer method is the internationally recognized gold standard for IOP measurement, but its clinical application is more cumbersome. The non-contact tonometer (NCT) method is non-invasive, requires no anesthetic and is easy to perform. It is widely used in the clinic and is more suitable for repeated IOP measurements within a 24-h period, the accuracy of which has been confirmed in previous studies. Additional methods were adopted in the present study, which included sitting in the daytime and sitting immediately after waking up at night; these factors minimize the influence of higher suprasceral vein pressure and BP on the IOP results during the nocturnal position (lying flat). Therefore, the sitting position was uniformly adopted and the comparison standard was unified.

In the current study, the overall IOP of the OHTN group was increased, the mean IOP was higher, and the fluctuation amplitude of the diurnal and nocturnal IOP (8.91 ± 3.07 mmHg) was significantly higher than that of the healthy control group (5.89 ± 0.86 mmHg). Xu et al.[11] studied the repeatability of 24-h IOP monitoring in OHTN, and found that the two 24-h IOP fluctuation values were 8.94 ± 3.03 mmHg and 9.06 ± 3.19 mmHg, which is similar to the results of the current study (8.91 ± 3.07 mmHg). At the same time, Xu et al reported that the peak IOP occurred at 6:00 h, and that the trough IOP was observed at 20:00 h, which is similar to the results of the current study. Grippo et al[12] revealed that in habitual positions (diurnal sitting and nocturnal supine), the peak IOP occurred at 11:30 – 5:30 h, and the trough at 5:30 – 21:30 h; while in the supine position, the peak IOP was primarily observed at 7:30 – 3:30 h, and the trough occurred at 17:30 – 23:30 h. In the present study, a sitting position was adopted. Although the IOP peak time was at 9:00 h in patients with OHTN, the peak IOP occurred most frequently at 1:00 and 5:00 h, which is not consistent with the results of the aforementioned studies. The IOP value can be influenced by various random factors, such as light, activity or fluid intake, in addition to the habitual activities of the subject during the day, which may increase IOP variability. A large number of studies have confirmed that elevated IOP and higher IOP diurnal and nocturnal fluctuations are important risk factors for POAG[13,14], but that OHTN does not result in glaucoma-associated optic nerve damage. In recent years, scholars have discovered that the pressure difference across the sieve plate, which is the difference between IOP and intracranial cerebrospinal fluid pressure, is an important factor for the pathogenesis of glaucoma. It is speculated that patients with OHTN may experience high intracranial pressure resulting in low-pressure differences across the sieve plate, such that glaucoma-associated optic nerve injury does not occur [15].

A large number of studies have confirmed that the vascular mechanism is an influencing factor for the pathogenesis of glaucomatous optic nerve injury. Insufficient or unstable blood supply to the eye can cause optic nerve and axon ischemia and/or reperfusion injury. OPP is an important factor in determining blood flow in the eye. Using the OPP calculation formula, it can be seen that an increase in IOP or a decrease in BP results in a decrease in OPP, which may cause hypoxia and ischemia in the optic nerve, initiating or aggravating visual field defects in patients with POAG.

A Handan Eye Study revealed that the SOPP, DOPP and MOPP of patients with POAG were consistently lower than those of suspected POAG patients, indicating that OPP plays an important role in the
development of glaucoma [3]. An epidemiological study in Singapore indicated that lower MOPP, SOPP and DOPP were independent risk factors for POAG [9]. Early research in Barbados demonstrated that DOPP was decreased by 20% and that the incidence of glaucoma was increased by 3.3 times in patients with POAG. After a 9-year follow-up study, low SOPP, low DOPP and low MOPP were confirmed to be risk factors for glaucoma [16]. Additionally, Topouzis et al [17] suggested that DOPP was more highly correlated with the progression of POAG than SOPP.

Low perfusion pressure and vascular autoregulatory dysfunction are important factors in the pathogenesis of glaucoma. Choi et al [8] assessed patients with normal tension glaucoma for > 6 years, and found that the progression of visual field defects was closely associated with the fluctuation amplitude of the 24-h OPP. Moreover, Sung et al [14] followed 101 patients with normal-tension glaucoma for > 4 years and found that the 24-h MOPP fluctuations of those with progressive visual field damage were significantly greater than those without progression.

Sehi et al [18] revealed that the daily percentage reduction in MOPP of untreated POAG patients was significantly higher than that of normal subjects, indicating that relative diurnal changes in MOPP may be a risk factor for POAG. These findings suggest that the alterations in OPP are closely associated with the occurrence and development of glaucoma. Although countless individuals experience low OPP, they do not develop glaucoma due to a normal self-adjusting ability which compensates for the low blood supply caused by low OPP. In the capillary bed of these individuals, and in the range of automatic adjustment ability, a change in perfusion pressure will not cause a change in blood flow [19,20]. When the posture changes, IOP increases or blood pressure decreases, and the vascular autoregulation mechanism is required to maintain OPP stability. OHTN may be due to the normal automatic adjustment ability, which can compensate for the low blood supply resulting from low OPP, thus glaucoma does not develop.

In the present study, the MOPP trough times were between 1:00 and 3:00 h, which are considered to be non-working hours. This suggests that it is best to monitor changes in the 24-h OPP when observing the OHTN perfusion pressure, and to pay particular attention to the occurrence of low OPP at night. The average and fluctuating DOPP values in OHTN subjects were significantly higher than those in the healthy control group. Furthermore, compared with MOPP and SOPP, no significant change in trend was observed, suggesting that changes in DOPP are more sensitive indicators of OHTN than those in MOPP and SOPP. These findings are consistent with the results of Topouzis et al [17], suggesting that DOPP is more highly correlated with POAG progression than SOPP. Therefore, for the future diagnosis and treatment of OHTN, more attention should be paid to changes in DOPP.

There are some shortcomings to the present study. Firstly, the study was conducted over a 1-year period; seasonal changes in temperature may influence IOP and BP, which require further research in the future. Secondly, the traditional posture was adopted, and the IOP at night was measured after waking. At this time, the subject’s physiological status, such as hormone levels and the effect of the eyelids, may change, and may cause differences from the IOP measured in the lying position. Thirdly, taking measurements every 2 h cannot fully reflect these physiological changes, and measurements at night will inevitably be
affected by other factors, such as exposure to light. In future studies, measurements may be taken using a 24-h tonometer \cite{21}, or a simpler tool might be developed to allow measurements to be taken in the patients’ home. Ultimately, carrying out day and night IOP and OPP monitoring will help to improve our understanding of IOP and OPP fluctuations to guide the treatment of those with OHTN.

**Declarations**

**Acknowledgements**

Not applicable.

**Funding**

This study was supported by grants from the National Natural Science Foundation of China (grant numbers 81300760).

**Conflicts of Interest:** RAN XIA, None; NA SHU, None; HUIXIAN CUI, None; JORGE AGUSTÍN TRUJILLO PERDOMO, None; HONG ZHANG, None; ZHIQI CHEN, None.

**Availability of data and materials**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate**

The present study was approved by the Ethics Committee of Tongji Hospital (Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China) and written informed consent was obtained from each subject prior to study commencement.

**Patient consent for publication**

All of the patients have informed consent and signed an informed consent form.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

HZ, NS, JORGE ATP and RX perform the patient's intraocular pressure and blood pressure measurement. RX and HXC analyzed and interpreted the patient data. RX and NS were a major contributor in writing the manuscript. ZQC is the corresponding author. Ran Xia and Na Shu contribute equally to the work presented here and should therefore be regarded as equivalent authors. All authors read and approved the final manuscript.
References

1. Friedman DS, Wolfs RC, O'Colmain BJ, Klein BE, Taylor HR, West S, et al. Prevalence of open-angle glaucoma among adults in the United States. Arch Ophthalmol. 2004;122:532-538.

2. Varma R, Ying-Lai M, Francis BA, Nguyen BB, Deneen J, Wilson MR, et al. Prevalence of open-angle glaucoma and ocular hypertension in Latinos: the Los Angeles Latino Eye Study. Ophthalmology. 2004;111:1439-1448.

3. Liang YB, Friedman DS, Zhou Q, Yang X, Sun LP, Guo LX, et al. Prevalence of primary open angle glaucoma in a rural adult Chinese population: the Handan eye study. Invest Ophthalmol Vis Sci. 2011; 52:8250-8257.

4. Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002; 120:714-720.

5. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP et al. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002; 120:701-713.

6. Salvetat ML, Zeppieri M, Tosoni C, Brusini P; Medscape. Baseline factors predicting the risk of conversion from ocular hypertension to primary open-angle glaucoma during a 10-year follow-up. Eye (Lond). 2016; 30:784-795.

7. Ramdas WD, Wolfs RC, Hofman A, de Jong PT, Vingerling JR, Jansonius NM. Ocular perfusion pressure and the incidence of glaucoma: real effect or artifact? The Rotterdam Study. Invest Ophthalmol Vis Sci. 2011, 52:6875-6881.

8. Choi J, Lee JR, Lee Y, Lee KS, Na JH, Han S, et al. Relationship between 24-hour mean ocular perfusion pressure fluctuation and rate of paracentral visual field progression in normal-tension glaucoma. Invest Ophthalmol Vis Sci. 2013;54: 6150-6157.

9. Zheng Y, Wong TY, Mitchell P, Friedman DS, He M, Aung T. Distribution of ocular perfusion pressure and its relationship with open-angle glaucoma: the Singapore Malay Eye Study. Invest Ophthalmol Vis Sci. 2020; 51:3399-3404.

10. National Collaborating Centre for Acute Care (UK). Glaucoma: Diagnosis and Management of Chronic Open Angle Glaucoma and Ocular Hypertension. London: National Collaborating Centre for Acute Care (UK). 2009.

11. Xu S, Jiao Q, Cheng Y, Sun J, Lu Q, Zhong Y. Short-Term Reproducibility of Twenty-Four-Hour Intraocular Pressure Curves in Untreated Patients with Primary Open-Angle Glaucoma and Ocular Hypertension. PLOS ONE. 2015;14.

12. Grippo TM, Liu JH, Zebardast N, Arnold TB, Moore GH, Weinreb RN. Twenty-four-hour pattern of intraocular pressure in untreated patients with ocular hypertension. Invest Ophthalmol Vis Sci. 2013; 54:512-517.
13. Asrani S, Zeimer R, Wilensky J, Gieser D, Vitale S, Lindenmuth K. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. J Glaucoma. 2000;9:134-142.

14. Sung KR, Lee S, Park SB, Choi J, Kim ST, Yun SC, et al. Twenty-four hour ocular perfusion pressure fluctuation and risk of normal-tension glaucoma progression. Invest Ophthalmol Vis Sci. 2009; 50:5266-5274.

15. Ren R, Zhang X, Wang N, Li B, Tian G, Jonas JB. Cerebrospinal fluid pressure in ocular hypertension. Acta Ophthalmol. 2011;89: e142-148.

16. Leske MC, Connell AM, Wu SY, Hyman LG, Schachat AP. Risk factors for open-angle glaucoma. The Barbados Eye Study. Arch Ophthalmol. 1995;113:918-924.

17. Topouzis F, Wilson MR, Harris A, Founti P, Yu F, Anastasopoulos E, et al. Association of open-angle glaucoma with perfusion pressure status in the Thessaloniki Eye Study. Am J Ophthalmol. 2013;155(5):843-851.

18. Sehi M, Flanagan JG, Zeng L, Cook RJ, Trope GE. Relative change in diurnal mean ocular perfusion pressure: a risk factor for the diagnosis of primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 2005; 46:561-567.

19. Portmann N, Gugleta K, Kochkorov A, Polunina A, Flammer J, Orgul S. Choroidal blood flow response to isometric exercise in glaucoma patients and patients with ocular hypertension. Invest Ophthalmol Vis Sci. 2011; 52:7068-7073.

20. Flammer J, Mozaffarieh M. Autoregulation, a balancing act between supply and demand. Can J Ophthalmol. 2008;43:317-321.

21. Molaei A, Karamzadeh V, Safi S, Esfandiari H, Dargahi J, Khosravi MA. Upcoming Methods and Specifications of Continuous Intraocular Pressure Monitoring Systems for Glaucoma. J Ophthalmic Vis Res. 2018; 13:66-71.