Diurnal Variation of Intraocular Pressure in Normal and Ocular Hypertensive Subjects of China

Xiao Rong Xi, Xiang Dong Wu, Yang Bin Huang, HuiJuan Lu, Ekhtiar Shiarkar (The School of Basic Medical Sciences, Shanghai Medical University, Shanghai, People’s Republic of China.)
Imran Ahniad Queshi (Department of Physiology, Rawalpindi Medical College, Rawalpindi.)

Abstract
This study evaluated the distribution of Intraocular pressure (IOP) levels in 67 normal and 59 ocular hypertensive (OHT) subjects during the day after placing control on all those factors that can affect IOP. The IOP was measured with the Goldmann applanation tonometer. All the subjects were examined according to standard protocols. Both in the normal and OHT subjects, the peak of mean IOP appeared in the morning when the subjects woke up and the trough of mean IOP occurred between 2 a.m. to 4 a.m. The mean diurnal variation was (mean±sem) 2.9±0.7 and 3.5±0.7 mmHg in the normal and in OHT subjects, respectively. Ninety-four percent of the normal subjects and sixty-eight percent of the OHT subjects exhibited a similar diurnal behaviour in both eyes. The IOP variation did not correlate with the variations of blood pressure. The diurnal variation of IOP, found in Chinese, is lower than in other nations. The clinical importance of findings that the peaks of IOP occur in the early morning, raised a serious question as to the necessity of extending the diurnal IOP curves beyond the usual working time (JPMA 46:171, 1996).

Introduction
Maslenikwo first described the diurnal variation of intraocular pressure (IOP) in 1904. IOP is subject to chronobiological rhythms similar to other physiological values in the human body, such as body temperature, heart rate, blood pressure and hormone secretion. Many investigators have postulated that the diurnal variation does not usually exceed 3-6 mmHg in normal eyes. There are conflicting reports in the literature, however, as to the time of the day at which the peak IOP occurs during the IOP curves. Weitzman et al described the 24-hour pattern of IOP in normal subjects with measurements made hourly. They reported that the lowest ocular tension occurred between 2 and 4 a.m., with the subsequent rise taking place during the later third of the night’s sleep. Zeimer et al considered that the momentary IOP elevation is associated with wakening. In contrast to this, other investigators have shown that IOP was highest at 2 p.m. Most of the previous studies have several drawbacks. In recent years it has been noted that intraocular pressure is a dynamic function and is subject to many influences both acutely and over the long term. Many investigators have reported that IOP varies with sex and seasons. It has been reported that drinking water, coffee or alcohol before measurement of IOP has a significant effect on it. Acute hyperglycaemia decreases, while chronic hyperglycaemia as in diabetes, increases IOP. Several studies have shown that intraocular pressure is positively correlated with systemic blood pressure. Moreover, racial differences and environmental conditions also have a significant influence on IOP.

After placing control on all the above mentioned IOP influencing factors, this study was planned to evaluate the distribution of IOP levels, during the day, in the normal and ocular hypertensive (OHT) subjects of Shanghai, the largest city of People’s Republic of China.
**Patients and Methods**

All experimental procedures adhered to the Declaration of Helsinki of the World Medical Association. The sample of present study consisted of 67 healthy and 59 OHT subjects with a mean age of 32±S.D. 7 years and 38±S.D. 9 years respectively. All were males. No OFIT subject was taking any medicine. History concerning previous ocular diseases, presence of diabetes mellitus and the occurrence of glaucoma in the family was taken. The criteria for inclusion were absence of any history of eye surgery and diabetes, normal body temperature and blood pressure. Subjects were asked not to smoke or drink and have a complete rest at least 30 minutes before the measurement of IOP. The OHT subjects had at least three TOP readings equal to or greater than 22 mmHg, but nonnal visual fields and normal optic nerves without evidence of asymmetric cupping. To avoid the seasonal variations, this study was conducted only in winter. The subjects were asked to live in the hospital during the three days of examination. The blood pressure was taken in sitting position. After installation of 0.25% fluorescein and 0.4% benoxinate hydrochloride (Fluress) eye drops, the IOP was measured with the Goldmann applation tonometer (Goldmann Topocon, Germany), first in the right eye and then in the left. The measuring drum was turned until the innerborders of the fluorescein rings (adjusted for equal size) just touched each other at the midpoint of the ocular pulse and the overlap and separation of the mires with each pulse swing was equidistant from the midpoint on both sides. The measuring drum was not to be observed until this defined point was reached. Three consecutive readings of each eye were taken. After each reading the tonometer was removed from the contact and the measuring scale was returned to 10 mmHg. The practice of returning the tonometer to 10 mmHg, after each reading would minimize observer bias. After waking, the TOPs were measured immediately, which were repeated after 30 minutes, 1 hour and every three hours till next waking. During the period of these three hours, to minimize the effect of food and water, only in the first hour, subjects were allowed to eat and drink. Before each measurement, the subjects took a rest of 30 minutes in supine posture.

**Statistical Analyses.** The mean of the three readings was computed separately for each eye. Intraocular pressures were measured in whole numbers, but for statistical accuracy, the mean values have been expressed up to one decimal point. For all variables descriptive statistics (mean, standard deviation, standard error of mean) were calculated by Statistical Analysis System 76. All data are expressed as mean and standard error of the mean. Analysis of variance (ANOVA) was used to compare results between different times. Differences are regarded as significant when the P value was less than 0.05. Actual P values are given where appropriate.

**Results**

Intraocular pressure determined for 24 hours are shown in Figure 1.
Both in the normal subjects and OHT subjects, the peak mean IOP appeared in the morning when the subject woke and the trough of mean IOP occurred at 2 a.m. to 4 a.m.. The diurnal intraocular pressure curves revealed that the IOP peak was 15.6±0.8 mmHg in the normal and 24.3±1.5 mmHg in OHT subjects. Whereas, the trough were 12.7±0.6 and 20.8±1.7 mmHg in the normal and OHT subjects.

Figure 1. Mean IOP recorded at various times in ocular hypertensive (●) and normal (△) subjects.
respectively. The mean diurnal variation was 2.9±0.5 mmHg (P<0.02) in the normal and 3.5±0.6 mmHg (P<0.01) in OHT subjects. Ninety-four percent of normal subjects and sixty-eight percent of OHT subjects exhibited a similar diurnal behaviour in both eyes.

In Figure 2 the distribution of peak IOP reading in the normal and ocular hypertensive subjects, at the seven different times, is presented. Among the normal subjects, overall 56% of peaks were found on the first earliest IOP measurement in the morning, whereas in the OHT subjects, at the same time, about 58% of peaks were found. The blood pressure of all the subjects was in normal range. The IOP did not correlate with the variation of blood pressure determined along with IOP (data not shown).

Discussion

This study demonstrates the IOP peak presents upon waking. Review of previous studies of the diurnal variation in IOP shows considerable variation when compared to the current study. The difference among studies may be due to various factors. In recent years, it has been noted that intraocular pressure is a dynamic function and is subject to many endogenous influences both acutely and over the long term. The variability in the results of previous studies may be due to negligence of several variables, including sex, drinking of water, coffee or alcohol before IOP measurement, seasonal variations etc. After taking into account all those factors that can affect intraocular pressure, the diurnal variation of IOP in Chinese, reported by this study, is lower than that in other nations reported by previous studies. The presence of an elevated IOP upon awaking is puzzling. Some investigations suggested a mechanism that could account for both the rise and the decline of IOP. Hormonal
variation\textsuperscript{14,15} autonomic or humeral control\textsuperscript{16,17} and changes in the vascular tone\textsuperscript{18} have been suggested as factors affecting the aqueous outflow. Gloster and Pinoosawmy\textsuperscript{19} concluded that one hour in darkness caused an increase in IOP that decreased upon exposure to light. They also pointed out that the dilatation and constriction of the pupil were not the main cause of IOP variations. Brown et al\textsuperscript{20} mentioned that melatonin could be involved in the process, but as they point out, the fact that the IOP increases also with sleep, when the melatonin level is presumably low, tends to cast doubts on this explanation. The IOP is expected to be low at night based on the fact that aqueous production is decreased during sleep\textsuperscript{21}. Therefore, it seems that the elevated IOP is related to sleep close to the time of awaking or to the wakening process itself. The sudden rise in blood pressure has been reported to occur upon waking\textsuperscript{22}. This could cause an increase in ocular blood volume, mostly in the choroid and thereby lead to an increase in IOP. This pressure peak would only be momentary because it would decrease with time due to flow of aqueous out of the eye and/or regulatory vascular mechanisms\textsuperscript{5}. In ocular hypertensive subjects, if the decline is mainly governed by outflow, the time decay can be expected to be in the range of tonographic decay, which is approximately 10 mmHg in 4 minutes for IOPs, between 20 and 30 mmHg\textsuperscript{23}

It is commonly believed that there is a fair degree of symmetry between fellow eyes\textsuperscript{24}. In the current study, a considerable prevalence of differences in the diurnal IOP pattern between the two eyes of ocular hypertensive and normal persons has been noted. This suggests that factors specific to each affected eye may interfere with systemic regulatory components and thus play an important role in determining the IOP.

The diurnal IOP variation, a physiological rhythm, is essentially a metabolic cycle synchronized with the external periodicity of day and night through the influence of variations in illumination, temperature and other environmental factors, on the nervous and endocrine systems. The existing literature shows the influence of hormones upon intraocular pressure. There is evidence that corticotropin, vasopressin, thyroxin, insulin, glucocorticoids and mineralocorticoids play a role in the physiologic regulation of intraocular pressure. Growth hormone, progesterone, estrogen, chorionic gonadotropin and relaxin may influence intraocular pressure when administered in pharmacologic doses. Some of these hormones increase, while others decrease intraocular pressure\textsuperscript{25}. Diurnal changes in intraocular pressure have been correlated with circulating eosinophil levels\textsuperscript{26}, although this relationship has been challenged by other investigators\textsuperscript{27}. Patients with Cushing’s syndrome have been reported to have increased diurnal variations of intraocular pressure\textsuperscript{28} and conversely, patients with adrenal or pituitary insufficiency have shown decreased diurnal variations of intraocular pressure\textsuperscript{28,29}. Linner\textsuperscript{29} felt that this was due to a lack of variation in aqueous flow. Correlations between diurnal fluctuations in intraocular pressure and plasma glucocorticoid levels have been found in normal individuals and in patients with glaucoma\textsuperscript{30}. There seemed to be a four-hour lag between the peak level of the plasma glucocorticoids and the peak in intraocular pressure\textsuperscript{30}. Administration of SU4885, an inhibitor of glucocorticoid and mineralocorticoid synthesis\textsuperscript{30} diminished the diurnal fluctuation of intraocular pressure\textsuperscript{31}. Alterations in the mucopolysaccharide content of the anterior chamber or the trabecular tissues have been noted after administration of glucocorticoids by some investigators\textsuperscript{21}. while other investigators failed to find this alteration\textsuperscript{32}. Radnor\textsuperscript{33} noted that unilateral adrenalectomy in rabbits decreased intraocular pressure on the ipsilateral side. Bilateral adrenalectomy decreased intraocular pressure and aqueous flow\textsuperscript{34}. In summary, it would appear that endogenous glucocorticoids may play a role in the physiologic regulation of IOP through aqueous inflow and perhaps aqueous outflow. Pharmacologic doses of glucocorticoids affect both facilities of outflow and aqueous inflow, although it is unknown whether this is a direct effect of the glucocorticoids or a secondary effect. In one review, Waitzmar concluded that the hypothalamus might be the major central nervous system...
controlling site for changes in IOP. Certainly, the 24-hour correlative relationships with differing hypothalamic controlled circadian events, such as neuroendocrine processes, body temperature, sleep-waking functions and autonomic activity would support that this central nervous system area may be critically involved.

We realize that starting the diurnal variation curve of IOP in the clinic around 8 am. is less than ideal, because the highest IOP occurs immediately after waking. It is also possible that the home tonometry, as advocated by Zeimer, covers a larger portion of the 24 hour cycle. Nevertheless, the widely employed practice today is IOP measurement by ophthalmologists in their offices and therefore, the information collected and presented here is still useful. The clinical importance of our finding, that the peak IOPs occur in the early morning, raised a serious question as to the necessity of extending the diurnal IOP curves beyond the usual working time. More important, it emphasises the fact that solitary IOP examination taken in the afternoon may miss most of IOP peaks. This finding indicates that a revision of the timetable for IOP examination in the ocular hypertensive patients may be warranted.

References
1. Maslenikwo, A. Uber Thgseschwankungen des intraokularen druckes bei glaukom. Z. Augenheilkd., 1904;11:564-570
32. Futa, R. Enzymatic histochemical studies on the angle of the anterior chamber.