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ORIGINAL ARTICLE

PHYSIOLOGICAL VARIABLE AFFECTING INTRA OCULAR PRESSURE: DIURNAL VARIATIONS

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ABSTRACT: BACKGROUND: The existence of a diurnal variation in the Intra ocular Pressure (IOP) of both normal and glaucomatous eyes is well documented. However, the magnitude and pattern of that variation remains in conjecture. **AIM:** To study the diurnal fluctuation of the IOP in the normal subjects. **MATERIALS AND METHODS:** The study group consisted of 92 volunteers, visually normal as subjects, 50 boys and 42 girls in the age group of 18 to 20 years. Independent measurements of the IOP of each eye were obtained during the day with the subject in the upright position. The first measurement was undertaken between 8-9AM, the second between 12 Noon-1PM and the final reading between 5-6PM. The subjects carried normal routine activity during the period of measurement. Keelar Pulsair air impulse tonometer was used in all the subjects for IOP measurement. IOP was measured in the department of Ophthalmology, Teaching Hospital. **STATISTICAL ANALYSIS**: were done using Paired 't' test. **RESULTS:** The mean IOP of all the subjects decreased by 2.304 mmHg during the day. The change was statistically significant (<0.001). Mean IOP decreased by 2.977mmHg during the day in 83.69% of the subjects, all showing peak pressures in the morning. In a small proportion of subjects (10.86%) the mean increased by 1.75mm Hg which was not statistically significant. In 5.43% of the subjects the IOP remained the same during the day. The present study did not find any association between age, sex and the IOP parameters examined (Time of peak, trough and diurnal fluctuation). **CONCLUSION:** IOP decreased during the in a large number of subjects (83.69%). The peak IOP was before noon. The diurnal IOP variation is quite minimal averaging 3-4 mm Hg but a single measurement taken during the late afternoon or evening may miss IOP peak. There is no method to continually measure IOP. Even a large number of pressure measurements dispersed through a 24-hour period may miss the peak pressure for that day. Thus, it is obvious that any choice of measurement is arbitrary. Many factors are responsible for daily fluctuations in IOP. Some of these factors operate at the level of the eye.

KEYWORDS: Intra Ocular Pressure (IOP), diurnal variation, Keelar Pulsair Non-Contact Tonometer, cortisol, melatonin.

INTRODUCTION: Intra Ocular Pressure (IOP) is subject to chronobiological rhythms similar to other physiological values in the human body. The diurnal phasic variations in IOP have been known for a long time. Understanding this cyclical changes in IOP, as well as their scope and potential factors inducing change, is very significant not only from a research viewpoint but also from a clinical perspective in terms of diagnosis and management of patients with IOP related conditions for 1) In patients with ocular hypertension it is essential to obtain baseline levels and monitor the condition 2) In glaucomatous patients with progressive damage whenever single IOP measurement are within 'normal' range, and 3) in cases when a suspicious looking optic disc is discovered in patients without apparent IOP elevation.[1]

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The advantages of recording the diurnal variation as opposed to single IOP reading are manifold. 1) It gives a better indication of the IOP levels since the solitary reading taken in the office may not reveal the peak IOP level 2) it identifies the time of the day when the peak IOP occurs 3) it clarifies the range of IOP fluctuation during the examination period[1]. By means of mechanisms that are not yet well known, the IOP increase is considered to be one of the main risk factors leading to the development of glaucoma.[2] Although 21 mmHg is commonly accepted as the maximum arbitrary value for normalcy.[3] one should bear in mind, as with many other biological parameters, that this is a variable value determined by multiple factors: age.[4] gender.[5] race.[6] tobacco consumption.[7] local ocular problems.[8] obesity.[9] hormonal changes.[10] physical exercise.[11] etc. Furthermore, it seems to follow a circadian rhythm, although this has not clearly been established among humans, with a maximum peak in the morning and the lowest point by late evening; the even more confusing changes occurring during the night have not been taken into account.[12-15]

AIMS and OBJECTIVES: The diurnal variations in IOP are well known. Since A solitary IOP reading taken during office hours may not reveal the peak IOP level. The purpose of the present study is to find out whether there were differences in the intraocular pressure values of a certain population during those times in the day when measurements were taken and to quantify the resulting differences.

MATERILS AND METHODS: 92 subjects (184 eyes)aged range from 18-24 years 40 girls and 52 boys, formed part of the investigation of the diurnal variations of the IOP. Informed consent was obtained from each subject prior to participation. All participating volunteers were submitted to a questionnaire on systemic and ocular diseases as well on use of systemic and topical medication. Each subject then underwent an ophthalmic examination to confirm that both eyes were normal. All subjects underwent physical examination including ocular examination, refractive error determination, cardiovascular and neurological examination. 34 of them had corrected visual acuities Slit lamp examination of the anterior segment was done to exclude potential causes for high IOP.. No other ocular abnormality was found.

Inclusion Criteria:

1. Incipient refractive error.
2. IOP less than 21mmHg.
3. No history of ocular, cardiovascular or neurological disease or any other systemic abnormality.
4. None of the subjects was having any medication that is known to influence IOP.

Exclusion Criteria:

1. Obesity.
2. Systemic illness related to glaucoma.
3. Use of any topical or systemic medication that might influence IOP in any way.
4. Myopia greater than -2.00, Hypermetropia greater than +3.00, astigmatism greater than 2.00.
5. IOP less than 9.0 or over 22.0 mmHg in the sitting position, episcleral venous
6. Congestion, or any other eye disease capable to cause glaucoma or to influence IOP or the measurement of IOP.
7. Not agreeing to sign the informed consent of the procedure.

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Keelar Pulsair air impulse tonometer was used in all the subjects for IOP measurement. IOP was measured in the department of Ophthalmology, Teaching hospital. IOP were recorded in the upright position first at 7.45 to 8.45 AM and then at 12 Noon to 1PM and finally between 5-6 PM.

Every IOP measurement was performed at least twice and in case of more than a 2 mmHg difference a third measurement was performed, finally taking into account the mean of the two higher values. IOP ob both the eyes are measured. The subjects are made to relax by sitting for at least 10 minutes before subjecting for IOP measurement. The calander month of the year which the measurement is done is recorded. All subjects had normal sleep-waking cycle in their daily lives that they routinely slept from approximately 11Pm to 7AM. During the day time the subjects were free to pursue any normal daily activity.

RESULTS:

Age and Sex distribution and Anthropometric Measurements: The average age was 20.38±1.63 years, height was 160.446±7.4cms and weight was 59.45±7.41Kgs. There were 50 males, with the ages ranged between 18 and 24 years, with an average of 20.34±1.61 years and their average height 164.22±6.96cms, weight, 63.76±6.7kgs and there were 42 females with their ages ranged between 18 and 24 years with an average of 20.38±1.63 years, average height of 155.95±5.04cms, average weight of 54.31±4.31kgs.

There was no significant difference between the right and the left eyes with respect to the IOP. Therefore, the pressures for each subject were represented by the average of both eyes.

The IOP of all the subjects during the morning hours (8-9AM) was 15.0842±2.5694 mm Hg, during the afternoon (12 noon-1PM) was 13.7525±2.2594 mm Hg and during the evening hours (5-6PM) was 12.7828±2.4374 mm Hg (Table I).

The mean difference in the IOP of all subjects between the recordings at 8AM and 12 Noon was 1.3317 mmHg (Table II) This was statistically significant. ($P<0.0001$).

The mean difference in the IOP of all the subjects between the recordings at Noon and 5 PM was 0.9697 mm Hg (Table III) this was statistically significant. ($P<0.0001$).

The mean difference in the IOP of all the subjects between the recordings at 8AM and 5PM was 2.3014 mm Hg (Table IV) this was statistically significant. ($P<0.0001$).

The IOP of the subjects showing decrease during the morning hours(8-9AM) was 15.1671±2.5378 mm Hg, during the afternoon(12 noon-1PM) was 13.4575±2.0375 mm Hg and during the evening hours(5-6PM) was 12.1901±2.4374 mm Hg(Table V).

The mean difference in IOP of subjects showing decrease between the recordings at 8AM and 12 Noon was 1.7092 mm Hg(Table VI) This was statistically significant.($P<0.0001$).

The mean difference in the IOP of the subjects showing decrease between the recordings at Noon and 5 PM was 1.2678 mm Hg(Table VII)This was statistically significant.($P<0.0001$).

The mean difference in IOP of subjects showing decrease between the recordings at 8AM and 5PM was 2.977 mm Hg(Table VIII) This was statistically significant.($P<0.0001$).

The IOP of the subjects showing increase during the morning hours(8-9AM) was 1.8260±2.874 mm Hg, during the afternoon(12 noon-1PM) was 15.735±2.7561 mm Hg and during the evening hours(5-6PM) was 16.576±2.4846 mm Hg(Table IX).

The mean difference in IOP of subjects showing increase between the recordings at 8AM and 12 Noon was 0.909 mm Hg(Table X) This was statistically not significant.($P=0.4794$).

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The mean difference in the IOP of the subjects showing increase between the recordings at Noon and 5 PM was 0.841 mm Hg(Table XI)This was statistically not significant.(P=0.4828).

The mean IOP of subjects showing increase between the recordings at 8AM and 5PM was 1.75 mm Hg(Table XII) This was statistically not significant.(P=0.1621).

The % of subjects showing IOP decrease from the morning levels, increase from their morning levels and the subjects whose IOP remained the same are tabulated as follows:

Subjects	%	% change in IOP		
		8AM-12NOON	12NOON-5PM	8AM-5PM
77(154 eyes)	83.69↑	8.86	7.05	15.25
10	10.86↓	11.26	9.42	19.63
05	5.43(-)	No change	No change	No change

Table I: Showing IOP of all subjects at different time of the day N=92(184 eyes)

	8AM	12 NOON	5 PM
Mean	15.084	13.753	12.783
SD	2.569	2.259	2.437
SEM	0.268	0.236	0.254

Table II: Showing IOP of all subjects at 8AM and 12 Noon N=92 Mean difference is 1.3317

	8AM	12NOON
Mean	15.0842	13.7525
SD	2.5694	2.2594
SEM	0.2679	0.2356

T= 6.2329; df=182; Std error of difference: 0.369;
Two tailed 'P' value is 0.0003 which is statistically highly significant.

Table III showing IOP of all subjects at 12Noon and 5PM N=92
Mean difference is 0.9697

	12 NOON	5 PM
Mean	13.7525	12.7828
SD	2.2594	2.4374
SEM	0.2356	0.2541

T= 2.795; df=182; Std error of difference: 0.346;
Two tailed 'P' value =0.0057 which is statistically very significant.

Table IV showing IOP of all subjects at 8AM and 5PM N=92
Mean difference is 2.3014

	8AM	5 PM
Mean	15.0842	12.7828
SD	2.5694	2.4374
SEM	0.2679	0.2541

T= 6.2329; df=182; Std error of difference: 0.369;
Two tailed 'P' value is <0.0001 which is statistically highly significant.

DOI: 10.14260/jemds/2015/2083

Table V showing IOP of subjects at different time of the day showing decrease N=77(154 eyes)

	8AM	12 NOON	5 PM
Mean	15.1671	13.4579	12.1901
SD	2.5378	2.0375	1.8819
SEM	0.2892	0.2322	0.2145

Table VI showing IOP of subjects at 8AM and 12 Noon showing decrease N=77 Mean difference is 1.7092

	8AM	12NOON
Mean	15.1671	13.4579
SD	2.5378	2.0375
SEM	0.2892	0.2322

T= 4.6085; df=152; Std error of difference: 0.371;
Two tailed 'P' value is <0.0001 which is statistically highly significant.

Table VII showing IOP of subjects showing decrease at 12Noon and 5PM N=77 Mean difference is 1.2678

	12 NOON	5 PM
Mean	13.4579	12.1901
SD	2.0375	1.8819
SEM	0.2322	0.2145

T= 4.011; df=152; Std error of difference: 0.316;
Two tailed 'P' value is <0.0001 which is statistically highly significant.

Table VIII showing IOP of subjects showing decrease at 8AM and 5PM N=77 Mean difference is 2.977

	8AM	5 PM
Mean	15.1671	12.1901
SD	2.5378	1.8819
SEM	0.2892	0.2145

T= 8.2683; df=152; Std error of difference: 0.36;
Two tailed 'P' value is <0.0001 which is statistically highly significant.

Table IX showing IOP of subjects at different time of the day showing increase N=10(20 eyes)

	8AM	12 NOON	5 PM
Mean	14.8260	15.735	16.576
SD	2.8704	2.7561	2.4846
SEM	0.9077	0.8715	0.7857

DOI: 10.14260/jemds/2015/2083

Table X showing IOP of subjects at 8AM and 12 Noon showing increase N=10
Mean difference is 0.909

	8AM	12NOON
Mean	14.8260	15.735
SD	2.8704	2.7561
SEM	0.9077	0.8715

T= 0.7224; df=18; Std error of difference: 1.258;
Two tailed 'P' value is 0.4794 which is statistically **NOT** significant.

Table XI showing IOP of subjects showing increase at 12Noon and 5PM N=10
Mean difference is 0.841

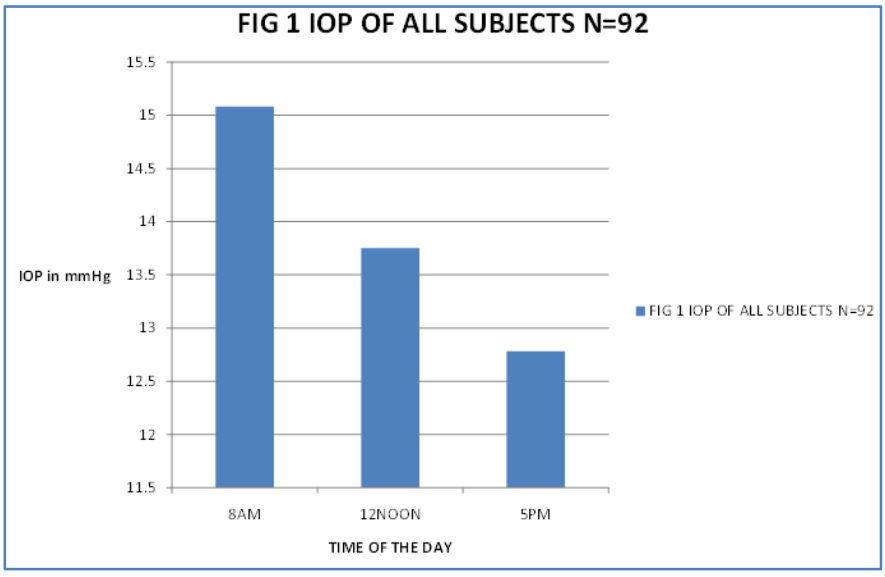
	12 NOON	5 PM
Mean	15.735	16.576
SD	2.7561	2.4846
SEM	0.8715	0.7857

T= 0.7167; df=18; Std error of difference: 1.173;
Two tailed 'P' value is 0.4828 which is statistically **NOT** significant.

Table XII showing IOP of subjects showing increase at 8AM and 5PM N=10
Mean difference is 1.75

	8AM	5 PM
Mean	14.8260	16.576
SD	2.8704	2.4846
SEM	0.9077	0.7857

T= 1.4577; df=18; Std error of difference: 1.201;
Two tailed 'P' value is 0.1621 which is statistically **NOT** significant.



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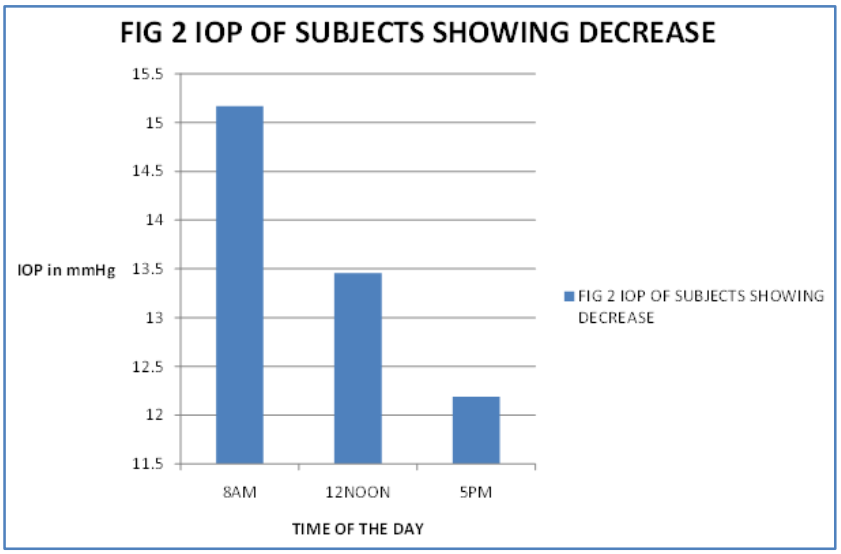

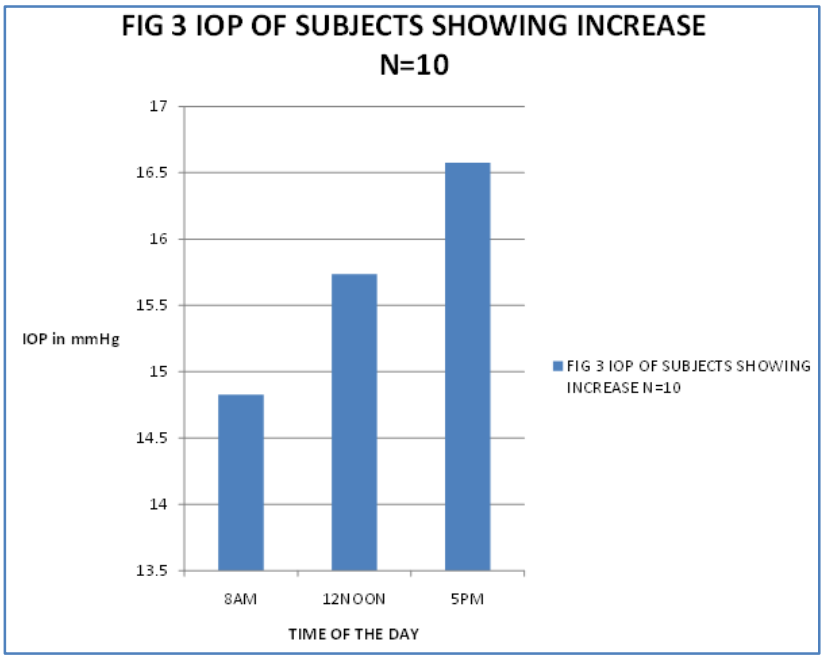

DISCUSSION: There are reports that although the peak of the diurnal variation was most frequently between 6-8AM, it may occur any time of the day or night. Furthermore, the timing & magnitude of the peak IOP may vary from day to day.[16] Thus, it is obvious that any choice of times of measurement is arbitrary. We have no method to continually measure IOP. Even a large number of pressure measurements dispersed through a 24 h period may miss the peak pressure for that day.[16] We realize that starting the procedure around 8 AM is less than ideal; there are reports claiming the highest IOP occurs immediately after waking[17]; Nevertheless the widely employed practice today is IOP measurement by ophthalmologists in their offices, & therefore, the information collected and presented here is still useful.

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The mechanism controlling the diurnal variation of the IOP as well as daily variations in many other physiological "Constants" (Circadian fluctuations) appears to be situated at some distance from the eye, possibly in the hypothalamus and might act upon the IOP by producing changes in one or more of three factors determining variations in the "Steady-State"- the production of aqueous, the resistance to aqueous outflow or the episcleral venous pressure- but the exact mechanism is not yet clear. In the phase of raised pressure this was found to be increased by Grant.[18] using tonography, a finding confirmed by Ericson.[19] in normal subjects by using the suction-cup technique, when he showed that there was a correlation between changes in the flow of aqueous and the diurnal variation of tension, the production being lowest at mid night and 4AM.[18] It is obvious that the mechanism of the diurnal variation is not yet clear but it is evident that small changes as in the formation of aqueous, will give rise to great alterations in the IOP when it is high and particularly if the drainage is impeded. Studies on the resistance to the outflow of aqueous have yielded inconsistent results.

Stepanik and Boyd have found a direct relationship between this and the ocular tension.[20,21] Others concluded that any variation with the resistance was not in phase with the diurnal variation in tension.[22] while others again have found that the resistance was unchanged throughout the day.[18,23]

Few investigators.[20.21] detect small diurnal fluctuations in out flow facility which in some eyes appear to reciprocate with diurnal variations in concomitantly measured IOP. Nevertheless, the fluctuations of out flow facility do not follow a consistent pattern.[18,22-24] a reciprocal relationship with IOP is frequently not present and the variations in outflow facility are usually of insufficient magnitude to account fully for the variations in IOP. Finally with regard to the pressure in the episceral veins although Thomassen and his associates[25] and Bain[26] claimed to have observed an increase in venous pressure preceding the rising phase in the diurnal variation others have detected little change and certainly no direct relationship between the two (Goldmann,[27] Linneer.[28])

There has been considerable in interest in the relationship between adreno cortical steroids and IOP changes. It has been known for some time that there is a correlative temporal relationship between the circadian pattern of IOP and blood cortisol concentrations (Smith and others 1962).[29]

In the studies by Elliot D Weitzman.[30] have shown clearly a high degree of temporal correlation between the two with a phase difference of 3 hours. However, the lack of change in the 24-hour IOP curve in both eyes when cortisol secretion is totally suppressed suggests that the temporal phase relationship between cortisol and IOP may be only correlative not causative. There may be one or more systemic factors control the temporal changes in IOP.

In the recent review, Waitzmen.[30] concluded that hypothalamus might be the Major CNS controlling for the changes in IOP. Certainly the 24-hour correlative relationships with differing hypothalamic controlled circadian events, such as neuroendocrine processes, body temperature, sleep –waking functions, autonomic activity etc., would support that this CNS area may be critically involved. (Conroy and Mills.[31]) It has been proposed recently that melatonin may play a role in regulation of IOP; Melatonin levels in blood and retinal tissues have been linked to IOP.[32,33] Melatonin concentration in ocular tissues increases in the dark and is inhibited by light.[34] IOP increases in the dark when subjects are asleep. However, plasma melatonin levels increase at night even if subjects remain awake but IOP is low is sleep is deprived.[35]

Although the IOP may be raised or lowered temporarily by changes in systemic arterial or venous pressure, it is unlikely that either factor is of great significance in diurnal tension fluctuations.[22]

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Usually, although not continuously, healthy subjects yield the highest IOP values at the beginning of the day, upon waking up, slowly decreasing during the day until bedtime and gradually increasing again during the night. Differences between maximum and minimum values may amount to 8 mmHg.[36] in the present study, we found the difference between the maximum and minimum values amounting to 3mm Hg. The present study did not find any association between age, sex and the IOP parameters examined time of peak, trough and diurnal fluctuation).

CONCLUSION: IOP was measured in 92 healthy subjects (184 eyes) with no ocular pathology with age range 18-20 years by using Non-Contact Keeler Pulsair tonometer in a teaching Hospital 3 times during the day, 08AM-9AM, 12NOON-1PM and between 5-6PM. IOP decreased in 83.69% of the subjects and IOP increased in 10.86% of the subjects and in 5.43% of the subjects, the IOP remained same during the day. The fall in mean IOP from the baseline was statistically significant. The rise in IOP noted in a small percentage of subjects was not statistically significant. Our findings attempted to resolve conflicts in the literature over the diurnal variation of IOP in normal subjects. The clinical importance of our finding, that 87% of the peak IOP occurs before noon and only 5.5% during the following 09 h in this series, raises a serious question as to the necessity of extending the measurement beyond 6PM.

More important it emphasizes the fact that solitary IOP examination taken in the late afternoon or early evening may miss up to 84% of IOP peaks! Bearing in mind that some glaucoma clinics are held in the afternoon and in many private practices the patients prefer the late appointments (After business hours, traffic rush etc.,) this finding indicates that a revision of the time table for IOP examination in the glaucoma population may be warranted. The result of this study lend weight to the currently held opinion that borderline pressures recorded during office hours should not be too lightly dismissed, for the IOP may be a good deal higher at the time of the peak of the diurnal tension variation. A significant limitation of this study is that we have attempted to detect the peak of the diurnal variation of IOP from only 3 measurements obtained during a 24-hour period.

There is no question that measurement of IOP at more frequent intervals, over a period of several days, would have provided a more accurate representation of the diurnal IOP variation. Such an exacting study, however desirable is highly impractical. Thus, our conclusions are to some extent limited. Nevertheless, the implication of this study is clear. Until a better predictive tool becomes available, the most likely way to detect the highest IOP during the diurnal variation will remain laborious, time consuming and inconvenient method of measuring IOP round the clock. The limitations of measuring IOP an arbitrary number of times over a limited time span make the development of a practical telemetric device for the continuous measurement of IOP a most desirable future research goal.

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