DIURNAL VARIATIONS IN INTRAOCULAR PRESSURE

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INTRODUCTION

INTRAOCULAR PRESSURE (IOP) IS NOT A CONSTANT VALUE. RATHER, IT varies considerably based on a number of factors.[1,2] Some of these factors act over periods ranging from seconds to minutes or hours; others act over a longer duration.[3] Among the short-acting influences are food or fluid intake,[4] variations in systemic blood pressure,[5,6] and heavy physical activity.[7-9] Most of these are random events and are erratic in nature. On the other hand, there seems to be a pattern to the variation in the IOP over the course of 24 hours that in a given individual has a reasonable amount of consistency and reproducibility. This pattern may be related to other diurnal endogenous variations in the body, such as the production of cortisol.[10] Similarly, there appear to be consistent seasonal variations in IOP.[11] Such variations are of particular interest in glaucoma, where elevated IOP is assumed to be associated with damage to retinal nerve fibers leading to loss in the visual field and even blindness.[12] Because the main option currently available for the treatment of glaucoma is the reduction of IOP, accurate determination of the IOP and the effects of therapy on it are of utmost concern in the management of patients with glaucoma.

Diurnal variation in glaucoma was first reported in 1898[13] and has been studied extensively since that time.[1,2,14-36] Even so, a great deal remains unknown about diurnal IOP variation in normal eyes in general, and in glaucoma in particular. There are a number of reasons for this. The first has to do with the methods used for studying the diurnal curve. In many cases, patients have been hospitalized for these studies. Hospitalization markedly alters the patients' normal activity patterns; how this affects the resulting IOP measurements is unclear. There is some evidence suggesting that there is a significant alteration.[19] Other studies have tried to avoid this artifact by measuring the IOP in the doctor's office[31,34] or by having the patient come in for an IOP check several days in a row, but at different times each day.[28] In most cases this results in the measurements being limited to a period from approximately 8 AM to 6 PM, thus accounting for less than half of the day. Moreover, the first measurement in the morning is probably not accomplished until 1 or 2 hours after the patient

has awakened and could, therefore, miss variations in IOP that are present immediately upon awakening.[37]

A related aspect of these variations in the measurement techniques is the frequency with which the IOP measurements are made. From a review of the literature, it appears that in most of the studies four to six measurements a day were made, but in some studies the measurements were as frequent as every hour around the clock. Another variation relates to the measurement of IOP during the sleeping hours. If the IOP is checked at frequent intervals during this period, the normal sleep pattern is disrupted, and the values obtained may not be representative of what normally would be present.[38] There is also the question of how the IOP is measured during the night. If the patient is awakened and taken from the bed to a slit lamp to measure the IOP, does this very activity alter the value obtained?

Finally, there has been considerable variation in the instruments used to measure IOP. Most of the earlier studies used Schiøtz tonometers, but in later studies the Goldmann applanation tonometer became more popular. Other tonometers, including the Mackay-Marg and the noncontact tonometer, have also been used. Schiøtz tonometry requires that the patient be in a supine position, whereas Goldmann applanation tonometry requires that the patient sit at a slit lamp. There is definite evidence that this positional difference affects IOP, and the effect may be greater in eyes with glaucoma.[39-41]

At present, there is still much uncertainty about the significance of diurnal variations in IOP, particularly in glaucoma. It is not known whether diurnal measurements of IOP are indicated for the diagnosis of glaucoma patients, whether they can help explain progression of glaucomatous damage in individuals whose IOP appears to be controlled, or whether they can better guide the therapeutic decisions for these patients. The present study was designed to yield new, more reliable information that might provide some answers to these questions. This study utilized a portable applanation self-tonometer that patients could use at home or at work to measure their IOP several times a day for several days. This allowed for minimal disruption of the patients' life style, and, therefore, more accurate representations of the true variations in IOP. The study also allowed nighttime measurements of IOP in glaucoma patients during sleep, with a technique that was less likely to affect the values than had been the case in previous studies.

BACKGROUND

Variations in IOP were first measured by Sidler-Huguenin in 1898.[13] He measured the IOP in ten glaucomatous patients with the use of digital tonometry and reported that the pressure peaked at night before going to sleep and in the morning 30 to 60 minutes after waking. In 1904, Maslenikow[29] was the first ophthalmologist to quantitate daily fluctuations in IOP. He measured the IOP at 9 AM and 5:30 PM using a Macklakof tonometer. Since then a large number of studies of the diurnal variations in IOP have been conducted. These studies have varied greatly in the types of subjects studied (normal IOP, primary open-angle glaucoma, unselected glaucoma, etc), the type of tonometer used, the frequency of the measurements, and whether testing was performed on an in-patient or out-patient basis. Not surprisingly, these various studies have yielded quite different and sometimes contradictory results.

NORMAL SUBJECTS

In 1963, de Venecia and Davis[14] studied the diurnal variations of IOP in 115 prison inmates with normal IOPs over a 3-day period. All of the subjects were men, and 80% were less than 40 years of age. They were supposed to continue their normal daily activities. The highest IOP was found at 5 AM (38% of subjects) and midnight (26% of subjects). The range of diurnal variation decreased from 5.9 mm Hg on the first of the three days to 4.9 mm Hg on the third day. In another study, Thiel[35] found that the highest IOP occurred between 5 and 7 AM before the patients arose. Ericson[17] studied 50 female nursing students aged 20 to 28 years. Their IOP values were given as Schiøtz readings rather than millimeters of mercury. The values were highest at 8 AM and noon, declined until midnight, and began to rise again by 4 AM. Ericson also studied 10 women who worked at night. In these women he found a greater variability in the time of maximum IOP, but the lowest value was during the day at 4 PM.

Katavisto[23] studied 50 hospitalized individuals with normal IOP, half men and half women. The highest IOP values were detected at 8 AM (41% of the eyes), but over 20% of the subjects had their highest values at midnight. The diurnal variation averaged 3.17 mm Hg. Drance[16] studied 306 eyes of hospitalized individuals with normal IOP and found that 42% had their highest IOP at 6 AM; the mean diurnal range was 3.7 mm Hg. In contrast, Kitazawa and Horie[25] studied 12 hospitalized individuals with normal IOP, taking hourly IOP measurements using a Goldmann applanation tonometer. They found that the highest IOP occurred at 2 PM and the mean diurnal range was 6.5 mm Hg. Henkind and co-workers[21] studied five hospitalized normal individuals with hourly measurements employ-

ing a protocol similar to that of Kitazawa and Horie, but using a Mackay-Marg tonometer. They found the peak IOP occurred at 11 AM.

In summary, the various studies of diurnal variation of IOP in normal eyes agree only in finding that a rhythmic pattern of diurnal variation does occur. There is disagreement as to the time of peak pressure, the pattern of the curve, and the range of the variation.

GLAUCOMATOUS PATIENTS

One of the most extensive studies of IOP in glaucoma patients was conducted by Thiel,[35] who measured the IOP up to ten times a day. He reported that the IOP increased from midnight to 3 AM, reaching a peak between 3 and 7 AM. In contrast, Langley and Swanljung[27] studied 34 patients with "glaucoma simplex." They reported that 55% of these patients demonstrated a double-peak curve, with a morning peak at 9 AM and an evening peak between 4 and 6 PM. Drance[16] found that 46% of 138 eyes with untreated open-angle glaucoma had a peak IOP at 6 AM. (It should be noted that some of Drance's glaucoma patients had no visual field loss. These patients were diagnosed as having glaucoma on the basis of elevated IOP or poor facility of outflow on tonography. Today some of these patients probably would be diagnosed as having ocular hypertension rather than glaucoma.) Kitazawa and Horie[25] found that in 14 patients with primary open-angle glaucoma the highest IOP occurred at noon, 6 hours later than the peak IOP in Drance's study. In Drance's patients the mean diurnal variation in IOP was 11 mm Hg, whereas in Kitazawa and Horie's patients it was 16 mm Hg.

Katavisto[23] also studied a large number of patients with open-angle glaucoma but classified them as to the pattern of the diurnal curve rather than giving the precise time of the peak IOP. He reported that 24% of 80 eyes in men and 28% of 258 eyes in women had "morning type" curves (peak IOP between 4 AM and 8 AM), 53% of men and 26% of women had "day type" curves (peak IOP between 8 AM and 2 PM), while only 8% of men but 33% of women had "night type" curves (peak IOP between midnight and 4 AM).

Merritt and co-workers[30] studied ten patients with juvenile glaucoma. Six of these patients had their highest IOP at 6 PM and three others had an IOP peak at midnight. Shapiro and Zauberman[33] studied 11 patients with angle-closure glaucoma prior to iridectomy and found the highest IOP to be at midnight.

In many of these studies the IOP was not measured between midnight and 5 to 6 AM. Two particular exceptions to this were the studies of Kitazawa and Horie[25] and of Henkind and co-workers[21] in which the IOP

was measured hourly for 24 hours. In both studies the IOP was at its lowest level between midnight and 6 AM. In another study, by Sampaolesi and co-workers,[32] a portion of a group of subjects whose diurnal IOP curves were being measured had their IOP measured in bed at 3 AM with a Schiøtz tonometer. Sampaolesi concluded that the 3 AM values "are of no importance in the study of the behavior of intraocular pressure and its daily variation." The study of Brown and co-workers[42] resulted in a very different conclusion. They measured the IOP in ten normal individuals before sleep and then 30 minutes to 4 hours after the subjects fell asleep. The IOP in these individuals while asleep was 3.45 to 6.41 mm Hg higher (increasing with the duration of sleep) than their presleep values.

As was the case with normal eyes, the various studies of diurnal variation of IOP in glaucomatous eyes have yielded conflicting data. There is general agreement that the range of diurnal IOP variations is greater in glaucomatous eyes than in normal ones and that the pattern of the diurnal curve varies in different types of glaucoma. But even in open-angle glaucoma, there is no agreement as to the time of highest IOP or the predominant pattern present. There is much disagreement as to what happens to IOP during sleep.

EFFECTS OF GLAUCOMA THERAPY ON THE DIURNAL CURVE

There have been numerous studies to assess the effect of various types of ocular hypotensive therapy on the diurnal curve of patients with glaucoma.[43-51] Drance[43] studied 132 patients receiving "medical therapy" whose applanation IOP in the eye clinic was 19 mm Hg or less. These eyes continued to exhibit a diurnal variation in IOP of about 7 to 8 mm Hg. This was lower than the 11 mm Hg variation that had been seen in his untreated glaucoma population.[16] There also appeared to be some changes in the timing of the IOP peaks. In untreated patients 46% had their peaks at 6 AM and only 14% at 10 PM. In the treated patients only 25% had their peaks at 6 AM, while 23% had their peaks at 10 PM.

Several studies have assessed the effect of a single topical drug such as pilocarpine[44,45] or a beta blocker,[46,47] and one study[48] compared these two types of drugs. Like the study by Drance,[43] all of these studies demonstrated maintenance of a diurnal pattern with a lowering of the mean IOP and a reduction in the range of the diurnal variation.

Other studies have assessed the effect of other forms of glaucoma therapy. Greenidge and co-workers[49] studied a group of patients with primary open-angle glaucoma before and 8 weeks after the performance of argon laser trabeculoplasty. After the laser treatment the mean IOP fell 22%; the peak IOP, 25%. The pressure fluctuation also fell 25%. Sterk and

co-workers[50] studied the effects of therapeutic ultrasound therapy in 17 patients with "therapy-resistant" glaucoma (the majority had neovascular glaucoma). The decrease in mean IOP was approximately 18 mm Hg, and the decrease in mean range in IOP was from 12.9 mm Hg to 6.6 mm Hg. Suda and co-workers[51] reported on the effect of glaucoma filtration surgery in 26 eyes. Again, they found a decrease in the mean IOP and a reduction from 18.1 to 7 mm Hg in range, but the diurnal pattern continued to be present.

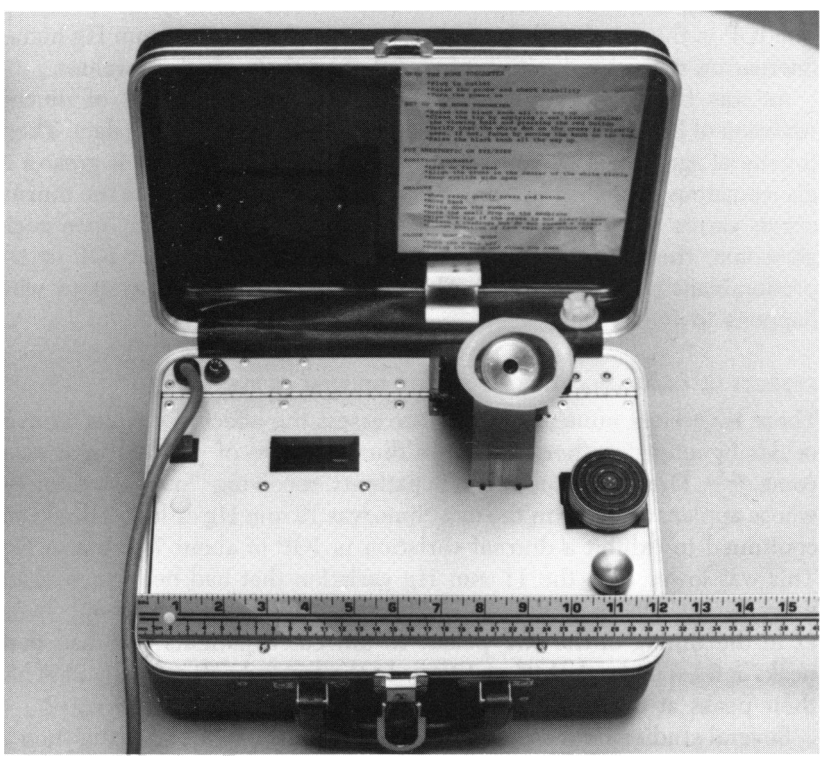

FIGURE 1A
Photograph of self-tonometer. Digital display is on the left and eye cup with applanation piston in its center is on the right.

METHODS AND MATERIALS

DIURNAL IOP STUDY

The diurnal IOP measurements for this study were obtained using the

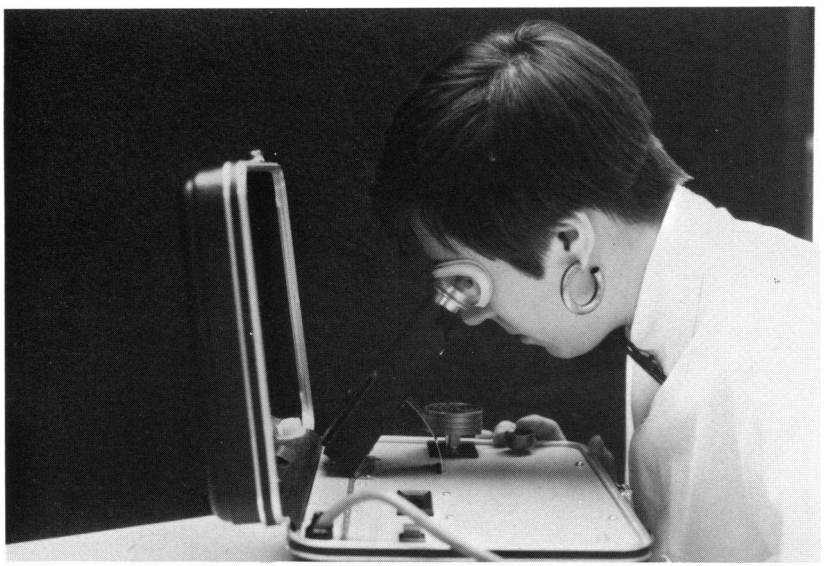

FIGURE 1B
Photograph of a subject using self-tonometer. Brow and cheek rest on the eye cup. Subject's finger is on the trigger button that activates applanation piston.

self-tonometer developed by Zeimer[52-54] (Fig 1). This instrument is an applanation-type device with a piston that is driven forward by air pressure. The tip of the piston is covered with a flexible membrane, which is designed to come in contact with the cornea. There is a light system within the instrument that shines up the barrel of the piston and is reflected back from the membrane at the tip. Maximum reflectance occurs when there is applanation of the cornea. This reflectance is determined by continual monitoring of the reflected light and is correlated to the air pressure at the point when maximum reflectance occurs. Because the piston must be located at, and perpendicular to, the apex of the cornea, the instrument is provided with a self-alignment system used by the patient.

The instrument then provides a digital readout, which is representative of the air pressure driving the piston at the time of maximum reflectance. This reading is not equal to the IOP. In order to convert this reading into an IOP value, a correction factor must be calculated for the patient. This value is calculated using paired self-tonometry and applanation tonometry readings obtained from the patient on two separate occasions. This calculation is required to adjust for the force necessary to deform the cornea during applanation and is inherent in all tonometers.

FIGURE 1C
Photograph of a subject leaving clinic with self-tonometer.

Subjects who agreed to participate in the study were first checked to make sure that they could obtain valid readings using the self-tonometer. First they instilled a drop of local anesthetic solution (0.5% proparacaine hydrochloride) in their eyes. They were instructed on how to align the internal fixation target, how to press the button that activated the applanation piston, and how to record the reading obtained. The patient then obtained pressure readings in both eyes under the direct supervision of an ophthalmic technician who verified that the patient was utilizing the instrument properly and that a valid reading was being obtained.

Once it was determined that the patient used the tonometer properly, he or she was instructed to utilize the following protocol. IOP readings were to be obtained five times a day. These were in the morning on awakening, around noon, in the midafternoon, in the evening after supper, and at bedtime. Patients who were using ocular hypotensive medication were instructed to obtain their morning IOP measurements before using their medication. On each occasion the patients were to attempt to obtain four separate pressure readings for each eye, but they were only to make a maximum of six attempts to obtain these readings. For each of the readings, the patients recorded the values appearing on the digital display unit of the instrument in a special notebook given them, with proper notation of the date, time, and eye being tested. IOP measurements were obtained on 3 to 6 consecutive days in most patients.

For the Diurnal IOP Study several different patient populations were included. Some of these patients were studied to help with their clinical management, while others were recruited to participate because of our desire to evaluate particular types of glaucoma. These included:

Normal control subjects. These were individuals who had normal IOPs, normal visual acuity, healthy-looking optic nerveheads, and no history of ocular disease.

Individuals with presumed low-tension glaucoma. These were individuals who had optic nervehead cupping and/or visual field loss compatible with a diagnosis of glaucoma, but with applanation IOP readings in our office of 22 mm Hg or less on several occasions.

Individuals with open-angle glaucoma who were believed to be stable. These were individuals who had serial visual field examinations over a period of time who were judged to have shown no change and who also showed no change in optic nervehead cupping. Included among these patients were individuals with primary open-angle glaucoma, juvenile glaucoma, pigmentary glaucoma, and exfoliation syndrome glaucoma.

Individuals with open-angle glaucoma with indeterminate clinical status. These were individuals with borderline control of IOP, insufficient

TABLE I: DISTRIBUTION OF PATIENTS IN DIURNAL IOP STUDY*

CATEGORY	NO. OF PATIENTS
Normal eyes	20
Low-tension glaucoma	64
Stable open-angle glaucoma	28
Indeterminate open-angle glaucoma	101
Deteriorating open-angle glaucoma	23
Ocular hypertension	74
Surgical therapy	19
Changing medical therapy	53

*Some patients qualified for more than one category.

follow-up, or unreliable visual field data so that judgment could not be made as to whether their disease was stable or not.

Individuals with open-angle glaucoma who were suspected of having progression of disease. These were individuals who had been referred to our consultation practice with a report from the referring ophthalmologist indicating progression of optic nervehead cupping and/or visual field loss, or individuals from our practice whose visual fields and/or cups were judged to have shown possible or definite deterioration.

Individuals with ocular hypertension. These were individuals with documented IOPs in our office greater than 22 mm Hg, but who had normal visual fields and no significant asymmetry of cupping.

Individuals with open-angle glaucoma who either were scheduled for laser or surgical therapy or had had recent surgical therapy.

Patients with open-angle glaucoma who were about to undergo changes in their medical therapy. The intent of these individuals was to study the effect of the change in therapy on their diurnal IOP curve.

Table I lists the number of subjects included in each group. Some patients had diurnal IOP measurements performed on subsequent occasions.

The diurnal IOP measurements over several days were categorized as to type of pattern present (Fig 2): (1) a *diurnal rhythm* where there were peaks of IOP that were similar on different days, (2) a *flat tracing* where there were no significant IOP elevations throughout any of the days, or (3)

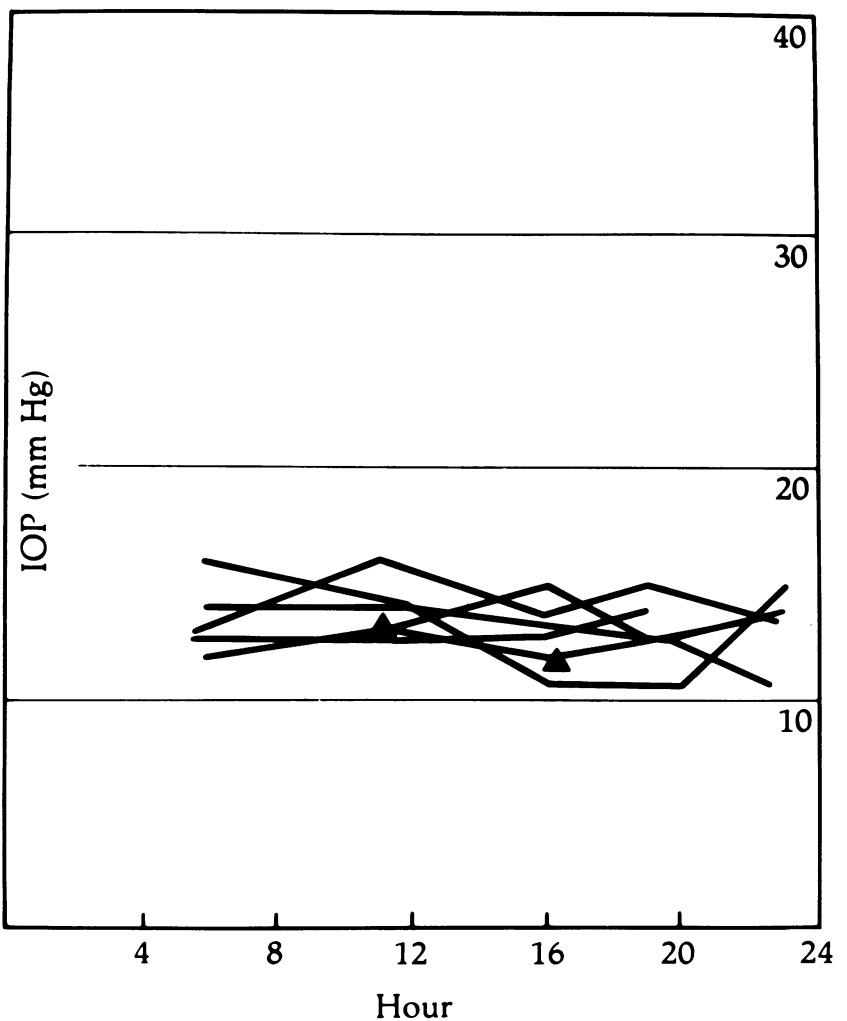

FIGURE 2A
Example of a flat type diurnal IOP pattern. Each line represents a different day of testing. Triangles designate Goldmann applanation tonometry values. (Taken from Zeimer[1] with permission of CV Mosby Co).

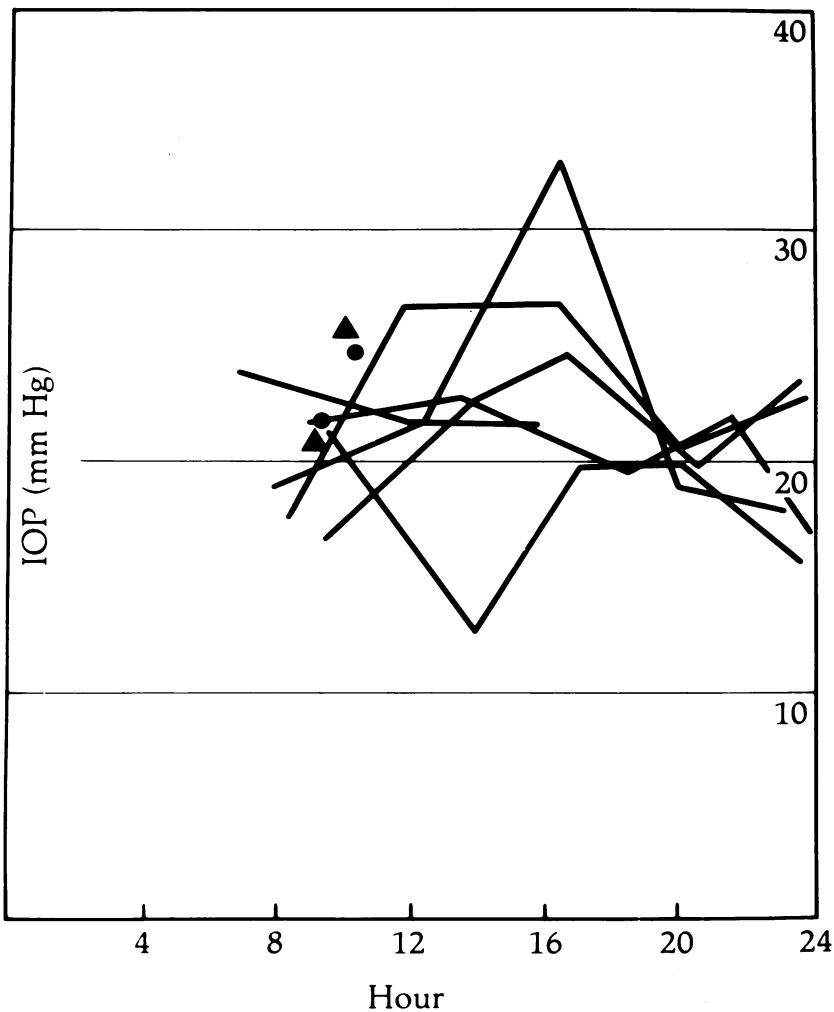

FIGURE 2B
Example of an erratic diurnal IOP pattern. (Taken from Zeimer[1] with permission of CV Mosby Co).

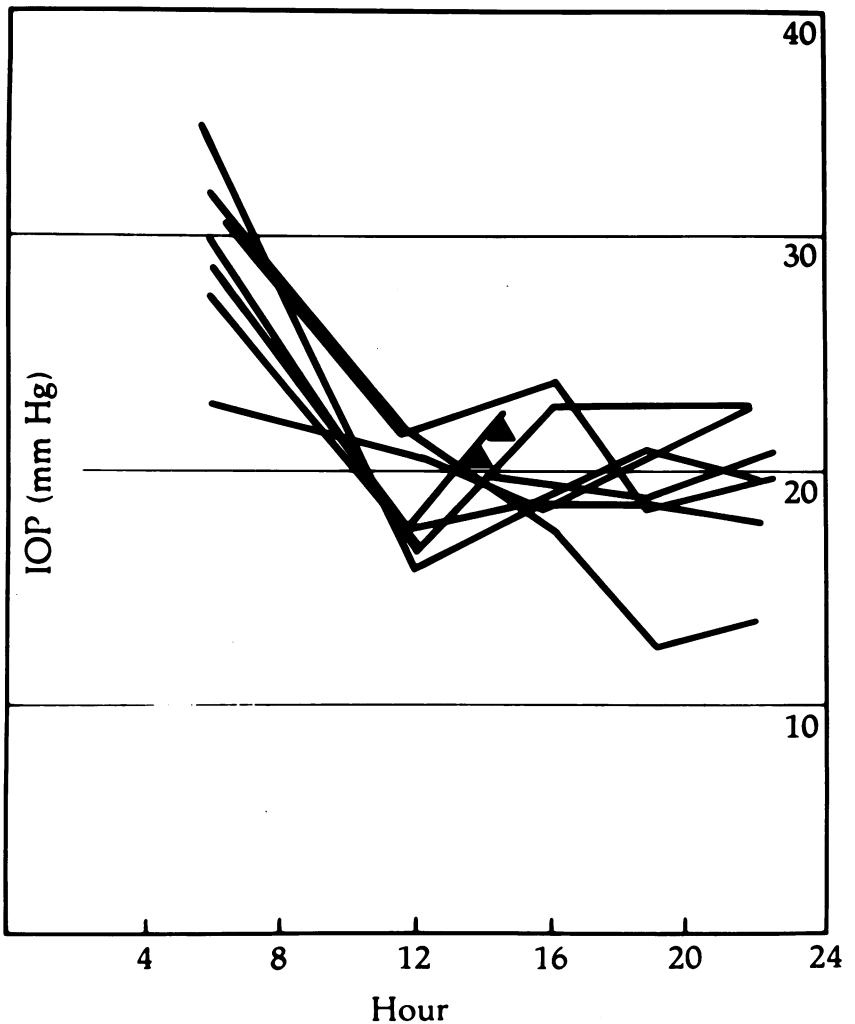

FIGURE 2C
Example of a rhythmic diurnal pattern with a morning type IP curve. (Taken from Zeimer[1] with permission of CV Mosby Co).

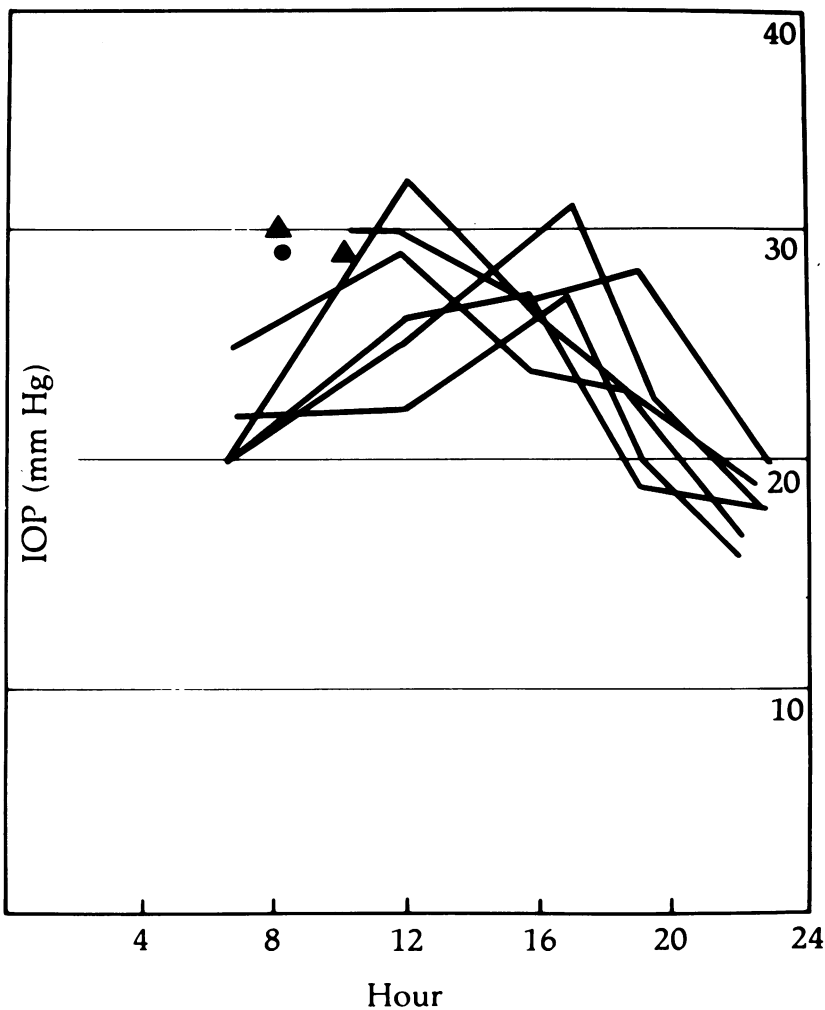

FIGURE 2D
Example of a rhythmic pattern with a day type IOP curve. (Taken from Zeimer[1] with permission of CV Mosby Co).

an *erratic tracing* where there were somewhat random IOP peaks that were not reproducible from day to day. The eyes that showed a diurnal rhythm were then classified as to the type of curve. The first curve was the *morning type*, in which the IOP peak occurred between 4 and 8 AM. The second curve was the *day type*, in which the peak occurred later in the morning, usually before noon but sometimes into the early afternoon. The third curve was the *biphasic type*, in which there was both a morning and later afternoon peak. Because the IOPs of the two eyes of an individual are thought not to vary independently,[55,56] only one eye from each patient was analyzed. Where IOP values were available for both eyes, only the values from the right eye were analyzed. In individuals whom values were obtained in the left eye only, those values were analyzed.

SLEEP IOP STUDY

This study was conducted in a SurgiCenter that was not normally used at night. The subjects arrived around 9 or 10 PM. A certified ophthalmic technician measured their IOPs using a Goldmann applanation tonometer with the subject seated at a slit lamp. The IOP measurements were repeated shortly thereafter using an Alcon pneumatonograph with the subject lying supine in bed. The pneumatonograph instrument used has both digital and paper tracing readouts. The digital readout was first adjusted to the zero mark, and then the recording pen on the paper was adjusted so that the pen tracing was just barely above the zero line. The probe was held perpendicular to the cornea with the subject looking straight up, and a recording strip at least 10 seconds long was obtained. The subjects were then allowed to go to sleep. Each subject was in a separate room except when a married couple was studied. Between 1 and 2 AM, the technician returned to the subjects' rooms, and, disturbing them as little as possible, instilled a drop of 0.5% proparacaine hydrochloride in each eye and repeated the IOP measurements using the pneumatonograph. This same procedure was repeated approximately 2 hours later in some of the subjects. Between 5:30 and 6 AM, the technician returned again and obtained an additional pneumatonographic IOP reading. The individuals then got out of bed and dressed. Following this, their IOPs were again measured at the slit lamp using the Goldmann applanation tonometer.

The Sleep IOP Study comprised two populations. The first population consisted of 12 normal volunteers. These were individuals with best corrected visual acuity of 20/30 or better, normal IOPs, normal slit lamp examinations, and no history of any ocular pathology. The age, race, and sex are listed in Table II. The second population consisted of 22 patients

TABLE II: NORMAL SUBJECTS IN THE SLEEP IOP STUDY

SUBJECT	AGE	SEX	RACE
1	51	F	B
2	47	M	B
3	35	F	B
4	50	F	B
5	64	M	B
6	42	M	W
7	45	M	W
8	48	M	W
9	44	M	W
10	50	M	W
11	31	F	W
12	57	F	W

with various types of glaucoma. Included in this group were individuals with primary and secondary glaucomas, with the disease stage ranging from very early to fairly advanced; patients receiving no therapy, medical therapy, or a combination of medical and laser therapy; and some who had had surgical therapy as well. The age, sex, race, diagnosis, and therapy of these 22 individuals are listed in Table III. Three of these individuals were retested on a second occasion to determine the reproducibility of our findings.

THERAPY STUDIES

Two separate glaucoma therapy studies were conducted. In the first study, 14 patients with ocular hypertension or open-angle glaucoma participated. The patients either were receiving no ocular hypotensive medication or had had their medication discontinued at least 4 weeks prior to their participation in the study. The patients measured their IOP five times daily for 3 consecutive days using the self-tonometer according to the protocol already described. They then began to instill one drop of a nonselective beta adrenergic blocking agent in their eyes once a day. After the drug had been used for 30 days, the 3-day diurnal IOP measurements were repeated using the same protocol. Only the right eye of each patient was analyzed.

In the second study, eight patients with open-angle glaucoma on maximally tolerated medical therapy performed diurnal IOP measurements using the self-tonometer according to the protocol already described. Some of the patients had this testing performed specifically because they were scheduled for glaucoma filtering surgery, but most had it performed as part of some other study protocol. Glaucoma filtering surgery was

TABLE III: GLAUCOMA PATIENTS IN THE SLEEP IOP STUDY

PATIENT	AGE	SEX	RACE	DIAGNOSIS	THERAPY
1	79	F	B	POAG*	T.5, P4 OU
2	41	M	W	POAG	P1 OD; filter OS
3	41	M	W	Juvenile glaucoma	T.5 OU; P4 OD; cyclocryotherapy OD
4	29	M	W	Pigmentary glaucoma	T.5 OU; P4 OD, ALT OU
5	60	F	B	POAG	T.5 OU, N50
6	46	F	B	POAG	T.25 OU
7	71	F	W	Ocular hypertension	None
8	73	M	W	POAG	Bt, Pilopine OU, N50; ALT OU
9	75	M	W	Ocular hypertension	Bg.25 OS
10	45	F	B	Ocular hypertension	None
11	28	F	W	Juvenile	T.25 OS; filter OU
12	57	F	B	POAG	Bg.5 OS
13	77	F	W	Pigmentary glaucoma	T.5, P1 OU; filter OD
14	34	F	B	Aphakia OAG	ALT, filter OU
15	70	M	H	Exfoliation syndrome	T.5, P2, Pro OU; ALT OU
16	48	M	W	Pigmentary glaucoma	Bg.5, Ocusert, Pro OU; ALT OU
17	64	M	B	POAG	Bg.4, P1 OU; ALT OU
18	55	M	W	Pigmentary glaucoma	T.5 OS; filter OU
19	76	M	B	POAG	T.5, P4 OU; ALT OU
20	51	M	W	POAG	None
21	39	M	B	Juvenile glaucoma	T.5 OU; P2, Pro OS; D250; filter OU
22	33	M	B	POAG	T.5, P4, Pro OU, D250; ALT OU

POAG, primary open-angle glaucoma; OAG, open-angle glaucoma; T.25, timolol 0.25%; T.5, timolol 0.50%; P1, pilocarpine 1%; P2, pilocarpine 2%; P4, pilocarpine 4%; Bt, betaxolol; Bg.25, levobunolol 0.25%; Bg.5, levobunolol 0.5%; Pro, dipivefrin; D250, acetazolamide 250 mg; D500, acetazolamide 500 mg; ALT, argon laser trabeculoplasty; N50, methazolamide 50 mg.

performed because of clinical indications. In all cases, it was a trabeculectomy-type procedure with a partial thickness scleral flap. The diurnal IOP measurements were repeated with the self-tonometer at least 3 months after the surgery, but in some cases as long as 2 years after surgery.

RESULTS

DIURNAL IOP STUDY

Diurnal IOP values of 286 patients were analyzed to determine whether diurnal curves were present. Twenty of these individuals were normal controls, 74 were ocular hypertensives, and 192 had various types of open-angle glaucoma. As can be seen in Table IV, 100% of the normal individuals, 78% of the ocular hypertensives, and 72% of the glaucoma patients showed a glaucoma rhythm pattern. Distribution of the types of the curves that were present in these 199 eyes that showed a glaucoma rhythm are shown in Table V. In general, daytime curves (IOP highest between 8 AM and 2 PM) were the most prevalent, although in the ocular hypertension group there were slightly more eyes with a morning curve (IOP highest between 4 AM and 8 AM) than with a daytime curve. Very few eyes in any of the groups had biphasic (morning and late afternoon peaks) curves.

In 43 ocular hypertensive subjects and 32 open-angle glaucoma subjects, the glaucoma IOP measurements had been repeated on a subsequent occasion, again for at least 3 consecutive days. In the ocular hypertensive group this was performed an average of 9 months (range, 2 to 21 months) after the initial measurement and in the open-angle glaucoma group it was performed an average of 12 months (range, 1 to 45 months) later. Only a minority of eyes (28% of the ocular hypertensive eyes and 35% of the glaucoma eyes) showed the same type of curve as they had on the initial examination (Table VI). In the ocular hypertensive group an additional 25% of the eyes continued to show a glaucoma rhythm, but with a shift in the peak to another time period. On the other hand, approximately one fifth of both the ocular hypertension and glaucoma eyes shifted to an erratic tracing.

There was a group of 193 patients in whom diurnal curves were available for both eyes. Comparison of the curves is shown in Table VII. There was a fairly high degree of concordance in the small number (16) of normal eyes, with 81% having the same type of curve and 6% showing a shift of the peak to a different time period but still showing a diurnal curve. In the ocular hypertensive and glaucoma groups, however, there was much less confidence. Only 58% and 53% of these groups, respectively, showed the same type of curve, and when a rhythmic pattern with a time shift of the peak was included, concordance between the two eyes was still only 73% for the ocular hypertensive individuals and 68% for the glaucoma patients.

TABLE IV: DIURNAL PATTERNS ACCORDING TO DIAGNOSIS

TYPE OF PATTERN	NORMAL	OCULAR HYPERTENSION	GLAUCOMA
Diurnal (%)	100	78	72
Flat (%)	0	8	6
Erratic (%)	0	14	22
No. of patients	20	74	192

TABLE V: PREVALENCE OF DIURNAL CURVES ACCORDING TO DIAGNOSIS

TYPE OF CURVE	NORMAL	OCULAR HYPERTENSION	GLAUCOMA
Morning (%)	30	51	35
Day (%)	65	42	60
Biphasic (%)	5	7	5
No. of patients	20	55	124

TABLE VI: REPRODUCIBILITY OF DIURNAL CURVES

TYPE OF CURVE ON REPEAT TESTING	OCULAR HYPERTENSION	GLAUCOMA
Same as previously (%)	28	35
Diurnal rhythm with 6-hour shift in peak (%)	25	14
Diurnal rhythm with 12-hour shift in peak (%)	3	7
Same, erratic (%)	0	9
Different, erratic (%)	19	21
Other (%)	25	14
No. of patients	43	32

SLEEP IOP STUDY

The mean IOP values of the 22 glaucoma patients and 12 normal control subjects who participated in the study of IOP during sleep are shown in Table VIII. Fifteen (68%) of the glaucoma patients and seven (58%) of the controls had an IOP at least 4 mm Hg higher during the night in at least one of their eyes than they had prior to going to sleep. In the subjects in whom both 1 AM and 3 AM IOP measurements were obtained, the values

TABLE VII: COMPARISON OF THE DIURNAL CURVES IN THE TWO EYES OF PATIENTS ACCORDING TO DIAGNOSIS

TYPE OF CURVE	NORMAL	OCULAR HYPERTENSION	GLAUCOMA
Same curve (%)	81	58	53
Rhythmic pattern with 6-hour shift in peak (%)	6	11	15
Rhythmic pattern with 1-hour shift in peak (%)	0	4	0
Same, erratic (%)	0	9	10
Different, erratic (%)	12	18	21
No. of patients	16	55	122

TABLE VIII: MEAN PNEUMATOGRAPHIC IOP VALUES IN THE SLEEP IOP STUDY

	PRESLEEP	1 AM	3 AM	6 AM
Normals	17.7 mm Hg 24 eyes	20.3 mm Hg 24 eyes	21.9 mm Hg 13 eyes	22.1 mm Hg 20 eyes
Glaucoma	20.9 mm Hg 43 eyes	26.2 mm Hg 43 eyes	26.1 mm Hg 7 eyes	26.1 mm Hg 43 eyes

TABLE IX: IOP (mm Hg) VALUES FOR REPEAT PATIENTS IN THE SLEEP IOP STUDY

PATIENT	FIRST VISIT			SECOND VISIT		
	PRESLEEP	1 AM	WAKE-UP	PRESLEEP	1 AM	WAKE-UP
1	25	27	29	16	30	25
	22	32	31	20	34	30
2	20	30	23	24	28	35
	19	29	22	24	33	33
3	24	33	26	20	30	28
	20	33	20	18	28	28

were quite similar at both times. In the normal subjects the wake-up IOPs were higher than those that had been obtained during sleep, but in the glaucoma patients they were virtually identical. (Two of the normal subjects awoke before the technician came in and were already out of bed, so their values were not included.) The increase in average IOP in the glaucoma patients from presleep to sleep of 5.3 mm Hg was statistically significant using a paired t-test ($P < 0.05$).

The three glaucoma patients who had their nighttime IOP measured on two separate occasions demonstrated rises in IOP during sleep on both occasions (Table IX). Given the small numbers, the finding may not be meaningful, but it is interesting to note that the 1 AM IOPs on the two occasions were more similar than were the presleep or wake-up readings.

THERAPY STUDIES

The mean diurnal IOP values with and without a topical beta adrenergic blocking agent in the 14 eyes that participated in the drug therapy study are illustrated in Fig 3. It can be seen that before therapy there was a definite diurnal curve in which the IOP peaked during the morning and then dropped steadily through the rest of the day. Following institution of therapy there was an overall lowering of IOP, but the diurnal curve remained present, albeit with a reduction in range. Fig 4 shows a similar tracing for a group of patients before and after glaucoma filtration surgery. Here there was a much greater reduction in the mean IOP. Some diurnal fluctuation remains for the group as a whole, but in four of the eight eyes the curves were virtually flat.

DISCUSSION

Although there are conflicting results from the many studies on variation in IOP over a 24-hour period, there seems to be little doubt that there is a diurnal rhythm present in IOP. In fact, it appears that animals also have a diurnal fluctuation in IOP.[57] On careful consideration, it is not hard to understand why these very different study results have been obtained. As has been pointed out, some of these differences are related to the testing techniques themselves. The differences in tonometers, the frequency of IOP measurements, and the environment in which they are conducted obviously have an impact on the results obtained. Also, there are many exogenous factors that influence the IOP level. Some of the short-acting factors, such as the osmotic effects of food or liquid intake, the effects of heavy exercise, and changes in systemic blood pressure, have already been mentioned. There are probably additional factors as well. For example, many ophthalmologists believe that emotional state can have a dramatic effect on the IOP, although this is difficult to quantitate.[58] Given such wide-ranging exogenous influences, in addition to the variations in testing protocols, it is not at all surprising that varied results have been obtained.

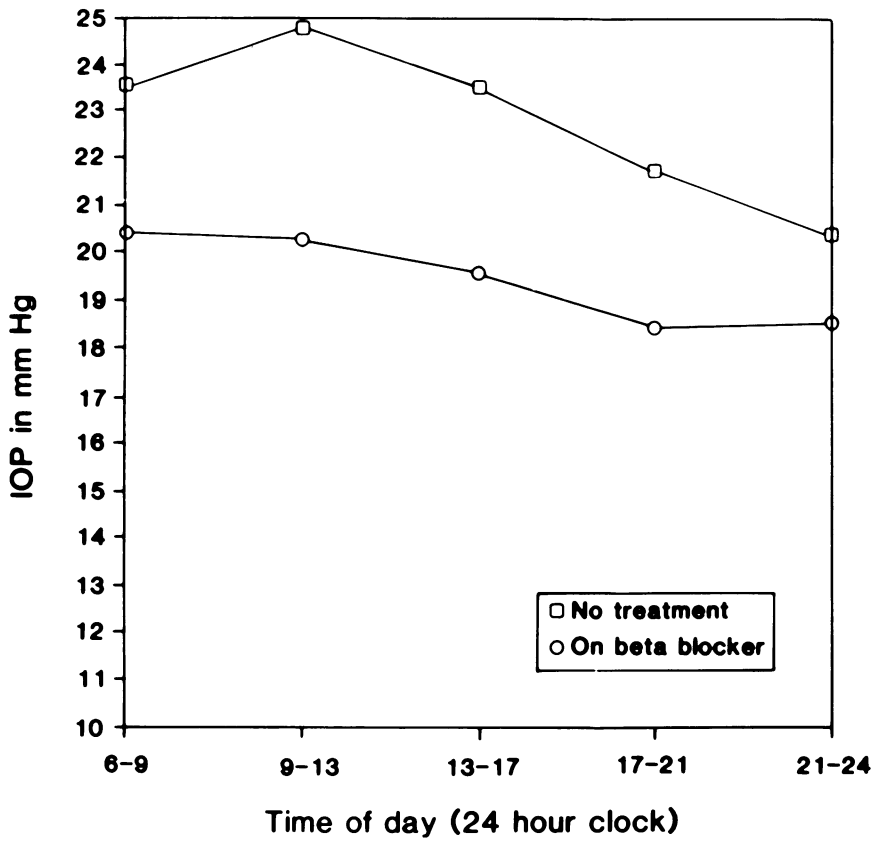

FIGURE 3
Mean diurnal curve of 14 eyes of 14 patients on no therapy, and after 1 month of treatment with 0.25% QD of a nonselective beta adrenergic blocking agent. Note decrease in mean IOP and reduction in range of diurnal variation.

POSSIBLE CAUSES OF THE DIURNAL VARIATIONS

Exogenous influences notwithstanding, there is little doubt that there are certain endogenous factors that do result in a rhythmic, albeit somewhat irregular, pattern in the IOP, which seems to have a 24-hour time course. A question naturally arises as to what these endogenous factors might be. There have been many suggestions, but there are no clear-cut answers. A hormonal basis for the variations in IOP has been suggested, and, in particular, it has been noted that there seems to be a diurnal variation in

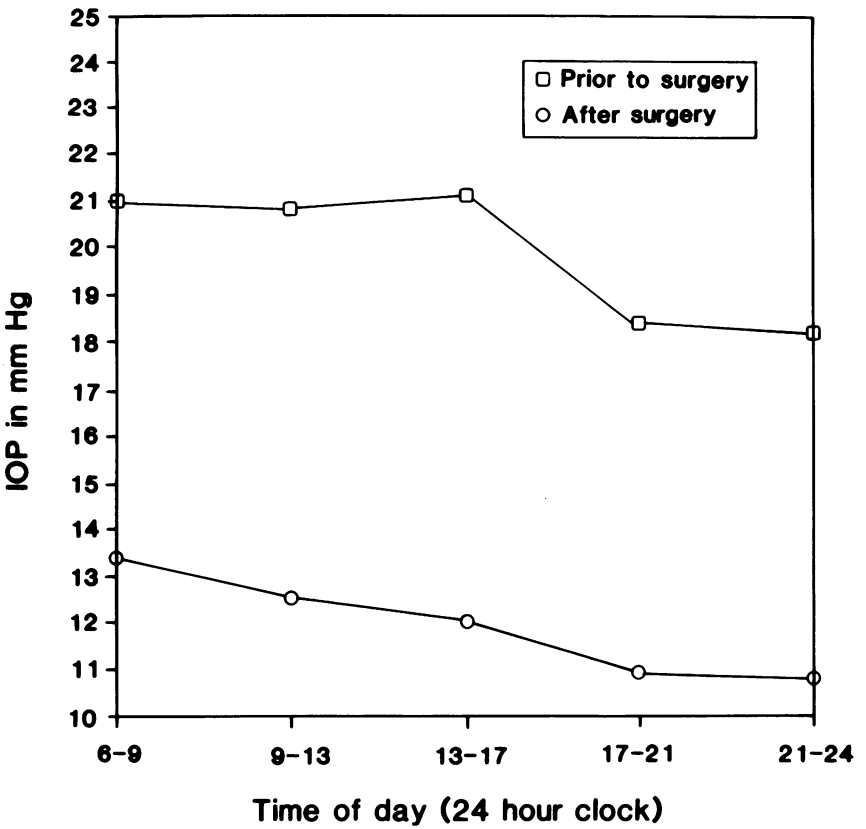

FIGURE 4

Mean diurnal curve of eight eyes before and after glaucoma filtration surgery. Note marked decrease in mean IOP (particularly when compared to decrease due to medical therapy seen in Fig 3) and decrease in range of diurnal variation.

cortisol levels in the body.[10] It has been well documented that long-term administration of corticosteroid preparations may lead to elevation of IOP,[59] and in one study[60] orally administered dexamethasone caused an increase in IOP in patients with open-angle glaucoma 4 to 8 hours after administration. Moreover, in another study, there was a 3- to 4-hour time lag between the elevation in the endogenous cortisol level and a corresponding elevation in IOP.[61] Therefore, it has been hypothesized that the diurnal variation in IOP is largely a reflection of diurnal variation in plasma cortisol.

Another hormone that has been suggested as playing a role in IOP control is melatonin,[62] a substance that is secreted by the pineal gland and may also be synthesized in the eye.[63] Experimental data from animal studies suggest that a rise in melatonin levels may be associated with increases in IOP.[64,65] At least one study in humans[66] has yielded results that appear contradictory to the animal findings.

A second suggested mechanism has been autonomic or humoral control of aqueous outflow from the eye. At least three studies have attempted to correlate the facility of aqueous outflow from the eye with variations in IOP. Serial daily tonographic measurements of outflow have shown variations in results at different times of the day that suggest to the authors of these papers that there are fluctuations in the actual facility of outflow through the trabecular meshwork.[67-69] Two of the studies,[68,69] however, failed to find a correlation between the diurnal fluctuations in IOP and the variations in facility of outflow that were detected. It should be pointed out that tonography is a somewhat imprecise measure that has a considerable amount of variability, and, therefore, it is difficult to separate true change from testing artifact in an individual's eye.

A variation of the outflow theory holds that, rather than being modulated by changes in the trabecular meshwork, the changes in outflow facility are the result of changes in vascular tone, which affect the collector channels and the episcleral veins.[15,70] Dobree[15] has reported on changes in the perilimbal episcleral vessels that he correlated with changes in IOP.

It also has been suggested that variation in IOP may be partially related to variation in aqueous production. Using a suction-cup technique to estimate aqueous inflow, Ericson[17] found that the level of inflow was relatively constant between 8 AM and 8 PM. Between 8 AM and midnight, there was a considerable drop in inflow. It then stabilized between midnight and 4 AM and began to rise again from 4 to 8 AM. More recently, Reiss and co-workers[71] have measured aqueous inflow using a fluorophotometric technique. They have confirmed Ericson's finding of decreased aqueous inflow during the sleeping hours. In a separate study, Topper and Brubaker[72] have shown that the beta adrenergic blocking agent timolol also reduces aqueous inflow and this amount of reduction is comparable to the reduction in inflow that is seen at night during sleep. The administration of timolol prior to sleep does not further reduce the aqueous inflow. Therefore, they have hypothesized that aqueous production may be dependent on a beta adrenergic tone that is mediated by circulating adrenaline levels. It must be pointed out that in these studies the calculations of flow rates are based on measurements performed at least 1 hour and

frequently several hours apart. Therefore, the values obtained are averages of the flow during the whole period, the large changes of short duration may not be apparent.

It also has been suggested that the variations in IOP simply may be due to mechanical factors. One such mechanical factor is the tension in the intraocular muscles and the effect they have as they compress the globe during contracture.[70] A second factor is accommodation with corresponding contraction of the ciliary muscles. Armaly and Jepson[73] showed that accommodation can reduce IOP. Obviously, during sleep there is less accommodative effort than at other times. A third possible factor is the effect that alterations in blink pattern, particularly during sleep, may have on the episcleral veins and the collector channel on the surface of the globe near the limbus.[74] It has been shown that blinking raises the IOP instantaneously and a forceful hard blink may raise the IOP by as much as 50 mm Hg.[75]

One of the early theories to explain the variations in IOP was that of Kollner[26] who suggested that it is varying degrees of blood congestion in the eye that lead to these changes. This view was supported by Hagen.[18] In a variation of this theme, Brubaker recently suggested (personal communication) that the acute rises in IOP following sleep reported by Brown and co-workers[42] and by Zeimer and co-workers[37] might be due to an acute rise in systemic blood pressure that pumped an increased volume of blood into the eye, which then dissipated rapidly.

Not surprisingly, a number of the theories about mechanisms that modulate the diurnal fluctuations in IOP are related to the clinical findings of the investigators. Thus, those who found the highest IOP in the morning on awakening have tended to concentrate on mechanical factors relating to sleeping and lying down. Investigators who have found higher IOP at other times have tended to concentrate on hormonal or neural factors. But no one explanation seems to cover all the findings. It may be that there are multiple factors, some dominating in certain circumstances while others dominate at different times.

USE OF THE SELF-TONOMETER

The accuracy of the self-tonometer developed by Zeimer that was used in this study has been reported in the literature.[53,54] The average reproducibility in the patient's natural environment was ± 1.4 mm Hg. The correlation coefficient between the readings of the self-tonometer and those of the Goldmann applanation tonometer was 0.89, and the difference between the readings of the two instruments varied by ± 2.5 mm Hg. This is equal to the variability reported in measurements performed

by two separate experienced ophthalmologists using a Goldmann applanation tonometer.[76]

No serious problems were encountered during the study. There were several occasions when the membrane over the tip of the piston was damaged and the patient was not able to obtain IOP readings. When this occurred, the membrane was replaced immediately, if possible, and the testing continued. If this could not be accomplished in a timely manner, the patient returned on another occasion and the entire test protocol was repeated.

SIGNIFICANCE OF DIURNAL VARIATIONS

The diurnal curves obtained from the subjects in the present study are within the range of those previously reported in the literature, as discussed earlier in this thesis. There was a somewhat higher degree of regularity of pattern in the normal individuals than in the ocular hypertensive and glaucoma patients. This might, perhaps, suggest that there could be an alteration in some of the normal homeostatic mechanisms in the more diseased eyes that has led to a less regular pattern. On the other hand, the number of normal subjects in the study is quite small, so we must be cautious about drawing any conclusions. The fact that there was a small but noticeable increase in the percentage of eyes (from 14% to 19% in the ocular hypertension eyes and from 22% to 35% in the glaucoma eyes) with erratic diurnal patterns on repeat testing 9 to 12 months after the original measurements also could be interpreted as indicating a loss of normal homeostatic mechanisms. Again, however, the numbers are small and this result must be interpreted with caution.

A somewhat surprising finding in our patients was the considerable between-eye variation in the diurnal IOP pattern. Although Katavisto[23] reported that 45% of the pairs of eyes in his study did not have comparable diurnal curves, most investigators have believed that there is a fair degree of symmetry between the two eyes.[77] For this reason we analyzed the diurnal curves by patient rather than by eye. Although it could be argued that the differences in the diurnal curves may be due to there being more severe glaucoma in one of the two eyes, the differences also may indicate that there is considerable variability in the test results that does not necessarily have clinical significance. This conclusion may also be supported by the rather high degree of change in diurnal rhythms that was noted in the patients who had repeated diurnal testing. Perhaps this variability was detected because the IOPs were measured for three or more days each time, whereas in many of the studies in the literature the IOP was measured for only one day. It should be pointed out that Kaneda

and Kiritoshi,[22] when reported that they had found a rather different distribution of diurnal curve patterns than had been reported by Langley and Swanljung,[27] suggested that the type of the variation is unimportant but that the variation itself is very important.

One recurring question that is asked about the IOP variation is: Which IOP value is most important? Is it the mean IOP, the peak IOP, the trough IOP, or the range of IOP? Different investigators have given different answers but there is little solid evidence to support these positions. In Smith's study[34] the range in IOP, the diurnal variation in IOP, the time of the highest IOP, and the time of the lowest IOP were found to be statistically similar in eyes with and without visual field loss. A recent study by Zeimer and co-workers[78] suggested that peak IOP may be more important than mean IOP, but the number of patients was small. More prospective data will be needed before this question can be answered.

In the past, there has been a great deal of discussion about the measurement of diurnal IOP levels and whether the results of such testing have diagnostic or prognostic significance.[32,36,43,70,79-82] It has been suggested that IOP peaks over a certain level or a diurnal range in IOP above a certain level might be diagnostic of glaucoma even in the absence of visual field loss or glaucomatous cupping. It is widely accepted that diurnal IOP measurement should play an important role in the differential diagnosis of low tension glaucoma.[36,58] Drance[43] has suggested that high diurnal peaks in IOP may explain why some patients with IOP apparently controlled by medical therapy continue to have progression of visual field loss. Of his patients being treated for open-angle glaucoma, all of whom had an applanation IOP of 19 mm Hg or lower, one third had diurnal IOP peaks of 24 mm Hg or greater.

The knowledge that there is a diurnal IOP variation has a special application in glaucoma screening programs. Most of these programs rely on IOP as a key criterion in deciding whether to refer an individual for further evaluation. Lennon and Turnbull[83] have shown that when such an IOP criterion was used a higher percentage of individuals were referred from morning screening sessions than from afternoon sessions.

SIGNIFICANCE OF THE SLEEP IOP STUDY

The elevated IOP detected during the Sleep IOP Study may be of considerable clinical importance. Many studies in the past found that IOP was lowest during early morning hours while sleeping, a time that Ericson,[17] and Reiss and co-workers[71] have suggested is the period of lowest aqueous inflow. On the other hand, some diurnal pressure studies have detected high IOP in glaucoma patients during the night or on arising in the

morning. Brown and co-workers[38,42,74] have studied normal individuals extensively and found high IOP in these individuals when they are awakened from sleep. Frampton and co-workers[38] have stated that elevated IOPs will not be detected in normals if the individual's sleep pattern is disrupted. If, however, the subjects are allowed to fall asleep naturally and the IOP is then measured, elevations will be detected. Our study, which allowed the patients to fall asleep and then measured the IOP in bed without the patients moving, has now confirmed this finding in glaucoma patients and indicates that the magnitude of this rise is greater in glaucoma patients than in normal individuals.

The key question that cannot be answered is whether the elevated IOPs that have been detected during these tests were relatively instantaneous elevations in pressures associated with waking up, as suggested by Brubaker, or whether they were present for some time during sleep before the measurement. If the latter is true, this finding has very obvious clinical significance, since it would indicate that some glaucoma patients may be experiencing IOP levels considerably in excess of those that are being detected in the ophthalmologist's office or even that have been detected by conventional diurnal pressure measurements. I don't know whether they bear on this question, but I will offer the following observations. I served as one of the normal controls in the study. Although sleeping soundly, each time I sensed the technician coming at least 30 seconds before she actually entered the room, and, therefore, was already awake when she administered the local anesthetic drop to measure IOP. Furthermore, it was the impression of the technician that every subject was awake at the time that she did measure their IOP with the pneumatonometer.

SIGNIFICANCE OF THE THERAPY STUDIES

The therapeutic studies we have performed have confirmed the findings of previous studies. The diurnal pattern of the IOP remains present although the mean IOP is reduced and the range of diurnal variation also is reduced. One point that was of special interest to us was the decrease in the IOP seen during the afternoon in the participants of our drug therapy study. The pretreatment diurnal curve (Fig 3) of our patients was such that the afternoon IOP was approximately 3 mm Hg lower than the morning IOP. The apparent therapeutic effect of the drug in the morning was also around 3 mm Hg. Therefore, in the afternoon, as these two effects merged and the two curves came closer together, it was more difficult to demonstrate whether there was a therapeutic effect. It may be that the spontaneous drop in IOP at this time reflects a decrease in

aqueous production. If this is true, one would expect that an aqueous outflow suppressant such as a beta adrenergic blocking agent would be less effective at this time of day and this might also contribute to the narrowing of the difference between the two curves that was seen.

Our findings suggest that both the mean IOP and the range of the diurnal variation are reduced to a greater extent with filtration surgery than with medical therapy. The persistence of the diurnal variation, however, suggests that the normal regulation of diurnal IOP variation cannot be modulated predominantly through the outflow system. Filtration surgery essentially eliminates the trabecular meshwork and the collector channels as major contributors to aqueous outflow from the eye, yet the diurnal variation remains. Therefore, the control must reside elsewhere.

It has been suggested that the diurnal IOP values may be of help in tailoring therapy for glaucoma patients. It has been suggested that drugs should be administered at specific times in an attempt to blunt diurnal peaks that have been detected.[77] This particular point was not investigated in the present study, so we cannot comment on it. Diurnal IOP measurements certainly can be valuable in assessing the impact of drug therapy on the IOP at different times of the day or night. However, the beta adrenergic blocking agents, which are now the most widely used antiglaucoma medications, have a prolonged duration of action, and recent studies have suggested that once-a-day therapy may be more than sufficient to maintain maximal beta blockade.[84] With such drugs, the timing of administration probably is relatively unimportant, and diurnal testing will, therefore, be of little importance in this regard. With the shorter-acting drugs, such as pilocarpine and the carbonic anhydrase inhibitors, it is possible that such tailoring of the timing of drug administration to peaks of IOP might be of some benefit.

ROLE OF HOME TONOMETRY

A number of ophthalmologists have suggested that home tonometry may be the ideal way to perform diurnal IOP measurements.[36,80-82] The advantages of such testing include minimal disruption of the patient's normal schedule and activities, low cost (since there are no hospital or professional fees), and the relative ease of obtaining such measurements on multiple occasions or on several consecutive days. With the Schiøtz tonometer, which has been used by several ophthalmologists[80,81] to obtain home tonometric values from their patients, a second individual must be taught to perform the measurements and the patients must be in an environment in which they can lie down to allow the measurements to be performed.

With Zeimer's self-tonometer, the patient requires no assistance to perform the measurement. It is packaged in a case that looks like a small briefcase and easily can be carried to work or elsewhere. The IOP can be measured anywhere there is a desk or table with a nearby electrical outlet. On the other hand, it does require a patient who has an intact central visual field and good enough visual acuity to line up the fixation target within the instrument accurately. This is essential to obtaining valid measurements. Nonetheless, we feel that the present study clearly demonstrates the ease and usefulness of this instrument for monitoring diurnal variations in IOP in many glaucoma patients.

CONCLUSIONS

It is widely agreed that IOP fluctuates in a somewhat rhythmical diurnal pattern and that this fluctuation is greater in eyes with glaucoma. On the other hand, there is disagreement as to the pattern of the variation and the timing of the peak IOP. In this study 266 glaucoma patients and 20 normal individuals measured their IOP five times a day at home for 3 to 6 consecutive days using a self-tonometer, with minimal disruption of their normal activity pattern. It was found that there was a relative lack of concordance between the two eyes of individuals. Similarly, on repeat testing of some of the subjects months later, almost one third of the eyes had a substantially different diurnal pattern. This indicates that the diurnal curves are much more variable than has been appreciated in the past, and many of the conflicting findings in the literature are merely representations of that variability rather than substantive differences. The data in this study suggest that too much emphasis has been placed on the pattern of the diurnal curve and the timing of the IOP peaks. The height of the peaks or the range of the variations is more likely to be of importance to clinical management of the patient.

The Sleep IOP Study has confirmed the finding that in normal eyes the IOP is higher when measured during sleep than it was before going to bed. Most importantly, this study demonstrated that this same phenomenon occurs in glaucoma patients with a mean increase of more than 5 mm Hg from presleep levels. In many eyes the increase in IOP was greater than 10 mm Hg. Clearly, this finding is of considerable clinical importance if the elevated IOPs that have been detected are present for any considerable period of time. If this is the case, it could require a complete reassessment of how IOP is monitored in glaucoma patients.

Finally, the therapy studies demonstrate that medical or surgical therapy lowers both the mean IOP and the range of diurnal variation, but a diurnal rhythm pattern does persist. It appears that surgical therapy may

narrow the range of diurnal variation to a greater extent than does medical therapy. Since recent evidence has suggested that peak IOP may be the parameter that best correlates with the prognosis of glaucoma, knowledge of how a given therapy affects the diurnal IOP peak may be more important than knowing how it affects the IOP measured in the ophthalmologist's office.

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