

# Diurnal and 24-h Intraocular Pressures in Glaucoma: Monitoring Strategies and Impact on Prognosis and Treatment

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## ABSTRACT

The present review casts a critical eye on intraocular pressure (IOP) monitoring and its value in current and future glaucoma care. Crucially, IOP is not fixed, but varies considerably during the 24-h cycle and between one visit and another. Consequently, a single IOP measurement during so-called office hours is insufficient to characterize the real IOP

pathology of a patient with glaucoma. To date IOP remains the principal and only modifiable risk factor for the development and progression of glaucoma. Only by evaluating IOP characteristics (mean, peak and fluctuation of IOP) at diagnosis and after IOP-lowering interventions can we appreciate the true efficacy of therapy. Unfortunately, a major limiting factor in glaucoma management is lack of robust IOP data collection. Treatment decisions, advancement of therapy and even surgery are often reached on the basis of limited IOP evidence. Clearly, there is much room to enhance our decision-making and to develop new algorithms for everyday practice. The precise way in which

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daytime IOP readings can be used as predictors of night-time or 24-h IOP characteristics remains to be determined. In practice it is important to identify those at-risk glaucoma patients for whom a complete 24-h curve is necessary and to distinguish them from those for whom a daytime curve consisting of three IOP measurements (at 10:00, 14:00 and 18:00) would suffice. By employing a staged approach in determining the amount of IOP evidence needed and the rigour required for our monitoring approach for the individual patient, our decisions will be based on more comprehensive data, while at the same time this will optimize use of resources. The patient's clinical picture should be the main factor that determines which method of IOP monitoring is most appropriate. A diurnal or ideally a 24-h IOP curve will positively impact the management of glaucoma patients who show functional/anatomical progression, despite an apparently acceptable IOP in the clinic. The potential impact of nocturnal IOP elevation remains poorly investigated. The ideal solution in the future is the development of non-invasive methods for obtaining continuous, Goldmann equivalent IOP data on all patients prior to key treatment decisions. Moreover, an important area of future research is to establish the precise relationship between 24-h IOP characteristics and glaucoma progression.

**Keywords:** 24-h efficacy; 24-h IOP; Circadian IOP; Diurnal IOP; IOP characteristics; Intraocular pressure; Glaucoma therapy; Ophthalmology

## A CRITICAL LOOK AT IOP MONITORING IN GLAUCOMA

As a biological phenomenon intraocular pressure (IOP) is not fixed, but varies during the 24-h cycle and between one visit and another [1]. Indeed, a single IOP measurement during

so-called office hours is a poor surrogate of the entire IOP profile of a patient with glaucoma. It would be tempting to think that every glaucoma patient should undergo a complete 24-h assessment to better characterize the IOP profile and optimize glaucoma therapy. However, such a choice is not feasible, both because monitoring 24-h IOP requires hospitalization and it consumes scarce resources.

The patient's clinical picture should be the main factor in determining which method of IOP monitoring is most appropriate. Patients with ocular hypertension generally do not need elaborate IOP monitoring. A single IOP measurement during office-hour visits may also be appropriate in stable patients with early to moderate glaucoma who do not need a steady constant IOP and who do not demonstrate anatomical or functional progression. In a study by Realini et al. [2] 'fair to good' agreement of IOP values was found at each time point in treated primary open angle glaucoma (POAG) patients who underwent two daytime IOP curves, 1 week apart (intraclass correlation coefficients ranging from 0.45 to 0.71 in right eyes and from 0.51 to 0.71 in left eyes). In consideration of these results, it may be useful to schedule follow-up visits for the same patient at different time points during the day. A useful surrogate of an IOP curve may be obtained in this way, assembling IOP values from previous follow-up visits. Obviously, this method has certain limitations, and is less accurate than diurnal IOP phasing (e.g. it does not allow for evaluation of short-term IOP fluctuation) [2], but can help characterize a patient's IOP profile with minimum effort and no waste of valuable resources.

In contrast, a diurnal or ideally a 24-h IOP curve will positively impact the management of at-risk glaucoma patients who show functional/anatomical progression despite an apparently acceptable IOP in the clinic. If 24-h IOP monitoring is not feasible, it may be useful to perform a diurnal IOP curve that can include a single supine IOP measurement, preferably in the first hours of the morning. Although currently available evidence has not adequately clarified the importance of this information in the natural history of the disease [3–5], a substantial IOP increase in the supine position may

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reflect a potentially detrimental IOP elevation during the night-time.

The mean, peak and fluctuation of 24-h IOP are all parameters that can exhibit significant variation both in the short and the long term. Each should be recorded and evaluated in glaucoma progression. There is strong evidence regarding the role of mean IOP as a risk factor for glaucoma progression. In the Early Manifest Glaucoma Trial, each 1 mmHg increase in mean IOP over all follow-up visits was associated with a 12% higher risk of progression [6]. In the Advanced Glaucoma Intervention Study, each 1 mmHg higher mean IOP level at the first 18 months of follow-up was associated with a 0.10 greater visual field defect score during the remainder of the follow-up [7]. It is worth noting that elevated mean IOP has also been found to be a significant risk factor for conversion from ocular hypertension to POAG [8, 9]. On the other hand, the role of peak IOP and fluctuation as independent risk factors in eyes with glaucoma is a subject of debate [1, 10–12].

The existence of a 24-h IOP rhythm, its characterization and its impact on glaucoma natural history are currently unclear. Studies in European countries have shown that the IOP in glaucoma patients is generally higher in the first morning hours. Konstas et al. [13] observed elevated peak IOP values in up to 45% of untreated exfoliative glaucoma (XFG) and 22.5% of untreated POAG patients outside office hours, with the mean peak IOP mainly occurring between 6 a.m. and 10 a.m. Quaranta et al. found similar IOP profiles in untreated and treated Italian POAG patients [14]. On the other hand, the 24-h IOP peak has been found to occur a few hours earlier during the night in studies performed in a sleep laboratory in the USA [15–17].

The potential impact of nocturnal IOP elevation remains poorly investigated. Whereas an IOP increase at night may be physiological, the detection of IOP peaks outside office hours has led in some cases to clinical management modifications that have included filtration surgery [18, 19]. Moreover, Konstas et al. [20] established that successful filtering surgery resulted in significant flattening of the nocturnal IOP curve. Interestingly, Quaranta et al. [21]

demonstrated that trabeculectomy is more effective than canaloplasty, a non-penetrating form of surgery, in diminishing the posture-induced IOP elevation during the transition from the sitting to the supine position. The potential clinical benefit related to these observations remains to be determined.

An inherent problem with IOP monitoring is the difficulty in obtaining continuous IOP measurements. The influence of some environmental factors, non-replicable in study conditions, and the effect of the procedure itself (i.e. awakening the patients to measure IOP) have been poorly investigated. Various attempts have been made to obtain continuous IOP measurements in “real life” conditions, akin to other biological parameters, such as arterial pressure. Miniaturization of electrical components has made possible the integration of IOP sensors into intraocular lenses, designed to be used after cataract extraction [22–24]. In these implants, signals related to IOP values are generally detected by a wireless external detector, embedded into spectacles. A different approach, comprising a directly implantable IOP sensor placed either in the ciliary sulcus or the capsular bag, has recently been developed (Implandata GmbH, Hannover, Germany) [25, 26]. This sensor uses microplate capacitors with thin diaphragms that deflect under pressure. Although promising, these implantable devices have only been used in very few human studies, with preliminary and sparse results. The Implandata sensor has been evaluated in two human studies with a small sample size [27, 28], and no conclusions about safety and accuracy can be drawn as yet. Currently, there is an open enrolment for a prospective, multicentre clinical trial to assess the safety and efficacy of the device for patients with POAG (<https://clinicaltrials.gov/ct2/show/NCT02434692>).

Leonardi et al. [29] developed the first “smart” contact lens for 24-h IOP monitoring at the Swiss Federal School of Technology more than 10 years ago. The device is based on a disposable silicone contact lens that incorporates two platinum–titanium sensing-resistive strain gauges that measure limbal strain associated with changes in IOP and volume. Today Leonardi’s Triggerfish contact lens sensor (CLS)

is available both in Europe and the USA (SENSIMED Triggerfish<sup>®</sup>, Sensimed AG, Lausanne, Switzerland). The CLS continually monitors IOP-related fluctuation via an electric signal, as it acquires a total of 288 data points over a 24-h period, each corresponding to 30 s of continuous measurements, repeated every 5 min. Unfortunately, the output of the device is in relative units rather than in millimetres of mercury. Given that simultaneous tonometry in eyes using the CLS is impossible, an algorithm that converts relative units to millimetres of mercury has yet to be developed. The CLS signal variations cannot be used to estimate IOP variations expressed in millimetres of mercury, because the relationship between relative units and millimetres of mercury variation is probably non-linear [30]. For these reasons, the use of this device is currently limited to the evaluation of day/night IOP rhythms. Most studies using the CLS have found an increase of output values during night hours, confirming results from some investigators conducted with non-continuous tonometry methods [31–36].

An important area of research is the potential relationship between 24-h IOP patterns and the risk of glaucoma progression. De Moraes et al. [35] investigated the correlation between 24-h data obtained with the CLS and the rate of visual field progression in 40 glaucoma patients. In mixed-effect linear model testing, the parameter “mean peak ratio during sleep” was found to have the greatest importance. For each additional peak during awake hours, the rate of visual field progression was accelerated by  $-0.14$  dB/year; for every 10-unit increase in the mean peak ratio while asleep, the rate of visual field progression accelerated by  $-0.20$  dB/year, while for every 10-unit increase in the wake to sleep slope it accelerated by  $-0.03$  dB/year. These data should be interpreted with caution because of the small sample size. However, they open the way for further clinical studies determining the potential role of the CLS in clinical practice.

The current article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## DIURNAL VERSUS 24-H IOP MONITORING IN GLAUCOMA

Pressure measurements throughout the 24-h cycle would offer valuable information on the true IOP profile of glaucoma suspects, or patients with established glaucoma in at least two distinct clinical scenarios: Firstly, in untreated cases, the true characteristics of the IOP curve would become evident before the pressure curve is altered by the commencement of treatment [1, 37, 38]. Secondly, in treated patients, the real efficacy of therapy and the quality of IOP control would become evident during the complete circadian cycle, instead of during a unique daytime moment in time [18, 19, 37–39].

There is evidence to suggest that the mean diurnal IOP of glaucoma patients may not differ significantly from the mean 24-h IOP [19, 40]. On the other hand, it has convincingly been shown that daytime measurements often fail to detect high fluctuation and pressure peaks outside office hours, especially in patients with glaucoma characterised by unpredictable IOP patterns, such as XFG, or chronic angle-closure glaucoma [3, 4, 13, 40, 41]. Consequently, daytime measurements may sometimes fail to identify a patient’s true IOP profile [1, 42–44]. Unfortunately, complete 24-h IOP measurements are not a practical option in the majority of glaucoma patients. Confronted with the need to develop more attainable surrogate measures that could be used instead of 24-h IOP measurements, a number of investigators have examined whether daytime IOP readings could be indicative of the full circadian IOP rhythm.

In a retrospective sleep laboratory study with 33 younger controls (aged 18–25 years), 35 older controls (aged 40–74 years) and 35 untreated older glaucoma patients (aged 40–79 years), Mosaed et al. [4] examined the correlation between daytime sitting, or supine IOP readings, and peak nocturnal IOP. The results showed that the peak nocturnal IOP for the majority of older glaucoma patients can be estimated using the average office-hour IOP according to the following formulae: peak nocturnal IOP =  $12.04 + 0.616 \times$  average office-

hour sitting IOP ( $r^2 = 0.0361$ ) or peak nocturnal IOP =  $5.98 + 0.771 \times$  average office-hour supine IOP ( $r^2 = 0.508$ ). In contrast, the correlation between office-hour measurements and peak nocturnal IOP was much weaker for normal controls [4].

A study performed by Nakakura et al. [40] also examined the association of daytime and 24-h IOP in 71 treated eyes of 42 patients with POAG. Daytime IOP was derived from three outpatient readings (9 a.m. to 6 p.m.) over a 6-month period. Circadian measurements were obtained with a Goldmann tonometer at 3-h intervals. According to this group of investigators the mean office and 24-h readings were similar (16.2 vs 16.3 mmHg respectively), but only a third of these eyes had peak 24-h IOP during office hours. Additionally, the 24-h IOP fluctuation was significantly higher than office-hour fluctuation (6.7 vs 2.7 mmHg respectively;  $P < 0.001$ ).

Fognolo et al. [3] investigated if office-hour IOP readings in the sitting and/or the supine position could provide meaningful alternatives to complete 24-h monitoring in healthy eyes ( $n = 29$ ) and untreated eyes with POAG ( $n = 30$ ). Importantly, office-hour sitting measurements were similar to 24-h readings for the peak, mean and IOP fluctuation in a mere 10% of the young controls, 32% of the elderly controls and 20% of the patients with glaucoma. On the other hand, using a combination of office-hour sitting and supine readings significantly improved the detection of 24-h IOP characteristics for all study groups. In a later retrospective study, the same group [45] examined if different combinations of daytime sitting and/or supine readings could predict IOP characteristics obtained with a 24-h pressure curve in 70 treated POAG patients. These authors observed that none of the strategies they employed was particularly accurate in correctly predicting the mean, peak or fluctuation of IOP over the 24-h cycle.

From the above research it becomes clear that the precise way in which daytime readings can be used as predictors of night-time or 24-h IOP characteristics has yet to be identified. Consequently, what seems to be of greater value is to identify those at-risk patients for whom a

complete 24-h curve is necessary versus those for whom a diurnal curve consisting of three or four IOP measurements during office hours would suffice [37, 38]. Notwithstanding the scant published evidence, common clinical wisdom suggests that glaucoma patients with exfoliative, pigmentary or chronic angle-closure glaucoma should be prime candidates for 24-h IOP monitoring, especially if single daytime readings do not shed light on the treated IOP characteristics and when there is evidence of progression during follow-up. Patients demonstrating progression of visual field loss despite apparently “adequate IOP control” in the clinic and good purported adherence may need to undergo a 24-h IOP assessment in an effort to identify out-of-office unfavourable IOP characteristics [37]. For example, in a retrospective chart review of 29 treated POAG and normal tension glaucoma (NTG) patients who were progressing despite seemingly good IOP control, Hughes et al. [19] documented that although the mean office IOP was similar to the mean 24-h value, the peak 24-h pressure was almost 5 mmHg higher than the peak office IOP. Further, more than half of the patients exhibited IOP peaks outside regular office hours, and in 14% of them the peak 24-h IOP was at least 12 mmHg higher than the office-hour peak [19]. In this study, 24-h measurements led to changes in clinical management in nearly 80% of patients, while 45% of them were offered surgery (trabeculectomy). On the other hand, POAG patients with consistent daytime IOP characteristics, low risk of progression and apparently adequate pressure control may be followed without resorting to anything more than a few IOP measurements scattered throughout office hours and between visits. Additionally, clinicians need to take into account the 24-h efficacy of topical medications, laser therapy or surgical interventions when considering a patient’s therapeutic options [37]. Although the precise 24-h ocular hypotensive profile of each treatment option may be unknown for any given patient, valuable information that can guide treatment decisions can be gained from previously published evidence [14, 20, 37, 38, 46–48].



## CAN DIURNAL/24-H IOP STRATEGIES PREDICT THE QUALITY OF IOP CONTROL IN GLAUCOMA?

It is well established that IOP is the main and only modifiable risk factor for the development and progression of glaucoma [7, 49–51]. Thus, IOP parameters (mean, peak and fluctuation) should be measured at diagnosis and after IOP-lowering interventions have been commenced, in order to better understand the true efficacy of therapy. Mean IOP has been consistently recognized as a major risk factor for glaucoma detection and progression [7, 49, 51] whereas the role of peak pressure [52, 53] and pressure fluctuation [12, 54–58] as independent risk factors is still not adequately defined. Although several studies have pointed out that mean IOP may not be significantly different when measured during office hours or over 24 h [3, 4, 18, 19], it is clear that office-hour evidence may significantly underestimate 24-h IOP peak and 24-h fluctuation. Importantly, many glaucoma patients exhibit their peak IOP outside office hours [3, 4, 16, 40, 59]. The most comprehensive procedure to investigate IOP characteristics is 24-h phasing [3, 4, 18, 19, 60] although it is impractical, expensive and can therefore only be performed in selected patients in hospitals. Moreover, as a result of the unavailability of non-invasive IOP-measuring technology at home that can monitor reliably sleeping IOP, night-time evaluation involves awakening of patients, potentially causing artefacts related to alteration of the sleep–wake rhythm. The difficulty in obtaining 24-h curves and the possible discrepancies between 24-h and office-hour data led several groups [3, 4, 16, 40] to develop strategies to estimate 24-h parameters from office-hour data.

Several studies [1, 14, 37–39, 42, 45] have shed light on the underlying value of 24-h IOP monitoring in documenting the 24-h efficacy of the various treatment strategies for the various forms of glaucoma. Indeed, Jonas et al. [61] performed a retrospective review of 855 eyes from 458 treated patients with POAG, NTG or ocular hypertension (OHT). They investigated the potential association of 24-h IOP parameters

with disease progression in glaucoma patients, or conversion to glaucoma in persons with OHT, after a mean follow-up of almost 56 months. In a multiple Cox proportional hazards analysis, for the whole study population, progression was associated with age and neuroretinal rim area. For the POAG group specifically, only age ( $P < 0.001$ ) was a significant prognostic factor, whereas in the NTG group, higher mean IOP ( $P = 0.036$ ) and lower fluctuation ( $P = 0.045$ ) were identified as predictors of disease progression. However, as participants were receiving topical medication that is known to reduce IOP levels and its fluctuation, the impact of 24-h IOP fluctuation may have been significantly reduced.

In a retrospective chart review of 29 treated POAG and NTG patients, Hughes et al. [19] reported that pressure characteristics cannot adequately be determined with only office IOP readings. In another study, Barkana et al. [18] reviewed the records of 32 progressive open-angle glaucoma patients who underwent Goldmann tonometry in the sitting position every 2 h, from 7 a.m. until midnight and Perkins tonometry in the supine position at 6 a.m. The authors compared office-hours and outside office-hours values recorded on the same 24-h monitoring for each patient, as well as IOP values determined in up to five previous outpatient visits. All eyes were medically treated or had undergone argon laser trabeculoplasty (ALT) and/or trabeculectomy. The mean peak 24-h IOP was higher than the mean peak office IOP (16.8 vs 14.7 mmHg;  $P < 0.001$ ) and the mean 24-h fluctuation was higher than the office-hours fluctuation (6.9 vs 3.8 mmHg;  $P < 0.001$ ). The peak IOP in at least one eye was found outside of office hours in almost 70% of the patients. These findings led the authors to alter therapy in 19 of 32 patients (59%), mostly offering laser and incisional surgery. Similar to the study by Hughes et al. [19], these patients were on medical therapy and underwent 24-h phasing due to progression despite apparently good office-hour IOP control. Therefore, the study identified a higher-than-expected proportion of eyes that were deemed to merit treatment modification (often surgery) due to worse than anticipated 24-h IOP characteristics.

Research by Nakakura et al. [40] also highlighted that only a third of the study eyes demonstrate peak 24-h IOP during office hours and 24-h IOP fluctuation was significantly greater than office-hour IOP fluctuation (6.7 vs 2.7 mmHg respectively;  $P < 0.001$ ).

The effect of topical glaucoma medications on the IOP profile has been the subject of intense investigation and debate. Prostaglandins administered either in the morning or the evening have been shown to have a significant IOP-lowering effect throughout the 24-h cycle. Nevertheless, a meta-analysis of 24-h efficacy data in 386 patients demonstrated that the night-time efficacy of latanoprost was significantly lower than its daytime efficacy ( $P = 0.031$ ) [47]. A study by Alm and Stjernschantz [62] demonstrated that latanoprost 0.005% administered in the evening exhibited greater IOP lowering than latanoprost given in the morning. Overall, the evening dosing of latanoprost showed significantly greater diurnal efficacy (1.1 mmHg or 4%) compared with the morning dosing [62]. In contrast, topical carbonic anhydrase inhibitors (CAIs) may be the only class of medications exhibiting better night-time than daytime efficacy [14, 47]. According to a meta-analysis of published 24-h studies [47], dorzolamide was the only topical medication showing better efficacy during the night (20–23% IOP reduction) than during the day (14–18% IOP reduction). Most reports indicate that  $\beta$ -blockers have a meaningful, albeit reduced, night-time efficacy [14, 47, 63, 64] that may be explained by the decreased nocturnal aqueous formation [65, 66]. However, sleep laboratory studies by Liu et al. [17, 67] employing a different methodology and measuring the IOP with a pneumotonometer have reported a virtually non-existent nocturnal IOP-lowering effect with timolol. Finally, brimonidine administered twice or three times daily has consistently been found to have reduced efficacy late in the afternoon and during the night [38, 68].

There is limited research on the effects of laser treatment and filtration surgery on circadian IOP rhythm [69]. In a study by Lee et al. [70] there was no significant reduction in mean, peak or fluctuation of office-hour IOP or diurnal

IOP after laser trabeculoplasty on 28 treated eyes of 18 glaucoma patients. However, a significant nocturnal IOP reduction was observed after laser trabeculoplasty [46] in 26 eyes of 13 patients. These authors reported that after appropriate washout no eyes managed a mean diurnal IOP reduction of 20% or more after laser. Nonetheless, the treatment resulted in a significant decrease in the amplitude of 24-h IOP fluctuation. With regard to filtration surgery, one study [20] observed that successful surgery provided better quality of 24-h IOP control compared with successful maximal medical therapy. In this prospective observational study, Konstas et al. [20] compared 30 advanced open-angle glaucoma patients successfully treated with trabeculectomy and 30 patients considered to be well controlled on maximal medical therapy. They established that following a successful trabeculectomy with mitomycin C, patients obtained lower mean, peak and fluctuation of 24-h IOP compared with patients on successful maximal medical therapy. The 24-h fluctuation of IOP was  $2.3 \pm 0.8$  mmHg for the surgical group and  $4.8 \pm 2.3$  mmHg for the medical group ( $P < 0.0001$ ). Most IOP peaks occurred outside usual office hours.

## INTRAOCULAR PRESSURE MONITORING STRATEGIES IN GLAUCOMA AND THEIR IMPACT ON PROGNOSIS AND TREATMENT

One of the major limiting factors in the treatment of glaucoma is the lack of robust IOP data collection capabilities. This limitation influences every step of our care for those suffering from glaucoma. At the time of diagnosis, we frequently make treatment decisions based on one or two IOP measurements that take place during clinic hours. Subsequently, assessment of treatment success or failure is often completed during the same office hours while relying on one or two measurements representing a small snapshot of the pressure experienced by the eyes in any given day. Perhaps more concerning is the fact that advancement of

treatment is often decided upon in similar fashion, based on a target pressure that was set with incomplete information. It is not uncommon for patients to undergo surgery on the basis of snapshot IOP measurements that appear out of range from a pre-set goal pressure. In essence, we begin treatment of glaucoma on the basis of limited information, and therapy is maintained or altered on the basis of spot checks of equally limited data. Clearly, there is much room to enhance how we approach our decision-making, and efforts are underway to incorporate new algorithms for decision-making into everyday practice.

Ideally, physicians would have available an extensive IOP data set that spans a prolonged period. These data would include maximum and minimum values along with diurnal variability of pressures for many consecutive days [1, 3, 37]. Continuous monitoring would be an ideal, and connecting the IOP profile with activities of daily living would add more in-depth information to help guide treatment decisions. For example, it would be of great value to know if a specific eye experiences pressure elevation during the nocturnal period but never during the diurnal period. Similarly, knowing if IOP elevation is related to a specific activity, playing the trumpet for example, could certainly influence patient education and treatment decisions. Unfortunately, we currently lack a method of IOP monitoring that is both continuous and reliable, and our efforts must be relegated to episodic measurements that often take place in the physician's office, in hospital or units called sleep laboratories. These limitations have resulted in a "one size fits all" therapy approach rather than one tailored to address individual peaks, troughs and individual patterns that are influenced by both disease and activities of daily living.

Given where we are today with limited ability to measure and monitor IOP, and to obtain robust data from each individual eye, how can we alter our current practice to achieve more informed decisions for our patients? We could begin by making initial treatment decisions based on several IOP measurements at various time points within usual office hours [37, 38, 71]. If diagnosis of glaucoma or OHT is

made in the early morning hours, any treatment decision can be delayed until the patient returns on a subsequent day for an afternoon visit to get the most crude data set consisting of two time points and different times during the day. Alternatively, the patient may return for full diurnal plotting of pressure, by spending the day in clinic and undergoing measurements every 1–2 h from morning through to late afternoon. The next level of vigilance would involve both diurnal and nocturnal plotting of IOP that usually involves an overnight stay for the patient in a facility that can accommodate such rigour (e.g. a formal sleep laboratory). It would be obvious to any busy clinician contemplating this information that it is not practical to implement these ideas on a regular basis given the time and expense related to running efficient practices as well as poor patient acceptance of the time required to obtain these data. The question then arises, what can we practically achieve with today's technology and real-world limitations that burden clinicians and patients alike?

Practically speaking, there are a few practice patterns that can be implemented by most clinicians with relative ease and little expense or burden. First, unless there is an urgent need to lower IOP, treatment decisions can be delayed for one or more visits in order to obtain a clearer understanding of visit-to-visit variability as well as time of day variability in IOP. Decisions regarding efficacy of the chosen therapy as well as the need to escalate therapy can be similarly delayed for several visits to collect more robust and actionable data. In those patients who appear to have advancing disease that does not correlate with the data obtained during regular office visits, the decision can be made to first obtain a diurnal pressure curve during regular office hours. Patients going through this more rigorous data collection process would represent a small fraction of the overall patient population and would thus exert a lesser burden on any given practice. Finally, for those patients who require even more information, for example a patient with advancing disease despite what appears to be controlled pressure on one or two diurnal curve measurements, a lengthier stay in the office into evening hours or a visit to



a sleep laboratory for nocturnal pressure checks might be in order. Patients with OHT often do not require the rigour of multiple checks that might be required in advancing late-stage glaucoma. Similarly, patients with labile secondary glaucomas may benefit from repeated measures on different days to better understand the IOP cycling that might be at play. By using this staged approach for the amount of rigour implemented for any given patient, physicians will be able to make decisions based on more complete data while limiting the impact of the exorbitant time required obtaining such information.

The ideal solution may involve a non-invasive method for obtaining continuous data on all patients prior to any treatment decision. The data would have to be presented in a manner that is concise and free of “noise”. Equally important is that we require more rigorous research into how such information truly impacts the disease process. Is variability of IOP as important as maximum or minimum IOP? Is variability of IOP within any given day equally important as variability between days? Is there a difference in disease impact between diurnal and nocturnal pressure profiles? How can we better define “goal IOP” for each patient given added information on IOP profile over time? We will not know the answers to these questions until technology catches up with the questions posed and allowing researchers to test hypotheses within a biologic environment that rarely conforms to a simple yes or no conclusion.

## DIURNAL/24-H IOP MONITORING STRATEGIES IN GLAUCOMA SUSPECTS

Glaucoma suspects are adults demonstrating findings consistent with an increased risk for glaucoma development in at least one eye [72]. Such findings include an enlarged cup (taking into account optic disc size) or asymmetric cup–disc ratios, notching or narrowing of the neuroretinal rim, visual field changes commensurate with glaucoma, or IOP readings above the statistically accepted upper limit

(over 21 mmHg) [72]. The last of these is particularly important since the possibility of glaucoma development is significantly correlated with an elevated IOP whereas glaucoma may progress faster in patients with higher levels of IOP [38]. Glaucoma suspects actually outnumber patients with established glaucoma in the average ophthalmologist’s practice and comprise the majority of patients receiving anti-glaucomatous medications in the USA, implying that adequate IOP monitoring strategies are required for their management [73].

Importantly, short- and long-term IOP fluctuation influenced by a variety of physiological factors including blood pressure and heart rate, breathing, accommodation, eyelid blink, pupillary size, eye movement, central venous pressure (Valsalva manoeuvre), ingestion of water and osmolarity, sleep, postural changes, physical activity and hormonal factors all need to be borne in mind [30]. Moreover, temperature-related and seasonal variations in IOP have also been reported [74]. A single office IOP measurement of a glaucoma suspect only provides a snapshot in the continuum of IOP change. However, since the IOP is considered the *primum movens* in glaucoma development, the decision to treat glaucoma suspects rests heavily on the IOP level documented during follow-up. Thus, an apparently low level of recorded IOP may prove misleading and may mask the real risk of glaucoma development. On the other hand, an erroneously high level of IOP may lead to unnecessary administration of medication with potentially toxic effects on a long-term basis [75]. Therefore, to obtain a true picture of IOP levels for a glaucoma suspect, several IOP readings are required [37, 76]. While a diurnal IOP curve may suffice in most cases, a complete 24-h or 48-h curve may be needed in selected cases to unmask periods of exposure to higher levels of IOP during the night [37, 76].

The concept of a biological rhythm of IOP has been well documented since the beginning of the twentieth century by the works of Maslenikow, Duke-Elder and Henkind and has been extensively examined, especially since the late 1970s by several controlled studies [30]. A biological rhythm may either be circadian (established in the absence of any

environmental influence) or nyctohemeral (established under the influence of alternating light and dark) [30]. To investigate the biological rhythm of IOP, recordings over a complete 24-h period are required [37, 76]. Moreover, there is some evidence that to establish detailed IOP fluctuation characteristics, in some cases 48-h monitoring is required [77, 78]. The probability of identifying a circadian or nyctohemeral rhythm increases when the measurement frequency of a biological parameter increases over time (thus the number of measurements over 24 h) and vice versa, rendering near-continuous rather than separate measurements the ideal method of recording [79]. Several studies have confirmed the existence of a nyctohemeral IOP rhythm, but not a true circadian IOP rhythm (i.e. not a rhythm generated by the internal biological clock of the suprachiasmatic nucleus in the absence of any influence of the environment) [30]. In healthy human subjects, the amplitude of IOP nyctohemeral fluctuation varies between 3 and 5 mmHg, ranging from a peak in the morning to a trough recorded any time during the 24-h period [30, 31, 37, 38, 79]. Interestingly, the amplitude of the IOP nyctohemeral fluctuation varies extensively among healthy individuals but is fairly consistent in the same individual and is relatively independent of postural change (i.e. horizontal body position at bedtime) [30, 31]. On the contrary, glaucomatous patients differ from non-glaucomatous subjects with significant deviations in the nyctohemeral IOP rhythm, including a higher IOP fluctuation, a shift in peak IOP from early morning to night-time or a lack of an evident peak throughout the monitoring period [30, 80]. Interestingly, in ocular hypertensive patients, the patterns of nyctohemeral IOP rhythms have been reported to align with non-glaucomatous subjects, decreasing progressively in the diurnal period with a trough in the late afternoon, and increasing during the nocturnal period with a peak in the early morning [81]. On the contrary, a previous study on glaucoma suspects has detected a peak IOP at 10–11 a.m. and a trough IOP at 2–3 a.m. (past midnight), while in control subjects the detected IOP peak

was at 6–7 p.m. and the trough at 2–3 a.m. [73]. Importantly, in that study, patients who developed POAG or OHT on follow-up were found to have a higher mean IOP (above 20 mmHg) at all measured intervals [73].

The current methodology for recording diurnal fluctuations of IOP involves repeated measurements by applying conventional applanation tonometry with the patient in a sitting or horizontal posture (“phasing”) [30, 38, 73]. Consequently, they are unable to detect dynamic variations of IOP in response to a wide range of daily activities (such as Valsalva manoeuvres or touching and rubbing the eyes) or by truly measuring sleeping pressure [30]. Efforts to monitor IOP conventionally during the day or the night may disrupt daily activities and normal sleep patterns. More importantly, isolated IOP measurements may not be sufficient to truly identify continuing IOP changes.

To address these issues, a variety of intraocular or extraocular devices with integrated pressure sensors have been developed and proposed for continuous IOP monitoring [22–24, 29, 82–87]. The obvious advantage of these devices apart from the possibility of continuous IOP monitoring is that they do not interrupt physiologic rhythms, thus providing better information on the “natural history” of IOP changes in the individual patient. Such designs include radiotelemetry from a device applanating the inferior sclera [82], various concepts of contact lens embedded piezoelectric sensors [29, 83, 84], tracking secondary speckle pattern trajectories produced by the reflection of an illuminating laser beam from the iris or the sclera [85] and various proposals for surgically implanted sensors with capabilities for external signal recording through telemetry. The first implantable device proposed by Collins in 1967 included a gas bubble encapsulated in a thin and flexible film [4]. Since then several other designs have been proposed such as an elastic band placed around the globe equator [86], a subchoroidal implant [87] or a variety of sensor-integrated intraocular lens designs [22–24, 26]. Although the level of agreement of all these devices with standard Goldmann

applanation tonometry varies [30], they may be of value in earlier glaucoma diagnosis and in the identification of true IOP characteristics and better delineation of the risk for glaucoma progression by revealing hidden peaks of IOP in glaucoma suspects.

Although the theoretical value of obtaining more information on the continuous changes of IOP may be important, the optimal practical way to take advantage of this increased amount of information is currently not known [30]. Continuous IOP monitoring may reveal higher IOP peaks than isolated measurements, but the mean IOP should be roughly the same for both strategies and currently there is no consensus on whether the mean or peak IOP is the most relevant determinant factor for glaucoma diagnosis [38]. Moreover, associated factors such as the long-term role of IOP nyctohemeral fluctuations and the significance of the nocturnal IOP rise in glaucoma progression has not so far been sufficiently investigated [30], although a previous study has reported that the best time to catch the peak IOP in glaucoma suspects is in the period from early morning until mid-afternoon, and the best time to record the minimum IOP would be from the late evening until past midnight [73]. Moreover, the common practice of hospitalizing patients to perform phasing of the IOP may underestimate the IOP, since evidence has shown that IOP recordings are consistently lower during hospitalization than after discharge from the hospital [88].

Since the ideal strategy for glaucoma detection should be tailor-made for each case, the goal of IOP monitoring should be to create a more comprehensive, individualized pressure profile for each glaucoma suspect, identifying his or her individual patterns of IOP peaks and troughs, and focusing on these time points for the early detection of unacceptable IOP characteristics, necessitating timely intervention. Taking into account that glaucomatous optic nerve damage results from a combination of pathogenetic factors, measurements could be expanded to additional physiological parameters, such as the continuous recording of ocular perfusion and breathing patterns, which may

play an even more critical role than IOP in glaucoma development and progression [89, 90]. Concomitant ophthalmic conditions predisposing to different forms of glaucoma should also be taken into consideration. The concept of obtaining better evidence on diurnal or 24-h IOP characteristics (peak, mean and fluctuation) in glaucoma suspects may be particularly important in patients with narrow or occludable angles, with a view to detecting earlier subclinical repeated episodes of asymptomatic acute IOP elevation [91]. Furthermore, ophthalmic conditions predisposing to the development of secondary open-angle glaucoma with potentially non-linear and fast progression, such as exfoliation syndrome (XFS) or pigment dispersion syndrome, should be taken into account in any IOP monitoring strategy, while clinicians need to have a lower threshold of concern for glaucoma suspects with XFS and pigment dispersion syndrome, obtaining more pressure measurements in these patients [92]. In any case, our management strategy with glaucoma suspects must aim at detecting the thin line that separates the indication for observation from the indication for treatment. It is not an easy task and certainly requires gathering as much useful IOP information as possible. A key role for clinicians is to accurately translate diurnal IOP characteristics into risk for glaucoma progression. For this purpose, the development and targeted use of future technologies enabling reliable and continuous IOP monitoring may be of great diagnostic value.

## WHAT IS THE BEST IOP MONITORING STRATEGY IN PRIMARY OPEN-ANGLE GLAUCOMA?

A pragmatic approach for the majority of POAG patients could entail three or four IOP measurements scattered throughout typical office hours (e.g. at 10:00, 14:00 and 18:00) before the commencement of therapy. Such a strategy would provide important information for the particular patient's initial IOP characteristics

over an appreciable part of the 24-h cycle. After the instigation of treatment, a diurnal curve offers valuable information on the quality of pressure control over a significant time period. In the case, however, of patients with erratic pressure profiles such as those found in exfoliation or narrow-angle glaucomas, or in progressive glaucoma despite apparently adequate diurnal IOP control and good compliance, a full 24-h curve would be warranted. Patients with very advanced damage and high risk for further progression may also be good candidates for a complete 24-h curve.

The added value of information derived from a complete circadian curve in a real-life setting has been revealed by published evidence showing that changes in treatment were deemed necessary in a significant proportion of progressive patients following a 24-h curve [18, 19]. Importantly, 24-h measurements can reveal problematic IOP characteristics such as high peak IOP or wide fluctuation of IOP that may increase the risk of progression [52]. In such cases, the modification of the treatment plan with more aggressive medical therapy, laser treatment or surgery may be decided on the basis of the overall patient profile.

Admittedly, currently available literature does not provide answers to several key issues concerning the role of IOP characteristics in glaucoma and our ability to record and interpret these in a clinically meaningful way. Future research will have to address the issue of reliable and easy 24-h IOP measurements, much in the same way as cardiologists employ Holter devices. A further necessity in this field is the production of more conclusive evidence on the specific role of different IOP characteristics, such as peak IOP and its fluctuation. In addition, it would be important to see research on the effects of numerous behaviour-related pressure changes that normally occur in daily life (yoga, weight-lifting, goggle use, prone sleeping position etc.) and may affect eyes with glaucoma. In the future, the development of a reliable monitoring method and a better understanding of how IOP characteristics affect glaucomatous eyes could allow the customization of therapy based on each patient's particular rhythm.

## VALUE OF DIURNAL/24-H IOP MONITORING IN THE MANAGEMENT OF NORMAL TENSION GLAUCOMA

### Intraocular Pressure and Normal Tension Glaucoma

Currently, a patient with POAG is expediently subclassified into two subtypes, i.e. POAG consistently associated with IOP within a statistically normal range (normal tension glaucoma, NTG) and POAG with IOP higher than the statistical upper limit of the normal range (POAG in the narrow sense). As an upper limit of the IOP, 21 mmHg is usually adopted. Although there may exist statistically significant small differences in the pattern of visual field damage and/or optic nerve head appearance between eyes with NTG defined as above and those with POAG in the narrow sense, these differences are of clinically insignificant levels and the diagnosis of NTG has been given after excluding recorded IOPs higher than the cut-off level and other co-existing non-glaucomatous optic nerve head abnormalities resembling those of glaucoma [93, 94]. In several hospital-based studies, the reported IOP of NTG eyes was somewhat higher than that in normal subjects [93–96], while other studies indicated that the IOP of NTG eyes showed little difference from that in normal eyes [97–101]. Since the first report by Maslenikow [102], it is well known that there is circadian fluctuation of the IOP which tends to be greater in eyes with glaucoma than in normal eyes [59, 103–109]. Therefore, the IOP of patients suspected of NTG should be monitored not only during office hours but also outside of office hours. This is the reason why many of the previous hospital-based studies included 24-h IOP fluctuation assessment results of consistently lower than a cut-off level (usually  $\leq 21$  mmHg) as one of the criteria for diagnosing NTG. Further, IOP may be gradually elevated during follow-up in some patients once diagnosed with NTG. One study reported that 5% of the patients who had been diagnosed with NTG after 24-h IOP fluctuation assessment

showed an office-hour IOP elevation above the cut-off level at 1-year follow-up [110].

In the population-based Kumejima Study that was carried out in a south-western rural island of Japan, the prevalence of NTG was 3.3% and the IOP of 124 NTG patients averaged 14.7 (standard deviation 2.6) mmHg, while that of 2473 normal subjects was 14.5 mmHg (2.7) ( $P > 0.30$ ) [111]. In a population-based study, however, the diagnosis of NTG was given by IOP recordings which were usually obtained only on two or three separate occasions at the screening and/or confirmative examinations. Thus, NTG diagnosed in a population-based study is more likely to include 'POAG in the narrow sense', with a large 24-h IOP fluctuation. Among NTG patients differentiated only on the basis of IOP recordings at the screening examination, 12% reportedly showed office-hour IOP higher than the cut-off level after 1 year of follow-up [112]. A fluorophotometric study in a small group of NTG patients showed no significant abnormality in the aqueous humour dynamics in NTG eyes [113].

#### Diagnosis and 24-h Intraocular Pressure Fluctuation in Normal Tension Glaucoma

The IOP of normal eyes shows 24-h fluctuation with an average range of about 5 mmHg [103, 105, 106, 109], while the 24-h IOP fluctuation in NTG in the sitting position is very similar [114–117]. Since a peak IOP higher than the cut-off value may be recorded outside of office hours, it is reasonable to carry out 24-h IOP measurements in patients suspected of NTG to exclude POAG in the narrow sense, with a large 24-h fluctuation. When patients suspected of NTG according to the untreated office-hour IOP recordings underwent 24-h fluctuation assessment in the sitting position, the timing of the peak pressure was encountered outside of office hours (08:00–18:00) in about 40% of cases, and 5.3% and 3.5% of patients showed a peak IOP higher than the cut-off level [115, 116]. The IOP measured after hospitalization for evaluation of its 24-h fluctuation was about 1.5 mmHg lower than that of an outpatient office measurement [118, 119], and it was

reported that eyes with mean office-hour IOP of 16 mmHg or lower were very unlikely to show a peak 24-h IOP of greater than 21 mmHg [115, 116]. The IOP is known to be influenced by the postural change from the sitting to the supine position, with higher values in the supine position [120–123]. Although aqueous humour dynamics as determined by fluorophotometry did not show any significant difference between NTG and normal eyes [113], IOP changes induced by a pharmacological agent, and those caused by postural change from the sitting to the supine position, or the relationship between IOP and episcleral venous pressure may differ between NTG and normal eyes [124–127]. Thus, the measurement of 24-h IOP fluctuation in habitual posture corresponding to the daily activities (sitting position during the day and supine position during sleep) is expected to provide more clinically useful information not only from the viewpoint of diagnosing NTG [15, 17] but also to guide more clinically effective management of IOP [71, 128].

Twenty-four-hour IOP fluctuation has been mainly assessed during hospitalization. On the other hand, a sleep laboratory assessment over a 24-h period is expected to yield more precise information on the physiological circadian rhythm of IOP by providing a more strictly controlled external environment [15, 17, 129]. However, it must be noted that a sleep laboratory would not completely mimic the typical home sleeping situation either, and results of 24-h IOP fluctuation assessment obtained in a sleep laboratory and those during hospitalization need not necessarily agree with each other. Liu and associates assessed 24-h IOP fluctuation in healthy volunteers and untreated POAG patients using a pneumotonometer in a sleep laboratory [16, 17]. They reported that the nocturnal supine IOP was higher than daytime seated and supine measurements, while the nocturnal seated IOP was higher than the daytime measures [16, 17]. Quaranta et al. used Goldmann tonometry during the day and Perkins tonometry for night-time supine IOP measurements of untreated POAG patients and reported that the daytime IOP measured in the sitting position was higher than the night-time



IOP measured in the sitting position, and similar to the night-time IOP measured in the supine position [5]. The exact reason for this discrepancy is unknown, but differences in the monitoring technology (Goldmann or Perkins tonometers versus pneumotonometers used in other studies) and in the subjects' ages may have been at least partly responsible for the discrepancy. Twenty-four-hour IOP assessment is impractical for most patients. A relatively strong correlation was reported between the mean sitting outpatient clinic IOP and the mean sitting 24-h IOP ( $r = 0.806$ ) or the peak of the sitting 24-h IOP ( $r = 0.747$ ) in NTG patients [115], and between the mean supine office-hour IOP and the peak supine nocturnal IOP in older untreated POAG patients ( $r = 0.713$ ) [4].

### **Glaucomatous Damage and 24-h Intraocular Pressure Fluctuation in Normal Tension Glaucoma**

Although not always confirmed [5, 130] many studies agree that a nocturnal peak pressure is more likely to be seen in NTG or normal eyes [16, 17, 60, 131–137]. One study showed a significant correlation between the peak and 24-h IOP fluctuation in the habitual position and the extent of visual field damage in NTG [80], while another study showed a significant correlation between the peak and range of the diurnal IOP, and the extent of perimetric damage in NTG [128]. However, it must be noted that another study did not confirm these results [80]. Longitudinal studies may provide more information on the relationship between the 24-h IOP fluctuation measurement results and extent of glaucomatous damage in NTG. Two earlier studies suggested that the peak of the 24-h IOP fluctuation or a larger fluctuation of diurnal IOP was a risk factor for future progression of POAG [54, 138], but this conclusion was not supported by later longitudinal follow-up studies in NTG patients [61, 139] which suggests that further studies are needed to elucidate the value of the 24-h IOP fluctuation measurement in relating it with the extent of glaucomatous damage in NTG.

Blood flow rather than IOP itself may have a greater contribution to the pathogenesis of glaucomatous optic neuropathy in some NTG patients [140]. Low nocturnal blood pressure or the difference between blood pressure and IOP, ocular perfusion pressure (OPP), or larger 24-h fluctuation of mean OPP is reportedly associated with the extent of glaucomatous damage in NTG [141–143]. Being compatible with these findings, retrospective longitudinal studies showed that greater 24-h fluctuation of mean OPP in the habitual position was a risk factor for progression of visual field damage in NTG eyes [144, 145], especially in the central 10° of the visual field [146, 147]. The results of the aforementioned studies imply that 24-h monitoring of IOP combined with 24-h monitoring of blood pressure in the habitual position would be of value in evaluating prognosis of patients with NTG.

### **Treatment and 24-h Intraocular Pressure Fluctuation in Normal Tension Glaucoma**

Although the level of evidence regarding whether the use of 24-h IOP measurements benefits NTG patients by leading to a more effective disease management strategy may be limited [136], IOP reduction is currently the only evidence-based therapeutic option in NTG eyes. Needless to say that the IOP has to be lowered over the full 24-h period, because the possible correlation between the range of 24-h IOP fluctuation with the extent of perimetric damage [137] suggests that a more narrow 24-h IOP fluctuation would be beneficial for visual outcome [71]. To confirm the effects of ocular hypotensive therapy over a 24-h period, 24-h IOP fluctuation without treatment must be compared to that with treatment in the same eye, or 24-h IOP values must be monitored with one eye treated while the other eye remains untreated to serve as a control. In NTG, no significant differences in the diurnal IOP fluctuation at the same time points of two successive days were reported [114], and intraclass correlation coefficients for the diurnal IOP peak, mean and fluctuation were reportedly 0.741, 0.798 and 0.209, respectively [148]. The diurnal

IOP fluctuation between the two eyes in NTG was reportedly largely concordant, and the probability of bilateral difference in the IOP within 3 mmHg was between 86% and 93% [117]. Reported effects on diurnal IOP in NTG eyes averaged about 20% reduction for topical prostaglandins, about 16% reduction for topical  $\beta$ -antagonists and about a 13% reduction for topical CAIs [149, 150]. One study reported no effects on nocturnal IOP with topical  $\beta$ -antagonists in NTG eyes [151]. The effect of  $\beta$ -antagonist/CAI fixed combinations on diurnal IOP was reported to be similar to topical prostaglandins in NTG eyes [152]. Glaucoma filtering surgery significantly reduced the range of diurnal fluctuation [153, 154]. Selective laser trabeculoplasty (SLT) reportedly reduced the range of nocturnal IOP fluctuation without changing it during the diurnal period [155].

## SHOULD WE MONITOR IOP IN SUBJECTS WITH EXFOLIATION SYNDROME?

The current understanding is that XFS is not a disease but a genetically and environmentally determined condition which cannot be medically modified, and, when no complication is present, it requires no treatment [156, 157]. However, since XFS is the underlying cause of XFG, and the progression from XFS to XFG is common [156, 158, 159], in order to detect conversion early and initiate effective pressure-lowering treatment, regular and detailed IOP evaluation is desirable in all normotensive XFS eyes [157]. In conventional clinical terms, IOP elevation in eyes with XFS represents the first step of conversion to XFG, the most common type of secondary open-angle glaucoma worldwide, in which high IOP, large IOP fluctuation and rapid progression are typical [156–160]. Increased IOP fluctuation without elevation of the daytime (office-hour) IOP has been shown to be associated with decreased retinal nerve fibre layer thickness in XFS eyes, even prior to fulfilling the definition of XFG [160]. XFS eyes with elevated IOP but with no glaucomatous structural and visual field changes have an approximately 30% risk for conversion to XFG

in 5–10 years [159]. These data clearly show that a single normal IOP value measured on a healthy XFS eye does not provide sufficient evidence for ruling out an increased risk of conversion to XFG in a span of a few years, and does not provide information about the optimal timing of the next pressure check during the follow-up. Further, on the basis of normal IOP values measured during office hours, no decision can be made on the presence or absence of increased diurnal IOP fluctuation during the 24 h of the day [37, 157, 160].

These considerations have practical clinical implications: to identify conversion of XFS to XFG early, diurnal IOP fluctuation needs to be assessed with repeated IOP measurements; and careful regular assessment of the early structural indicators of the conversion to XFG (e.g. retinal nerve fibre layer thickness and macular inner retinal thickness changes) is necessary [161, 162]. However, currently no information is available on the optimal timing of these assessments during the long-term follow-up of the XFS eyes. We do not even know if more frequent and more detailed IOP assessment is indicated for eyes with long-standing XFS or older patients. Since early initiation of IOP-lowering treatment with a correctly set target IOP (< 17 mmHg) and accurate checking of IOP under treatment are all needed to preserve visual function in XFG [41, 157, 163], we believe that a diurnal IOP curve (in addition to regular pressure measurements) is advisable if the optical coherence tomography parameters show structural progression in patients with XFS, even when clinically detectable glaucomatous disc and visual field deterioration have yet to develop.

## 24-H IOP EVIDENCE: HOW CAN IT CHANGE TREATMENT PATTERNS AND TREATMENT SELECTION?

One major limitation to a clear understanding of the role of IOP in glaucoma is the “extremely short-term” information that can be obtained from measurements: perhaps one or a few seconds per year, i.e. the time the tonometer probe is actually touching the patient’s cornea. In fact,

there is reliable evidence that IOP largely varies—to begin on a circadian basis—and this has been shown in healthy subjects [164], in patients with a diagnosis of OHT [81] or glaucoma [3]. Several papers have evaluated the 24-h IOP curves in patients untreated [5] or treated with different therapies [68, 165–167] and in different settings (i.e. clinical or sleep laboratory) [68, 164] and have all reported significant fluctuation.

As the “target pressure” is one main goal of glaucoma management, at least ideally, the best approach should consider reaching a circadian IOP profile, always within an IOP range that is deemed “safe” for each individual patient. In clinical practice this is rather hard to do, first because with the currently available tools for 24-h IOP assessment, this requires admission to the hospital and a considerable amount of effort and resources, and second because it has been observed that circadian profiles also tend to vary within the same patient [168]. Therefore, at least theoretically, in order to adopt the best possible management, more than one 24-h curve would be needed for each individual patient. If not feasible, diurnal monitoring will provide most of the information needed.

### Treatment Patterns

In real life, ophthalmologists limit the assessment of IOP to office hours mostly for practical reasons. However, there is evidence that sporadic office IOP measurements will increase the risk of missing IOP peaks [3, 169]. Despite the fact that the role of peak IOP as an independent predictor of glaucoma progression is still debated, lack of information on IOP changes and fluctuations would probably reduce the accuracy of the estimate of mean IOP value. Barkana et al. [18] have shown higher peaks and wider IOP fluctuations after a 24-h curve when compared to what was measured during a typical office assessment. Konstas et al. [13] compared 24-h IOP measurements in 40 eyes from 40 patients with XFG and 40 eyes from 40 patients with POAG. Patients were newly diagnosed and untreated. They found that in 45% of patients with XFG and 30% of patients with POAG, the

peak IOP was measured outside of office hours. These findings would suggest that 24-h IOP monitoring is worthwhile, at least in selected at-risk patients where target IOP seems to be achieved but visual fields keep worsening. Strategies to improve the information from a daytime IOP evaluation have been proposed [3, 169, 170]. Fogagnolo et al. [3] showed that glaucoma patients have 42% of IOP peaks outside office hours; in order to maximize the likelihood of finding such peaks, the authors suggest measuring both supine and sitting IOP during office hours in all patients with unexplained progression of the disease.

No matter if a “true” 24-h curve can be obtained, or some surrogate (e.g. supine assessment of IOP, collection of IOP values from different time points of the day, etc.) procedure is adopted, the most complete information on IOP variability should be recorded, at least in some patients. A viable option is to try to identify the IOP pattern of the particular patient and select the type of treatment and the time of administration accordingly [171]. A number of reports have provided information about the different patterns of IOP profile in untreated patients with glaucoma, OHT and healthy young or aged subjects [17, 133, 164]. In addition to type of diagnosis, other factors like age and axial length should be taken into account. Mansouri et al. [133] evaluated the effect of age and body positions on IOP in healthy patients; interestingly they found that the younger group had an IOP peak before awakening (5.30 a.m.) while the older one showed a delay of the peak by about 2 h (about 7.30 a.m.). Hypermetropic eyes with a shorter axial length (healthy, age range 18–25 years) were found to have larger IOP fluctuations when compared with age-matched subjects with emmetropia or mild myopia. In these eyes the IOP peak occurred before awakening (about 5.30 a.m.) [172]. All this information should help in deciding the most appropriate treatment.

Despite the possibility of various types of IOP patterns in glaucoma patients (e.g. morning-type, night-type, day-type, etc.), studies performed in laboratory settings [15, 173] have shown that the IOP of glaucoma patients tends to be higher early in the morning in the

habitual (supine) body position. This can be considered a “critical” time, when the concomitant nocturnal dip of blood pressure could result in a general reduction of the perfusion of the optic nerve head [174–176].

### Treatment Selection

Different treatment options can be offered also on the basis of their circadian IOP-lowering potential. There are a number of scientific contributions about the different drug effect during the 24 h of the day [47]. There is evidence that different types of drugs can show different types of IOP-reducing profiles with peak and trough values according to time of administration. For example, the 24-h IOP profile is rather stable after prostaglandin (PG) administration [177–179], in particular if the drug is administered in the evening; on the other hand, drugs like beta-blockers [177, 178] and alpha<sub>2</sub>-agonists [68, 180] tend to be less effective during the night than during the day. A study found a significant advantage of adding brinzolamide to latanoprost therapy to improve IOP control during the night [67]. How can the scientific information from these clinical trials be incorporated into clinical practice? There are patients who will benefit from a morning administration of a PG therapy if, for example, their peak IOP is during the night. As the majority of glaucoma patients tend to have a peak IOP in the morning, the preferable time of administration of a PG is in the evening, given the greatest effect of such drugs between 12 and 18 h after administration [62]. A similar approach should be considered for the PG/beta-blockers fixed combinations [181, 182].

There is also evidence coming from studies on non-pharmacologic therapy. Both ALT and SLT were found to decrease diurnal IOP fluctuation [46, 70, 183] in patients with POAG and NTG [155]. In 2007 Lee et al. [70] published a study demonstrating the effect of ALT on 24-h IOP measured under carefully controlled conditions (sleep laboratory) in the habitual body position. Following the treatment, they observed significant nocturnal IOP reduction but no significant effect during office hours.

Interestingly, data recently published by Kiddee and Atthavuttisilp [184] showed similar findings after SLT. Greenidge et al. [183] reported significant reductions in mean, peak and IOP fluctuation in the range of 22–30% after ALT in patients with glaucoma. The long-term effects of ALT and SLT on the 24-h IOP still need to be further evaluated.

In 2006 Konstas et al. [20] suggested that a well-functioning trabeculectomy can provide a statistically lower mean, peak and fluctuation of 24-h IOP than maximum tolerated medical therapy in advanced glaucoma patients. In this trial all the patients underwent 24-h circadian IOP curves. Of note, none of the surgically treated patients showed a peak IOP of 18 mmHg or higher. These data are consistent with the findings of Medeiros et al. [154] who compared diurnal IOP curves in medically treated versus surgically treated patients with POAG; again, IOP peak and fluctuation were significantly lower in the surgically treated group. These findings are reasonable and may help explain the reduced progression rates that have been observed after surgery [185]. More recently, Matsuoka et al. [186] studied the 24-h effect of combined trabeculectomy/sinusotomy in glaucoma patients. After the procedure, the diurnal IOP curves were flattened without a significant nocturnal rise. This study has confirmed results of previous reports that had suggested a better diurnal IOP-lowering profile after filtering surgery when compared to medications [20, 185, 187]. Although it seems intuitive that creation of an alternate outflow pathway through surgery would lead to a more uniform 24-h IOP, as of today there are no strong data available to support this interesting notion.

In conclusion, the evidence we have from 24-h studies on IOP can help us explain why glaucoma in some patients progresses despite apparently “good IOP control” in the clinic; in addition, information on circadian IOP profiles, without or after therapy, can improve the management of glaucoma by enabling the choice of the appropriate drug and the preferable time of administration. Moreover, for those progressive patients in whom IOP peaks could represent a serious threat to vision, evidence



from 24-h studies seems to support a surgical option.

## CLINICAL USEFULNESS OF DIURNAL/24-H IOP MONITORING FOR LONG-TERM GLAUCOMA MANAGEMENT

As previously discussed, IOP is the main risk factor for the onset and progression of glaucoma [188] and the goal of therapy is to preserve the visual function and the related quality of life by slowing down or halting disease progression by meaningfully reducing the IOP with medical, laser or surgical treatments [189]. IOP is a dynamic parameter that depends largely on the secretion and elimination of aqueous humour [30], which has been reported to be higher during the daytime and lower at night [190]. This is likely related to the diurnal activity of the sympathetic system as the major determinant of these changes [190]. The nocturnal IOP is then expected to be lower than the diurnal IOP, but the body position during sleep causes IOP levels to rise at a higher level than IOP in the sitting body position as a result of an increase in episcleral venous pressure and redistribution of body fluids [191]. This means that IOP is influenced also by body position, and to better describe its physiological rhythm it is preferred to measure the habitual IOP in conditions similar to the physiological ones: in the sitting position during the day and in the supine position during the night [16].

Studies conducted with non-continuous IOP measurement methods found inconsistent results regarding the IOP nyctohemeral rhythm in patients with untreated POAG: some have found a similar pattern to that seen in healthy subjects, with lower IOP during the diurnal period and higher during the nocturnal period, while other studies have suggested a phase delay in the periodic variations of IOP in subjects with glaucoma compared to healthy subjects. In these studies, the acrophase was observed in a significant proportion of the subjects during the day, usually in the morning and sometimes in the afternoon [13, 192–194].

Despite these controversial findings, it has been suggested that along with IOP peaks, fluctuations are also considered a potential risk factor for disease progression [54] and IOP measurements performed only during office hours may significantly underestimate both IOP peak and fluctuations. In the 24-h study by Barkana et al., peak IOP was recorded outside office hours in at least one eye in 69% of their sample population and this result led to immediate treatment change in 36% of these eyes, suggesting the important clinical utility of 24-h IOP monitoring [18].

Furthermore, the efficacy of IOP-lowering drugs may be variable across the 24 h as has been shown in previous 24-h IOP monitoring studies [67, 195]. Since 24-h IOP monitoring is not feasible in clinical practice as it is expensive and impractical, Mosaed et al. investigated the possibility of using office-hours IOP data to estimate the magnitude of peak nocturnal IOP [4]. They found in fact that supine daily IOP measurements may allow one to estimate peak nocturnal IOP better than sitting measurements [4].

The different results reported from 24-h IOP monitoring studies are probably due to different study populations involved, different frequency with which the IOP measurements were performed and different tonometers used. Furthermore, another source of variability relates to the measurement of IOP during sleeping hours. Sleeping IOP may not be reliably measured. Moreover, if the IOP is checked at frequent intervals during this period, the normal sleep pattern is altered, and the values obtained may not be representative of the actual values.

As already mentioned, the CLS continuous measurement system developed by Leonardi et al. [29] acquires a total of 288 data points over a 24-h period, each corresponding to 30 s of continuous measurements, repeated every 5 min and provides its measurements in millivolt equivalents instead of the usual millimetres of mercury units. Clinical interpretation of electric signals produced by the CLS remains a challenge, but preliminary data confirm a nocturnal acrophase in healthy subjects and glaucoma patients [32]. Additionally, the IOP-related parameters obtained with the CLS have



been found to be associated with the rate of visual field progression in treated glaucoma eyes, highlighting the importance of 24-h IOP for long-term glaucoma management [35].

In conclusion, continuous 24-h IOP monitoring could in the future help clinicians identify patterns and characteristics of 24-h IOP, such as time, amplitude, duration and frequency of spikes and fluctuations during the day and night, which constitute risk factors for progression. Nevertheless large, longitudinal, prospective clinical studies are required to better characterize the role of these factors in the course of the disease before 24-h IOP monitoring can be adopted in routine clinical practice.

## CURRENT AND FUTURE OPTIONS FOR 24-H IOP MONITORING

As discussed earlier in this review, a single IOP measurement during office hours provides very limited evidence for the 24-h and long-term IOP variability, fluctuation, pattern and dangerous IOP spikes [18, 196]. Even conventional daytime phasing provides limited information on the true IOP variability [4]. For most clinicians, hospitalization of glaucoma patients and suspects for 24-h IOP curves is not feasible, and even when it is available the night-time IOP measurement may not be made in the patients' habitual position. This is an important limitation since IOP is different in supine and lying position [15, 30]. In addition, during hospitalization the patients' routine activity rhythm may not be maintained, and in the modern world for many people there is not even a true rhythm in their daily life. In fact, influence of body position, activity rhythm, topical and systemic medication and actual psychological stress have a combined effect on IOP, which makes it very difficult to draw optimal conclusion on risk of glaucoma development or progression and success of pressure control based on a few conventional IOP measurements.

In several clinical decisions ophthalmologists rely on evidence-based information arriving from clinical trials. However, to estimate the diurnal IOP variability from limited daytime measurement values only limited data are

available [4]. Sleep laboratory and outpatient studies have shown several features of the circadian IOP variability in healthy subjects, POAG and NTG patients [15, 30, 135, 173, 197–200]. However, as a result of the complicated and expensive technical conditions necessary for a sleep laboratory, the amount of data is small and most studies were conducted in a single centre. From the existing data it is known that different glaucoma types may have different fluctuation patterns with IOP peaks in different times of the day [37, 135, 200, 201]. For example, in XFG the variability is large [201], and even in NTG the fluctuation may depend on clinical subtypes of the disease [135]. Self-tonometry with different portable tonometers (e.g. Proview, iCare, Ocu-ton S) is one possibility to increase the number of IOP measurements and to include early morning and late evening pressure measurements in the data collection [199, 202, 203]. However, this approach has serious limitations: though a subset of the glaucoma patients is able to obtain reliable pressure measurements with self-tonometry, a significant portion of glaucoma patients, in particular those with advanced visual field deterioration, poorer technical capabilities and older age, cannot perform the measurements [199, 202, 203]. In addition, the instruments are costly, and if one instrument is used for several patients, the amount of data per individual decreases. The most important limitation, however, is that no measurement can be obtained during sleep, thus IOP in a most important period of the night remains unknown. Even when the patient is intentionally awakened during night-time for self-tonometry, the stress related to the sudden awakening may have a considerable influence both on the measured IOP value and the measurement precision.

In order to provide more data on IOP for the 24-h period, and at the same time to automate the data acquisition and avoid the measurement-related stress, various implantable and contact lens connected systems have been investigated [27, 28, 30, 204]. Most of these techniques are still in the experimental phase or have not yet been evaluated for accuracy in clinical practice [27, 28, 204]. The only

exception is the CLS device, which, in fact, does not measure absolute IOP in millimetres of mercury, but provides information on the relative IOP changes and the circadian fluctuation using information derived from the mechanical changes of the corneal circumference, which (at least in part) are related to the IOP-induced corneal curvature changes [30, 31, 173, 197–200, 205, 206]. This instrument is not approved for IOP measurement but for the assessment of IOP-related fluctuation and IOP slopes in relative values. The results obtained with the CLS are interesting, but at the same time controversial and limited. Though the CLS is relatively well-tolerated, ocular hyperaemia after a 24-h contact lens wearing measurement session is common [199, 205]. Since a component of the CLS system covers a part of the patient's visual field, only one eye can be investigated in one session. The instrument is expensive and therefore not available for most ophthalmologists. This may be one reason why most of the publications derive from the same research groups. This represents a limitation against collecting real-life experience with the device in various populations and prevents information being obtained on the potential technical problems occurring in less experienced hands and in different ethnic groups. The published data obtained on both healthy and glaucoma eyes show that the diurnal CLS curves are highly reproducible [30, 173, 198, 205]. This is typically considered a proof of reliability of the measurements; however, the high reproducibility of the CLS curve may also be due to pressure-unrelated but CLS-related factors [205, 207]. Considering that the diurnal IOP curve is frequently not ideally repeatable [208], the assumption that non-IOP-related factors play a role in the high reproducibility of the diurnal CLS slopes is reasonable. In several published CLS studies the cosinor rhythmometry method was used to identify the repeated IOP fluctuation pattern [30, 198, 208]. This, in fact, strongly supports the identification of the reproducible parts of the curve but is not optimal to detect the between-visit differences. The relationship between IOP characteristics based on Goldmann applanation tonometry values and

corresponding CLS values remains contradictory [30, 205, 209], which further questions the real-life applicability of the results. Unfortunately, in some review articles only those CLS studies which show favourable results are reported and discussed [210], while those which report negative results [205, 209] are not mentioned.

For the topic of the current review it is of particular importance that the number of CLS studies that evaluate the influence of medication on IOP and its diurnal fluctuation is very limited even though the technique has been used for many years [211]. The results of the few published studies done on very few patients are contradictory, particularly regarding the effect of PG monotherapy on the CLS values and curves [34, 205, 212]. In one of these studies, introduction of a PG analogue monotherapy on open-angle glaucoma and OHT eyes in which medication was previously washed out did reduce IOP measured with Goldmann tonometry, but did not modify the CLS curves [205]. Decrease of IOP fluctuation measured with CLS was reported in a small number of eyes after combined canaloplasty and phacoemulsification [213], while both decreased and unchanged IOP fluctuation was reported after SLT [155, 207]. Considering the currently available peer-reviewed information published on the usefulness of the CLS [214] for clinical glaucoma care, no final conclusion can be drawn. Further development of the technology and wider clinical experience are necessary to clarify if the CLS remains a clinical research tool or can enter real-life clinical practice worldwide.

Continuous, automatic, true IOP measurement has been a long-term goal for all glaucoma specialists. By using such a “dream technology”, a large number of valid data on actual IOP expressed in millimetres of mercury for a wide range of values in all body positions would become available, and the analysis would reveal the true IOP fluctuation and its pattern for all individual eyes, as well as the changes of these characteristics under treatment and during the long-term follow-up of the patients. This “ideal technology” would be particularly useful for early recognition of insufficient IOP control of a treated glaucoma patient, and for optimizing

stepwise therapy. At the same time such “dream technology” would need to be affordable, non-invasive and well tolerated even in advanced age and when ocular surface disease or dry eye syndrome is present, should be applicable to both eyes at the same time, and should not be influenced by factors related to corneal properties, external pressure sources and limbal scar tissue due to earlier surgery. We are still far from fulfilling these requirements. Therefore, we need to use the currently available validated techniques, knowing and considering the limitations of the methods we use in clinical practice. It is important to emphasize that despite the several limitations of the current IOP measurement methods, we need to make all efforts to collect the best available information on IOP characteristics as this will ensure the best treatment for our patients.

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