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Is 24-hour Intraocular Pressure Monitoring Necessary in Glaucoma?

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Abstract

Although intraocular pressure (IOP) is the only treatable risk factor for glaucoma, its 24-hour behavior is poorly understood. Conflicting information is available in the literature with regard to the importance and predictive value of IOP peaks and fluctuations on the risk of glaucoma development and progression. This may be secondary to lack of prospective studies designed to address this issue. This article critically reviews the current evidence for the importance of 24-h IOP measurements in glaucoma and discusses shortcomings of current methods to assess 24-h IOP data, drawing attention to new developments in this field.

Keywords

intraocular pressure; glaucoma; fluctuations; 24-h monitoring

Background

Elevated intraocular pressure (IOP) is not only a major risk factor for glaucoma but also the only modifiable one. Consequently, current treatment for glaucoma is based on lowering IOP to reduce the rate of progression and preserve a patient's quality of vision.[1-6] The most widely used method to measure IOP is Goldmann applanation tonometry (GAT). This technique was described over half a century ago and has essentially remained unchanged.[7] It is easy to perform and accessible. GAT is considered the gold standard by most ophthalmologists for routine, in-office IOP measurement. It is also used by the Food and Drug Administration (FDA) for IOP related clinical trials. However, this tonometric technique has many limitations. GAT only measures IOP indirectly through applanation of the cornea. A practical instrument that directly measures IOP, the true gold standard against which other tonometric devices would be compared, does not currently exist. Furthermore, GAT measurements are influenced by operator bias as well as ocular factors, such as central corneal thickness, corneal biomechanical properties, and scleral rigidity that can vary widely among individuals.[8,9] The most significant shortcoming of GAT, however, is the static nature of its measurement, which represent a mere snapshot of an individual's IOP. Another important limitation is that measurements are taken in the physician's office, usually in the sitting position and fail to reflect the full range of an individual's activities over the 24-h period.

Intraocular pressure is a dynamic parameter with a circadian rhythm and spontaneous changes.[10] Although variations in IOP are commonly noticed, they are not well

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characterized and are often underappreciated in the management of glaucoma patients.[11] These variations are the result of complex interactions between external stimuli and intrinsic biological IOP rhythm. IOP fluctuations of as much as 4-5 mmHg in healthy individuals and, substantially higher, in some glaucoma patients have been reported.[12,13]

Measuring peak IOP in glaucoma care

There is evidence that single IOP measurement in the sitting position during normal office hours does not reflect the true range of an individual's IOP,[14] the peak IOP,[15] or variation throughout the day. Studies that measure IOP several times over the entire day find that approximately two-thirds of glaucoma patients had their peak IOPs outside regular office hours, most frequently occurring in the nocturnal/sleep period.[13,14] In one study, these findings led to an immediate change of therapy in 36% of glaucoma patients.[14] It has been suggested that a sub-optimal approach to IOP assessment may account for nearly one-third of treated glaucoma patients showing progressive vision loss.[16]

Previous studies have implicated peak IOP as a major contributor to glaucoma progression.[17,18] However, the effects of the circadian IOP peaks may depend on their time course as well as their magnitude. Data on the time course of IOP rhythms and their reproducibility in glaucoma are very limited. Evidence suggests that reproducibility of inter-day IOP measurements with GAT is only moderate at best in healthy volunteers and glaucoma patients.[19-21]

Today, the most common method for assessing glaucoma patients' IOP rhythm is through a diurnal tension curve (DTC), which represents multiple IOP readings at different time points during clinic hours. The main limitation of this approach is that nighttime IOP values are not captured. Nighttime IOP values can be obtained by hospitalization or within a sleep laboratory, but these are cumbersome, costly, and require awakening of patients during the nocturnal/sleep period, potentially introducing stress-related artifacts.[22] Consequently, it is estimated that far less than 1% of glaucoma patients undergo a DTC or IOP monitoring in a sleep laboratory. Studies performed under the controlled environment of sleep laboratories have shown that the IOP of most glaucoma patients is highest during the nocturnal/sleep period with the patient in the supine body position.[13,23] However, due to the unavailability of IOP-measuring techniques that measure IOP during physiological sleep, little is known about the contribution of nocturnal IOP rhythms to the pathophysiology of glaucomatous damage.[24]

Fluctuations – an independent risk factor?

Another contributor to glaucoma development and progression may be the frequency and amplitude of IOP changes, commonly referred to as IOP fluctuations. In the absence of an accepted consensus nomenclature, in this review IOP *fluctuation* is used to describe changes that occur over the 24-h period and IOP *variability* to describe changes during longer periods of time.[11] The impact of IOP fluctuations and/or variability on glaucoma progression has been discussed for some time. Several years ago, the hypothesis was advanced that both IOP fluctuations[25] and variability[26-29] are independent risk factors for glaucoma progression. However, several studies have not supported this hypothesis. Retrospective posthoc analyses of two large prospective studies (Early Manifest Glaucoma Treatment Trial (EMGT) and Ocular Hypertension Treatment Study) did not find this association.[30,31] More importantly, these studies (with the exception of the EMGT) did not obtain multiple IOP measurements on the same day but calculated IOP fluctuation as the standard deviation (SD) of IOP at applicable visits. Therefore, these studies were not able to address the question of whether (24-h) IOP fluctuations indeed incur an independent risk on glaucoma progression.

One prospective study assessed the relationship of same-day IOP fluctuations on risk of glaucoma progression.[25] Although this study suggested that IOP fluctuations are an independent risk factor for glaucoma, it used home tonometry to assess IOP fluctuations during the day, which can be a potentially unreliable method.[32] On the contrary, several retrospective studies have reported conflicting results.[27,33-35] Bergea et al.[27] studied the long-term effects of primary laser trabeculoplasty vs. pilocarpine eyedrops in 76 patients with newly diagnosed open-angle glaucoma. Patients were followed for up to 24 months. They obtained up to 12 diurnal IOP curves for each patient and evaluated the predictive value of six IOP parameters. They demonstrated improved preservation of visual fields in patients with smaller IOP fluctuations. However, they did not adjust for the confounding effects of follow-up mean IOP and follow-up IOP range simultaneously in the same model. Collaer et al.[33] reviewed the records of 93 consecutive glaucoma patients who underwent sequential office IOP measurements (every hour from 7 AM to 5 PM on a single day). The authors found that 35% of progressing patients had an IOP range greater than 5 mmHg and concluded that the IOP range may be more important than IOP peak. Jonas et al.[35] studied the effect of 24-h IOP (5 measurements) on glaucoma progression in a large group of patients with glaucoma and ocular hypertension. They suggested that it was the absolute IOP itself rather than its fluctuation that had the most significant effect on glaucoma progression. This study was limited by its design (registry study) and use of different antiglaucoma drugs with various IOP-lowering effects. Choi et al.[34] performed a retrospective chart review to evaluate the effect of 24-h IOP fluctuations in 113 patients with so-called “normal tension glaucoma.”Measurements were taken every two hours in a hospital setting. They found that both fluctuations in IOP and ocular perfusion pressure were related to worsening of glaucoma on both functional and structural tests. The strength of this study was the fact that patients had no previous or current use of antiglaucoma medications to confound the results.

Table 1 provides a summary of these studies. Differences in study design, definitions, data analysis, and study populations may explain these apparently contradictory findings. Singh and Sit provided additional explanation for these discrepancies.[36] They suggested that the percentage of IOP variability would be a better measure of glaucoma risk than absolute change. Use of standard deviation of the mean IOP as a surrogate for variability (as in previously mentioned studies) captures only absolute changes and may underestimate the risk at low IOPs and overestimate the risk at higher IOPs.

It should be emphasized that the prognostic value of 24-h IOP fluctuations has never been evaluated in properly designed longitudinal studies. As described above, the few available studies are limited by the use of imperfect surrogates for the 24-h IOP variations.

24-h effects of glaucoma treatments – lessons from the sleep laboratory

Glaucoma is often characterized by reduction in pressure-sensitive aqueous outflow facility through the trabecular meshwork. The impaired outflow facility causes high IOP and large diurnal IOP fluctuations. If credence is given to the evidence that large diurnal IOP fluctuations are a risk factor for glaucomatous progression, then IOP-lowering therapy should aim to achieve a low and stable IOP. Pressure-sensitive aqueous outflow helps prevent and dampen pressure spikes. Therefore, drugs that enhance outflow facility, in particular, may stabilize as well as lower IOP.

Stewart et al.,[37] conducted a meta-analysis of studies that assessed 24-h IOP efficacy of antiglaucoma medications. They concluded that of all monotherapies evaluated, bimatoprost followed by travoprost were the two most effective in reducing IOP fluctuations. Evaluating the effect of adjunctive therapy, they reported no further decrease in fluctuations with additional treatments compared to monotherapy.

The question of nighttime IOP reduction was addressed in a series of studies conducted in the sleep laboratory at the University of California, San Diego. These studies showed that 0.1% brimonidine[23] and 0.5% timolol[38] did not significantly lower IOP during the nocturnal/sleep period, whereas 0.005% latanoprost did.[38] When one drug was added to patients already under latanoprost montherapy, only 1% brinzolamide produced an additional IOP reduction during nocturnal/sleep period, whereas 0.5% timolol did not.[39]

Scarce 24-h data are available from glaucoma interventions. Only one study so far has addressed 24-h IOP-lowering profile of laser trabeculoplasty. Lee et al.[40] evaluated the effect of 180° laser trabeculoplasty on 28 eyes of 18 treated glaucoma patients. They reported that laser treatment reduced IOP more consistently during the nocturnal period than during the diurnal period. Recently, Matsuoka et al.[41] studied the 24-h effect of combined trabeculotomy/sinusotomy in 8 glaucoma patients. Preoperatively, all of these patients had IOP elevations above 20 mmHg during nocturnal hours. Postoperatively, the mean diurnal IOP curves were flattened without a significant nocturnal rise. Despite its small sample size, this study confirmed previous reports that had suggested a better diurnal IOP lowering profile for filtering surgery compared to medications.[42,43] Further research is needed to investigate circadian effects of glaucoma interventions. The introduction into clinical practice of practical devices to measure IOP continuously should significantly facilitate more research into this issue.

Present and future of 24-h IOP monitoring

The development of ambulatory, frequent, round-the-clock IOP measurement methods has been pursued for several decades.[44-47] These attempts have pursued three different strategies: 1) self-monitoring of IOP by the patient; 2) permanent IOP monitoring; and 3) temporary IOP monitoring.

Various devices for self-tonometry have been developed in recent years.[48-52] However, many appear inaccurate and technically challenging for the elderly glaucoma patients.[32] Most importantly, self-tonometry does not address the crucial issue of IOP behavior during undisturbed sleep.

Permanent IOP monitoring involves the surgical implantation of an IOP sensor. The concept was pioneered in the early sixties by Collins, [53] who proposed the use of a capacitive pressure sensor, consisting of a pair of parallel spiral coils within a gas-filled plastic “pill”. This pressure sensor was conceptually ahead of its time as it functioned wirelessly by means of a coupled magnetic field. Other investigators modified this approach by placing the pressure sensor in an intraocular lens (IOL), which could replace the natural lens at the time of cataract surgery.[54,55] However, it was only recently that advances in bio-engineering and nanotechnology have produced potentially viable approaches.

Downs et al.[56] adapted an existing implantable telemetric pressure transducer system to monitor IOP in non-human primates. They demonstrated that the system was able to provide accurate and continuous IOP monitoring for up to 7 months. However, the implantation of the transducer system requires extensive surgical intervention involving the orbital bone and insertion of a tube inside the anterior chamber. At present, no human data are available. Todani et al.[57] were able to measure IOP continuously using a ring-shaped intraocular device placed in the lens capsule of rabbit eyes for up to 25 months. Their results are promising, and data from human trials are eagerly awaited. Currently, the main limitation of all approaches to permanent continuous IOP monitoring is the safety concern associated with surgical implantation. Combining IOP-sensors with IOLs used in routine cataract surgery may facilitate patient acceptance. However, certain risks have to be addressed before these technologies can obtain regulatory approval and acceptance for use in humans.

These include the potential for device failure after implantation, leakage of potentially toxic materials, or inaccuracy of measurements due to signal drift over time with the necessity of subsequent intervention for re-calibration. Another drawback is that the group of patients who could benefit from this approach would be restricted to those requiring cataract or other ocular surgery.

Temporary IOP monitoring is a non-invasive alternative to the permanent approach and it offers potential advantages to permanent methods, mainly due to its reversibility. The first steps in this direction were taken more than 5 decades ago by Maurice[44] who developed an automated recording indentation tonometer. The device was a clunky metallic structure fixed to the head of the patient and was not pursued beyond the prototype. More recently, Twa et al.[58] proposed integrating the piezoresistive sensor tip of the dynamic contour tonometer (Pascal, Ziemer Ophthalmic Systems AG, Switzerland) into a hard contact lens. This tonometer uses a piezoresistive sensor that provides measurements at a rate of 100 Hz. The sensor is located in a contoured probe, which is assumed to minimize the effect of corneal parameters on measurement errors. It was shown that this approach could provide reliable IOP measurements for up to 100 seconds. Beyond the limited duration of the measurements, there are other limitations of this approach, including the use of a hard contact lens and the location of the sensor tip in the center of the contact lens with resulting decrease of vision.

Leonardi et al.[59] updated the concept of a soft contact lens with embedded strain gauges. More importantly, they were the first to develop a product beyond the prototype stage and obtain regulatory approval (CE-mark) for commercial product. The disposable contact lens sensor (CLS) (SENSIMED Triggerfish®, Sensimed AG, Lausanne, Switzerland) monitors IOP changes continuously. The device is based on the assumption that circumferential changes, measured at the corneo-scleral junction correspond to changes in IOP.[60] This relationship was previously validated using an in vitro model of cannulated porcine eyes.[6159] The CLS is powered by inductive coupling through an external antenna patched around the eye. The microprocessor reads the contact lens strain gauges at a frequency of 10 Hz and transmits data to the external antenna, which is connected to a portable recorder unit. The CLS acquires a total of 288 data points over a 24-h period, each corresponding to 30 seconds of continuous measurements, repeated every 5 minutes. Recorded profiles are visualized graphically on a computer interface. The output of the sensor is expressed in arbitrary units corresponding to micro Volts. The device is described in more detail elsewhere.[62] The major value of the device is that it can record IOP fluctuations in a real-life setting for up to 24 hours including during undisturbed sleep. Our group has shown that the repeated use of the CLS is safe and well-tolerated in glaucoma patients (Mansouri et al. *Arch Ophthalmol*. In Press). The fact that the CLS provides its values in an arbitrary unit (instead of mmHg) makes the clinical interpretation challenging. It is hoped that in the near future, algorithms will be developed that translate these units into a clinically relevant measurements.

Clinical impact of 24-hour IOP data

The recent availability of non-invasive ambulatory 24-h IOP monitoring permits the assessment of 24-h IOP rhythms and heralds a paradigm shift in the field of glaucoma, potentially similar to the impact of continuous 24-hour data on other chronic diseases. With IOP being one of the most important determinants in glaucoma, its better characterization is expected to affect glaucoma care in multiple ways (Table 2). Before a paradigm change can happen in routine clinical care, several challenges will have to be surmounted.

Generations of ophthalmologists were trained to rely on single IOP measurements for development of a treatment target and evaluation of the treatment response. The translation into practice of the plethora of data provided by the CLS and other future techniques poses a non-negligible challenge to every clinician. Mansouri and Shaarawy have shown how information obtained through 24-hour IOP monitoring can potentially impact the management of glaucoma patients.[63] In their study, patients with glaucoma progression despite normal IOPs during clinic hours underwent 24-hour IOP monitoring with the CLS. The peak IOP occurred in 69% of patients during the nocturnal/sleep period.

Currently, the CLS is the only commercially available device that provides 24-hour information on IOP fluctuations. In the future, it is likely that other approaches will be available for subsets of glaucoma patients.

Before 24-h IOP data can be widely translated into clinical practice, new analytical methods are needed to facilitate interpretation of the wealth of data generated. Studies will also have to elucidate the significance of 24-hour patterns, role of IOP-lowering medication on IOP patterns and the importance of nocturnal IOP changes on glaucoma development and progression. As IOP patterns are not necessarily conserved from one day to another even in healthy individuals,[21] the frequency at which 24-hour monitoring should be repeated in glaucoma patients is unknown. Our group has recently studied the reproducibility of repeated 24-hour IOP monitoring with the CLS in glaucoma patients and suspects.[64] We found that at a 1-week interval, there was fair reproducibility ($r = 0.59$) of 24-hour IOP patterns similar to daytime measurements with GAT, suggesting a need to establish IOP values not just on one day, but on different days, as well.[20] Prospective data are required to show how this technology can be incorporated into the long-term management of glaucoma.

Conclusion

The availability of 24-h ambulatory IOP monitoring technology is generating a series of new clinical questions that are directly linked to the chronobiology of aqueous humor production and the outflow system. It is hoped that continuous 24-h IOP data may provide guidance to the identification of deleterious IOP patterns in glaucomatous patients. Certain aspects of the shape of the 24-h IOP profile, such as the time course and amplitude of peak IOP, frequency of spontaneous spikes, fluctuations, and the magnitude and duration of the nocturnal IOP rise and morning fall may be relevant as determinants of glaucoma development and progression. However, prospective longitudinal studies are still necessary to evaluate the relevance of these parameters in determining clinical outcomes in the disease.

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Table 1

Summary of studies evaluating the effect of IOP fluctuations as a risk factor for glaucoma for glaucoma development and progression.

Studies (Year)	Design	Population	IOP measurement	Limitations
In support of IOP fluctuations as a risk factor				
CIGTS, 2011	Retrospective subset analysis; N = 578 participants	Newly detected glaucoma	Every 3 months until last visit	Retrospective; SD used as surrogate for fluctuation Retrospective; SD used as surrogate for fluctuation; Only IOPs after surgery and until evidence of progression used Retrospective
AGIS, 2008	Retrospective subset analysis; N = 301 eyes	Advanced glaucoma	3 months after intervention; every 6 months thereafter	
Choi et al., 2007	Retrospective chart review; N = 113 eyes	POAG (NTG)	24-h IOP (every 2-3 hours)	
Collaer et al., 2005	Retrospective chart review; N = 185 eyes	POAG	DTC (hourly 7 am to 5 pm)	Retrospective
Asrani et al., 2000	Prospective; N = 105 eyes	OAG	24-h IOP	Home monitoring by patients
Against IOP fluctuations as a risk factor				
DIGS, 2008	Subset analysis; N = 252 eyes	Untreated ocular hypertension	Annual	SD used as surrogate for fluctuation
EMGT, 2007	Retrospective subset analysis; N = 255 eyes	Newly detected untreated glaucoma	3 months after assignment to treatment to time of progression or last visit DTC (8am, 11:30 am and 3:30 pm); every 3 months	Retrospective, SD used as surrogate for fluctuation
Malmö OHTS, 2005	Retrospective subset analysis; N = 90 eyes	Ocular hypertension		Few IOP measurements during the day
Jonas et al., 2007	Registry study; N = 855 eyes	POAG	Minimum of 2 DTCs (5pm, 9pm, midnight, 7am and noon)	Retrospective; Patients on different antiglaucoma medications
Bergea et al., 1999	Retrospective analysis; N = 82 eyes	Newly detected POAG	DTC (3 measurements) every 3 months	Retrospective

Abbreviations: DTC: diurnal tension curves; IOP: intraocular pressure; NTG: normal tension glaucoma; (P)OAG: (primary) open angle glaucoma; SD: standard deviation

Table 2

The putative impact of continuous 24-hour IOP monitoring on glaucoma management.

Impact	
1. Early detection	Detection of unfavorable IOP patterns may enable better risk estimation for glaucoma development
2. Individualized treatment	Rapid evaluation of 24-h IOP effect of glaucoma treatment and interventions.
3. Improved adherence	Ability to visually demonstrate 24-h IOP patterns in glaucoma and the impact of therapy on these may increase patient understanding of the disease and lead to better adherence.
4. Behavioral changes	The ability to evaluate IOP in real-life settings may provide answers to the effect of behaviors/activities on individuals' IOP and facilitate the development of alternative treatment strategies.
5. Prevention of progression	Early and individually targeted adjustment of glaucoma treatment may reduce the rate of progression in glaucoma and preserve quality of life.

IOP = intraocular pressure.