A Minimally Invasive Device for the Monitoring of 24-hour Intraocular Pressure Patterns

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Abstract

Intraocular pressure (IOP) is the only modifiable risk factor for glaucoma, and lowering of IOP remains the mainstay of glaucoma treatment. IOP is a dynamic biologic parameter, nevertheless, current glaucoma management usually relies on single IOP measurements during clinic hours. However, a majority of glaucoma patients have their high, including their highest, IOP levels outside clinic hours. These undetected IOPs may explain why certain patients have progressive disease despite treatment. The interest in continuous 24-hour IOP monitoring started over half a century ago, but only recent technologic advances have provided clinicians with a practical device for continuous IOP monitoring. In this article, we discuss innovative approaches with permanent and temporary devices for 24-hour IOP monitoring, such as a contact lens sensor. Despite being in their infancy, these devices may soon enable clinicians to use 24-hour IOP data to improve glaucoma management and reduce the glaucoma-related burden of disease.

Keywords

Glaucoma, intraocular pressure, 24-hour, contact lens sensor, circadian

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Glaucoma is a progressive optic neuropathy, characterized by the loss of retinal ganglion cells and its axons ultimately leading to loss of vision and subsequent irreversible blindness.[1] Elevated intraocular pressure (IOP) is the only proven modifiable risk factor for the development and progression of glaucoma.[2–5] Despite dedicated efforts to develop alternative therapies, reduction of IOP remains the current mainstay of glaucoma treatment.

One important limitation in current glaucoma management is that IOP is normally only measured during office hours, usually by Goldmann applanation tonometry (GAT).[6] Yet IOP varies throughout the circadian period.[7–11]

In addition to the absolute IOP level,[12–16] IOP fluctuations,[2,13,17–20] and in particular peak IOP levels have been identified as risk factors for progression of glaucoma.[21–23] The role of IOP fluctuations in glaucoma pathogenesis remains controversial. Several studies have hypothesized that IOP fluctuation is an independent risk factor for glaucoma progression.[24–28] In an experimental setting in non-human primates, mean and maximum IOP but not IOP variability were able to predict the rate of structural change.[29] The same investigators also reported that IOP fluctuates by up to 10 mmHg within hours and between consecutive days in non-human primates.[30] However, other studies have not supported the predictive role of IOP fluctuation. Retrospective post-hoc analyses of two prospective studies did not find such an association or had it disappear after accounting for other ocular or demographic parameters.[31,32] Most importantly, these studies (with the exception of the Early Manifest Glaucoma Trial) only obtained single IOP measurements on the same day and calculated IOP fluctuation as the standard deviation of IOP at different visits. They are, therefore, not able to address the question of whether (24-hour) IOP fluctuations incur independent risk on glaucoma progression.

Given the dynamic behavior of IOP, it may be clinically insufficient to rely on isolated IOP measurements only, in particular in patients with progression of glaucoma. Even the modest goal of obtaining representative diurnal (versus circadian) IOP profiles, our current methods seem to be insufficient. In one study, the likelihood of a single IOP measurement taken between 07:00–09:00 hours to reflect the daytime peak IOP was a mere 25 %.[33] Other studies reported that 20–25 % of glaucoma patients who reached target IOP during isolated office measurements exhibited IOPs above the target level when submitted to a daytime IOP curve assessment.[9,24] Patients with progressive visual field loss are more likely to have IOP peaks. Among patients presenting with IOP peaks during self-tonometry, 75 % had progressive glaucomatous disease compared with the patients without IOP peaks out of which only 25 % progressed.[25] Compared with 24-hour IOP measurement curves, office hour IOP measurements did not correctly identify peak IOP in 80 % of patients with primary open angle glaucoma (POAG).[10] These studies attest to the weak predictive value of office hour IOP measurements for detecting peak circadian IOP.

In healthy and glaucomatous patients, IOP is higher than mean diurnal (daytime) IOP during the nocturnal period.[26,27,34–36] The nocturnal IOP

increase is in part due to increased episcleral venous pressure (EVP) and possibly to fluid redistribution, when assuming a recumbent position during sleep. Another study reported the variability in IOP pattern in patients with normal tension glaucoma, showing both daily and nocturnal acrophases.[28]

The dynamics and repeatability of the 24-hour IOP may indicate the existence of a circadian pattern, following the day/night light cycle. Preserved IOP patterns have been demonstrated in different species, including cats, rhesus macaques, and rabbits.[29,30] A variety of hormones, through regulation of aqueous humor production and outflow, have a circadian rhythm and have been linked to circadian IOP patterns in rabbits.[37] There also is a strong dependence of IOP on variable factors such as activity, posture, and emotions. Realini et al. in a series of studies found a fair to good reproducibility of repeated diurnal IOP measurements at two visits one week apart, both in healthy subjects (intraclass correlation coefficient [ICC] range 0.35–0.71) and in patients with POAG (ICC range 0.45–0.71).[38,39] By contrast, another study reported a high daytime reproducibility of the IOP measurements (every three hours) on two consecutive days in patients with OAG and ocular hypertension (ICC range 0.80–0.86).[40] In these studies, a lower than normal IOP reproducibility may in part be explained by the limited number of daytime IOP measurements.

Current treatment strategies for glaucoma are frequently based on setting a target IOP range at which the development of further glaucomatous damage is assumed be prevented or reduced to a minimum.[41,42] This target IOP is based on the patient's past IOP levels, glaucomatous changes of the optic disc, visual field status, and, if available, the rates of structural and functional change. Despite an IOP that remains within the target range, a significant proportion of patients progress.[20,43–47] Treatment strategies that rely solely on static IOP information do not account for the dynamic behavior of IOP and, therefore, have a limited predictive value for evaluating the risk for glaucoma progression.

Current Approaches to Continuous 24-hour Intraocular Pressure Monitoring

Automated and telemetric methods to continuously monitor IOP for 24 hours are an important unmet need in glaucoma. Several implantable telemetric devices are in development. One such approach, developed by Downs et al., has demonstrated its ability to measure continuous IOP and ocular pulsation in non-human primates.[30] This approach, however, requires surgical intervention. Todani et al. have recently reported on the feasibility of a wireless transducer based on pressure-sensor cells for continuous IOP monitoring in rabbits.[47] To our knowledge, no published data on the use of these devices in humans are currently available. An important drawback of implantable IOP monitoring devices is the potential need for subsequent re-intervention in cases of device failure or malfunction.

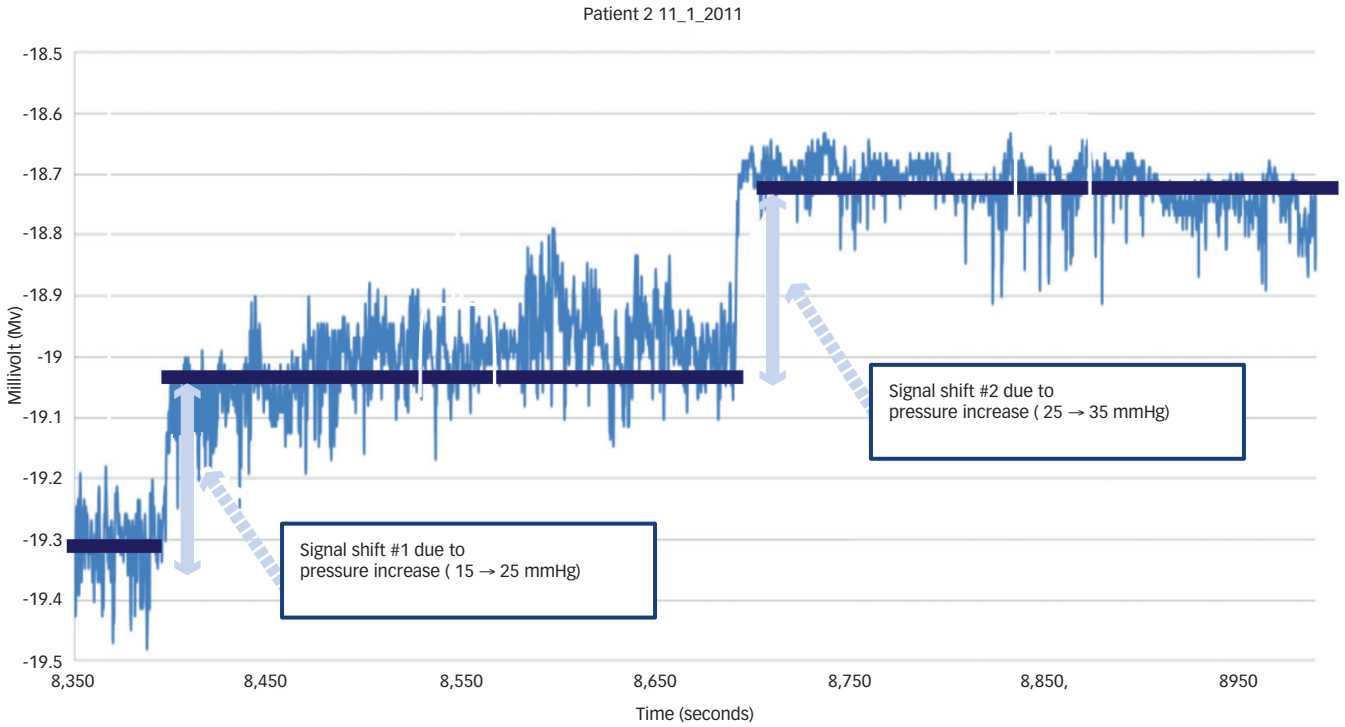
A variety of non-invasive contact lens sensor (CLS)-based technologies are in development. The SENSIMED Triggerfish® (Sensimed AG, Lausanne, Switzerland) is the only CLS-based technology that is commercially available and is being evaluated in clinical studies (as registered on www.clinicaltrials.gov).[48] This device is intended for the recording of the 24-hour IOP pattern. The core component is the soft medical grade, disposable, silicone CLS (see *Figure 1*) consisting of an embedded micro-electro-mechanical systems (MEMS) sensor, an antenna, and a telemetry

Figure 1: The SENSIMED Triggerfish® Contact Lens Sensor

Soft silicone contact lens with intelligent elements, such as strain gauges and an application-specific circuit embedded.

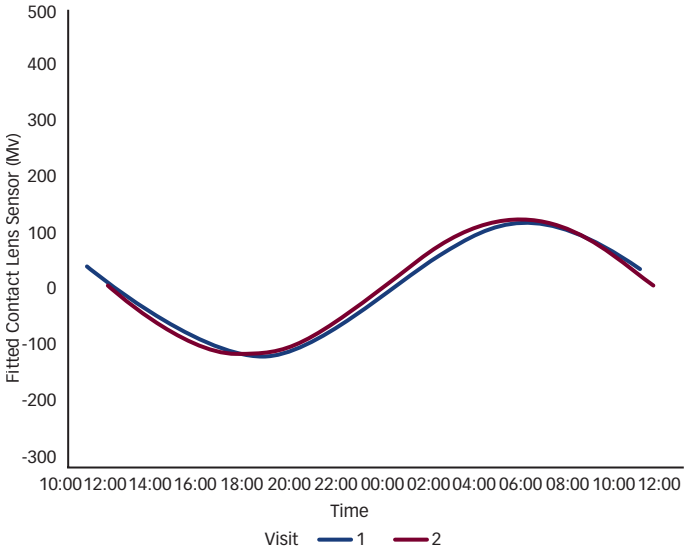
application-specific integrated circuit (ASIC). The CLS monitors the radial deformation of the eye shape near the corneoscleral junction, that correspond to IOP changes.[49] A change of IOP of 1 mmHg has previously been shown to result in a change of the central corneal radius of curvature of about $3{\cdot}10^{-6}$m over a typical corneal radius of 7.8 mm.[50] Three base curves are available (8.4 mm for steep, 8.7 mm for medium, and 9.0 mm for flat) with a diameter of 14.1 mm. A peri-orbital adhesive patch contains a flex antenna transmitting the information/energy via a data cable to the recorder. The portable recorder contains the battery of the system and hardware to store the CLS output. After the monitoring period, the data are downloaded from the recorder, via a Bluetooth connection to the physician's computer to visualize the 24-hour IOP pattern. Upon initiation of recording, the subject is allowed to undergo normal daily activities in an ambulatory setting, reflecting physiologic IOP changes including during undisturbed sleep. Upon completion of recording, the 24-hour IOP pattern is available for evaluation. Subjects are allowed to use artificial tears and prescribed eyedrops. The CLS output consists of 288 data points over 24 hours, one data point every five minutes during a 24-hour recording. Each data point represents 300 measures of the IOP over 30 seconds, equating to a sampling frequency of 10 Hz. The software is designed to plot the 24-hour IOP pattern, whereas each data point can be inspected for ocular pulsation, including the systolic and diastolic peaks, the ocular pulsation amplitude, and ocular pulsation frequency as the IOP fluctuates synchronically with the heart rate. The output is an equivalent of the electric voltage (mV) measured due to conformal changes at the corneoscleral junction that are transmitted to the recorder. The effect of the IOP at the corneoscleral junction as measured by the CLS reflects the relationship of the pressure and the volume of the eye under the assumption that ocular fluids can not be compressed.[51,52] Despite conformal changes of intraocular structures, the total volume of the eye

Figure 2: Comparison of Contact Lens Sensor Output with Manometry in a Non-glaucomatous Patient before Vitrectomy Surgery



The contact lens sensor (CLS) was successfully fitted on the globe and cannulation of the posterior chamber was performed through a 26 G needle. The graph shows the rapid increase and subsequent stabilization of the CLS signal when the intraocular pressure (IOP) was raised in two 10 mmHg steps.

Figure 3: Graph Showing a Cosinor Rhythmometry Model Applied on 24-hour Contact Lens Sensor Data



The acrophase occurred during the nocturnal sleep phase on two subsequent visits, one month apart.

is not affected. The pressure is exerted equally in all directions of the eye's external surface and is determined by the resistance to distension of the intraocular volume to these structures (e.g. cornea, sclera, etc.). IOP changes are a consequence of volume changes of the eye contents and are partially determined by the resistance offered by the cornea and sclera to distension of the volume.

Calibration of the CLS output to mmHg is a challenge as simultaneous use of the CLS and tonometry on the same eye is not feasible. Therefore, simultaneous comparison between the CLS and tonometry is to be performed in the contralateral eye, despite the moderate relationship of IOP measurements between eyes.[53] A better approach would be to compare IOP monitoring with the CLS and an implantable device in the same eye. This will be the subject of future research.

Contact Lens Sensor Safety and Tolerability

A recent study evaluated the safety and tolerability of 24-hour IOP recording by using the CLS in patients with suspected glaucoma and with POAG.[34] All 40 patients, 21 suspected and 19 established glaucoma, with a mean age 55.5±15.7 years (60 % male) were exposed to the CLS wear for 24 hours on the same eye during two sessions (S1 and S2) seven days apart. The mean exposure duration to CLS wear did not differ between the sessions, 24.0±0.5 h and 24.0±0.3 h, respectively. Of the 149 device-related adverse events (AEs) that occurred in 38 patients (95 %), 143 were considered to be mild (96 %) in 36 patients (90 %). The most common AEs were blurred vision (82 %), conjunctival hyperemia 80 %, and superficial punctate keratitis (15 %). Two moderate AEs occurred (1.3 %), superficial punctate keratitis and blurred vision, in one patient with POAG during S1.

Two other patients with established glaucoma (5.1 %) each had a severe AE (2.7 %) during both sessions—ocular hyperemia. The first clinical study used the CLS in 10 healthy subjects for 24 hours did not report any severe AEs.[54] Five severe AEs were reported, one in a healthy subject and four in patients with POAG, in a study designed to assess the safety of CLS exposure.[55] All device-related AEs resolved within 48 hours.

A total of 88 subjects across three trials, 29 healthy subjects, and 21 patients with suspected glaucoma and 38 with established glaucoma, reported tolerability by means of a visual analog scale equating to percentage comfort level to 24-hour wear of the CLS.[24, 54–56] The mean comfort level was good after 24-hour CLS wear (score 75 %). No apparent differences for the comfort level were observed across studies, for the different diagnostic groups, or the fact that 40 subjects were exposed to CLS wear twice one week apart.

Freiberg et al. demonstrated a significant mean change from baseline of the central corneal thickness (mCCT) (14.3±4.6 µm; p=0.015) after nine hours of overnight CLS wear.[57] There was no difference between study and contralateral eye (p=0.075). An analysis of pooled data was aimed to determine the effect on mCCT after CLS wear for 24-hour continuous recording of the IOP pattern.[58] A total of 191 sessions of 24-hour CLS wear in 151 subjects was analyzed. The mean CLS exposure was 23.9±0.04 for the 151 subjects. The overall mCCT across studies was –0.1±3.0 µm, for a total of 191 24-hour CLS exposures. The mCCT was not statistically significantly different in any of the five prospective, open label studies, ranging from –12.3 to 4.1 µm (–2.2 % to 0.7 %). The mCCT in healthy subjects (–5.6±2.4) was statistically significantly lower than in patients with suspected or established OAG (0.2±3.3; p<0.001). The first 24-hour CLS wear showed a statistically significantly higher increase of mCCT (4.1±2.7) than the second session six to nine days later (0.7±0.4; p<0.001).[34] Based on these data, the use of CLS is considered to be safe and well tolerated for the recording of the 24-hour IOP patterns.

Validation and Reproducibility of Intraocular Pressure Monitoring Patterns

The CLS has previously been validated *ex vivo* in enucleated porcine eyes with good agreement of the CLS output with manometry values.[50] For practical reasons, mostly related to obtaining a good fit of the sensor on the ocular surface, *in vivo* manometric studies in animal models and patients are more difficult. However, despite these difficulties, whenever a good fit is obtained, we find a close correlation of the CLS signal output and manometric measures. (see *Figure 2*).

Whenever a new diagnostic device is introduced, it is essential to investigate its repeatability and reproducibility. Contrary to imaging techniques that measure anatomic parameters, such as the retinal nerve fiber layer thickness, which remain mostly unchanged throughout the circadian period, IOP is a highly dynamic parameter, which is strongly influenced by intrinsic and extrinsic factors in addition to its well-known circadian rhythm. In fact, Realini et al. have shown that the week-to-week repeatability of diurnal IOP measurements using GAT in healthy and glaucomatous individuals is moderate at best.[38,39] Using the CLS, we found a moderate agreement between 24-hour IOP patterns in glaucoma patients and suspects, when monitoring was repeated at a one-week interval (r=0.59, Pearson correlation).[34]

A major challenge for the clinician is the analysis and interpretation of 24-hour IOP information obtained with the CLS. The output signal is not displayed in mmHg but in mV and, moreover, a large number of data points (288 instead of the current eight that are typically obtained in a diurnal tension curve) obfuscate data interpretation. We have recently reported on the use of modified cosinor rhythmometry for the analysis of 24-hour IOP patterns obtained with the CLS.[36] Applying this methodology to the CLS output simplifies the interpretation of data by providing a few key parameters of the circadian IOP rhythm: acrophase and bathyphase (timing of peak and through IOP) as well as the IOP amplitude. We found that 62.9 % of glaucoma patients had a repeatable nocturnal acrophase (e.g. occurring during sleep) (see *Figure 3*). Aptel et al., using a similar methodology, found similar results of repeat 24-hour CLS monitoring in healthy subjects (Aptel, personal communication). They found significant ICCs of the CLS acrophase (0.6 [0–0.9, 95 % CI]; p=0.03), with fair to good agreement. In their healthy subject cohort, however, 100 % of acrophases occurred during the sleep period, potentially indicating a modification of this parameter between healthy and glaucomatous subjects.

Conclusion

The use of the CLS for the recording of the 24-hour IOP pattern is safe and well-tolerated in healthy subjects and glaucomatous patients. Despite its infancy and the current existence of barriers to the use and interpretation of data in a clinical setting, recent evidence shows that this technology provides reproducible and clinically useful results for the entire 24-hour period, including the previously inaccessible sleep period. In the near future, introduction of alternative technologies is expected into clinical practice. With these advances, there will be an enhanced understanding of the IOP pattern and this should substantially improve the management of glaucoma patients. ■

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