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Pathophysiology of Glaucoma and Continuous Measurements of Intraocular Pressure

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Abstract: Glaucoma is a leading cause of visual impairment and blindness worldwide. The main risk factor for glaucoma is an elevated intraocular pressure (IOP), which is also the only currently treatable risk factor. Despite its importance, our understanding of IOP is incomplete and our ability to measure IOP is limited. IOP is known to undergo both random fluctuations as well as variations following a circadian pattern. In humans, IOP is highest at night and lower during the daytime, largely due to changes in body position, although other factors appear to contribute. In rabbits, IOP is also highest at night and lower during the day, likely due to circadian variations in sympathetic nervous system activity. Random and circadian IOP variations may be important to glaucoma pathogenesis, independent of the diurnal IOP level. However, due to limitations with current IOP measurement technology, clinical practice typically involves only a few IOP measurements per year. As well, current technology does not allow 24-hour monitoring of pressure without the use of sleep laboratories or hospital admission. Two strategies for automating IOP measurement are temporary (non-invasive) monitoring and permanent (implantable) monitoring. Efforts at developing devices to allow continuous IOP monitoring have occurred for over 40 years without producing a clinical device. Current technological progress would seem to suggest that such devices are possible at this time, and a review of previous attempts provides guidelines for their development.

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1 Introduction

Glaucoma, a progressive optic nerve neuropathy, is a leading cause of preventable vision loss worldwide, with over 60 million people estimated to be affected by 2010 (74). The pathogenesis of the disease is multifactorial and likely encompasses a group of conditions that share the common final pathway of retinal ganglion cell death, axonal loss, and a characteristic optic disc pattern and loss of visual field. Elevated intraocular pressure (IOP) is the major risk factor for the development and progression of glaucoma and is currently the only modifiable risk factor (29, 92). However, current management of glaucoma includes only periodic measurements of IOP in the sitting position during office hours. This is, at best, a sub-optimal approach which provides an incomplete description of the variable nature of IOP. Despite IOP lowering treatment, nearly 30% of patients will go on to develop visual loss and blindness (36). Inadequate measurement and control of IOP may be responsible for a significant proportion of individuals whose diseases progress despite seemingly adequate IOP control during office hours (4, 100). Even though these problems have long been identified, no device is currently available for clinical use that allows ambulatory monitoring of IOP. A review of past attempts at developing such a device can highlight the issues involved in achieving this goal and what steps may be required for future efforts.

2 Anatomy and physiology related to glaucoma

In the anterior segment of the eyeball, aqueous humor fills the anterior and posterior chambers and provides a flow pathway for the metabolic activities of the adjacent tissues that are avascu-

lar for optical reasons. Aqueous humor is produced by the non-pigmented ciliary epithelium of the ciliary body posterior to the iris, flows anteriorly through the pupil into the anterior chamber, and then exits through the trabecular meshwork into the episcleral venous circulation and independently through the pressure-insensitive uveoscleral pathway. A steady-state IOP is determined by several factors described by the modified Goldmann equation (12) based on Ohm's law:

$$Q = c(P_i - P_e) + U$$

where Q is the aqueous humor flow rate, c is the outflow facility (the inverse of fluid resistance), P_i is the IOP, P_e is the episcleral venous pressure, and U is the pressure insensitive uveoscleral outflow rate. Variations in any of these factors can affect IOP. In most glaucomatous eyes associated with elevated IOP, the cause is a decrease in the outflow facility (or an increase of fluid resistance) resulting from an obstruction of the outflow pathways, particularly at the trabecular meshwork. According to Pascal's law, wall stress in a closed eyeball is directly proportional to IOP, and elevated IOP increases the mechanical force against the retinal ganglion cells at the back of the eyeball, including the vulnerable optic nerve head where the axons transmit visual information to the brain.

The transduction of photo-stimuli into neurological stimuli begins with photons entering the eye and being absorbed by the photoreceptors of the retina. The signals from the photoreceptors are first processed and sorted in the retina. The summarized signals are then conveyed by the retinal ganglion cells and their axons through the optic nerve head, along the optic nerve and optic tract, ultimately synapsing in the lateral geniculate nucleus in the brain. Healthy human optic nerves contain approximately 750,000 to 1.25 million retinal ganglion cell axons (63). Glaucoma is characterized by progressive retinal ganglion cell death, loss of optic nerve axons, a characteristic change in the appearance of the optic nerve head (cupping), and associated visual defects when sufficient loss of optic nerves overwhelm the redundant visual process system.

3 IOP and glaucoma

Two major theories exist as to how an elevated IOP may contribute to the pathogenesis of glaucoma. The two theories may not exclude each other. The first theory is that elevated IOP causes direct mechanical stress to the axons of the optic nerve. When IOP is elevated, strain of the lamina cribrosa, the supporting structure behind the optic nerve head, can occur due to an abnormal pressure gradient from the intraocular environment to the intracranial environment (65). This may subsequently result in tissue deformation causing additional mechanical stress to the retinal ganglion cell axons (7, 14). Experimental models of glaucoma have indicated that a blockade of axonal transport can occur as a result of optic nerve head compression from elevated IOP (6, 75). This may impair the retrograde transport of trophic factors necessary for retinal ganglion cell survival (75).

A second theory for optic nerve injury from elevated IOP is the compromise of blood perfusion to local tissues (27). Blood perfusion pressure to the optic nerve head is determined by the difference between the local arterial pressure and the IOP (8, 51). As IOP increases, the perfusion pressure decreases unless there is a parallel increase in the arterial blood pressure. This decrease in perfusion pressure may lead to local optic nerve head ischemia/hypoxia which may contribute to glaucoma pathogenesis.

In addition to IOP, contributions of other factors to retinal ganglion cell and optic nerve damage in glaucoma have been proposed. These include excessive stimulation of the glutamate system, alterations in glial cells or astrocytes, and aberrant immunity (92). These factors may independently contribute to glaucoma, or may be concomitant with elevations in IOP.

4 Circadian variations of IOP in humans

Variations of IOP in humans have been known for at least a century (25, 26), with variations occurring in a repeatable pattern every 24 hours, or random fluctuations over short and long periods. Variation of IOP in humans during the diurnal/wake period in the sitting position has

been well documented, starting with the work of Drance in the 1960s (24). This work suggested that diurnal IOP was typically higher in the morning than later in the day, and more variable in glaucoma patients than normal controls. Subsequent investigators examined the 24-hour pattern of IOP variation and found that glaucoma patients exhibited a drop in IOP during the nocturnal/sleep period (39, 40). Because of the difficulties involved with performing measurements during the nocturnal/sleep period, these studies maintained the subjects' night environment similar to the diurnal/wake environment. In particular, IOP was measured in the sitting position using Goldmann applanation tonometry (the standard in clinical practice) and no adjustments were made to compensate for the changes in habitual body position that occur during sleep and the nocturnal lighting conditions.

Recent studies performed under carefully controlled sleep laboratory conditions with maintenance of strict light-dark cycles demonstrated that circadian (24-hour) IOP measured in the habitual body positions (sitting while awake and supine while asleep) was significantly higher during the nocturnal period than the diurnal period (52, 54, 56). This circadian IOP pattern was observed in younger and older healthy subjects, as well as glaucoma patients. Among individual subjects, two-thirds of glaucoma patients and over 90% of healthy controls had IOP peaks during the nocturnal period (66). Similar results have been found by other investigators under a hospital setting (35, 93). When the effects of changes in body position are eliminated by considering supine measurements only, nocturnal IOP in healthy adults was found to be slightly higher than diurnal IOP (52, 54). In myopic younger subjects and older glaucoma patients, the nocturnal IOP is slightly lower than the diurnal IOP (53, 56).

5 Animal models to study circadian variations of IOP

Circadian variations in IOP of rabbits was first described in 1961 by Anjou (3) who found IOP to be elevated at night and lower during the daytime. Unlike humans, the vertical distance between the eye and heart does not change significantly in habitual body positions in rabbits. Subsequent investigators confirmed these results although some concerns persisted about the effect of nocturnal light and manipulation of the rabbits for IOP measurements (48, 79). Nevertheless, studies utilizing implantable pressure sensors and telemetry have confirmed this pattern of circadian IOP change (2, 60, 73, 81). Similar patterns of circadian IOP, with an elevated IOP at night, have been described in anesthetized mice (1) and in conscious and restrained rats (64), cats (21), and non-human primates (67). However, continuous IOP monitoring using telemetry under conscious and freely moving conditions have not been reported in these animals. The effect of habitual body position on 24-hour IOP pattern in these animal species, particularly in cats and non-human primates, can be significant under more physiological conditions.

The previously mentioned implantable IOP telemetric monitors can also be used to monitor long-term IOP in rabbits. Schnell et al. (81) and McLaren et al. (22, 59, 60) used similar telemetric techniques to record IOP continuously in conscious and unrestrained rabbits. The transmitter was placed in the dorsal neck between the scapulae. A fluid-filled catheter was threaded from the transmitter, subcutaneously between the ears, over the orbital rim, then subconjunctivally to the anterior chamber (22, 59, 60) or vitreous (81). Pressure readings were broadcasted to receivers mounted in the animals' cages. This type of device was not suitable for human use because it required a battery powered extra-ocular pressure transducer and transmitter. However, it did demonstrate the feasibility of long-term or permanent IOP monitoring with telemetry.

6 Mechanisms for circadian IOP variations

Mechanisms for the nocturnal IOP elevations in animals are different from those in humans. Mechanisms for the nocturnal IOP elevation have been studied extensively in rabbits, suggesting a role of the sympathetic nervous system (10, 30, 33, 49, 50, 97, 98). Surgical removal or sectioning of the sympathetic pathway results in a significant reduction of the circadian IOP eleva-

tion (10, 33, 49, 50), while electrical stimulation of the cervical sympathetic trunk causes an IOP elevation in the late diurnal phase as well as an increase of aqueous humor norepinephrine level (30). Norepinephrine, the major neurotransmitter of the sympathetic system, has been found to be elevated in aqueous humor during the nocturnal phase, in conjunction with nocturnal IOP elevations (49, 97, 98).

In humans, the nocturnal IOP elevation in habitual body position is mainly due to the postural change to recumbent at night, which is generally associated with a decrease of sympathetic activities. Excluding the postural IOP effect, the effect of the sympathetic nervous system on human IOP is less clear. While intravenous epinephrine appears to increase aqueous flow (38), patients who have had adrenalectomy do not demonstrate any significant change in aqueous flow in either the diurnal or nocturnal periods (58). Furthermore, intravenous infusion of norepinephrine sufficient to change cardiovascular dynamics does not appear to have an effect on aqueous humor flow at night (89).

Further uncertainty about the mechanisms for the circadian variation of IOP in humans stems from the fact that humans are diurnally active while most of the non-primate mammals studied, including rabbits, are nocturnally active. Thus, while adrenergic levels in rabbits are elevated during the nocturnal phase, in conjunction with the IOP elevation (49), the reverse is true in humans with nocturnal IOP elevations occurring in the setting of reduced epinephrine and norepinephrine levels (89). Nocturnal reduction of these circulating hormones coincides with a nocturnal reduction in aqueous flow of 50% or more in healthy as well as glaucoma patients (44, 45, 76). The nocturnal reduction in aqueous flow is also not affected by eyelid opening, body position, or IOP level (15, 88). As well, subjects who were kept awake through their normal sleep phase demonstrated significant reduction in aqueous flow compared to daytime levels, although the magnitude of reduction was approximately half of the reduction in sleeping subjects (76). This suggests that aqueous flow rates are at least partly entrained to the circadian cycle, and not just a function of being asleep or awake. Therefore, if all other factors remained equal, it would be expected that a significant reduction in IOP occur at night in humans instead of the approximately unchanged IOP observed when the effect of body position is eliminated.

There are other factors that can influence IOP according to the Goldmann equation discussed above. A recent study examining the circadian variations in aqueous humor dynamics in young healthy subjects indicates that outflow facility does not change significantly at night and thus cannot account for the observed IOP pattern(82). Mathematical modeling based on measurements in this study indicates that circadian variation in episcleral venous pressure is a possible candidate to explain the 24-hour IOP pattern in humans.

7 Clinical significance of IOP variations

Some investigators have suggested that fluctuations in IOP may be an independent risk factor, other than the elevated IOP, for progression of glaucoma, and may even be more important than the average IOP measurement in the office (4, 61, 94, 100). Among IOP variations, 24-hour IOP variations may be particularly important to glaucoma pathogenesis due to the timing of 24-hour change of systemic blood pressure. It has been postulated that nocturnal elevation in IOP, combined with the drop in systemic blood pressure that normally occurs during sleep, may result in compromise of optic nerve head perfusion in susceptible individuals. In support of this concept, Graham et al. (31) have shown that glaucoma patients with exaggerated nocturnal declines in systemic blood pressure had significantly greater disease progression rates.

Exacerbating the potential significance of the nocturnal IOP elevation is the problem that not all IOP-lowering treatments are effective at night. Two classes of IOP-lowering drugs, prostaglandin analogues and carbonic anhydrase inhibitors, appear to maintain good efficacy at night (55, 70, 71, 83). The other two classes of IOP-lowering drugs, beta-adrenergic antagonists and alpha-2 adrenergic agonist appear to have a minimal to weak noc-

turnal efficacy (55, 70, 71). When diurnal IOP is sufficiently controlled by medical therapy during daytime, the nocturnal IOP may not be fully controlled since a non-invasive laser surgery can still lower nighttime IOP, but not the daytime IOP (46). It also appears that incisional glaucoma surgery provides better 24-hour control of IOP than medical therapy (41, 62).

The variability of IOP and treatment efficacy highlights the need for IOP measurements over a 24-hour period in patients. However, nocturnal pressure measurements are difficult to obtain. The only way of assessing nocturnal IOP in humans is with overnight admission of a patient into a sleep laboratory or hospital for periodic pressure measurements. Current clinical practice typically involves only periodic measurement of IOP every few months during office hours. This approach is sub-optimal, providing an incomplete picture of the complex IOP variation in a small number of patients.

8 Continuous IOP monitoring strategies and devices

Previous attempts to provide more frequent IOP measurements have not produced a device suitable for routine clinical use. However, a review of these efforts may provide insights into what is needed to overcome the difficulties associated with making a clinical device.

Periodic IOP measurements can be performed using a number of different devices including applanation tonometers, Mackay-Marg type tonometers, non-contact "air-puff" tonometers, and indentation tonometers. These devices are used to perform single IOP measurements or short tracings of IOP over 2-4 minutes. Diurnal IOP curves based on multiple office IOP measurements at different times of the day can provide additional data, but the process is labor intensive and time consuming for the patient if performed in a single day. Diurnal pressure curves typically will represent only a portion of the 24-hour IOP pattern. If nocturnal pressures are measured, the process becomes impractical for most clinics. Another issue is that while IOP measurements can be made during the nocturnal period, the patients are necessarily awakened and eyes need to be opened prior to the measurements. This creates some uncertainty as to whether or not nocturnal IOP measurements truly represent the pressure during sleep in humans.

Self-monitoring of IOP with various devices is a strategy that has been attempted by several groups of investigators to obtain more frequent IOP measurements (9, 11, 34, 37, 42, 43, 85, 87, 95, 99). The reliabilities of the results are variable and appear to be patient and device dependent. Only certain patients will be suitable for self-monitoring since it may require the use of topical anesthetics as well as a significant amount of manual dexterity for most devices. Expense can also be considerable for the patient depending on the type of device selected. As well, self-monitoring IOP cannot cover the sleeping period.

Continuous IOP monitoring is a strategy to automatically measure IOP throughout a 24-hour period, either on a temporary or permanent basis. Temporary monitoring would involve collection of IOP data over a finite period, likely 24 to 48 hours. It would necessarily be non-invasive using a contact or non-contact device coupled with a data collection system. This temporary procedure can be repeated when necessary. Permanent monitoring would likely involve an implantable pressure sensor coupled with an external data collection system. These two approaches will likely be complimentary, providing different types of data and having different clinical indications.

9 Temporary IOP monitoring

Temporary IOP monitoring over a finite period is not a new idea. Half a century ago, Maurice (57) developed an automated recording indentation tonometer mounted on the forehead and held in place on the eye with a headband. Nissen (68, 69) later developed a device termed an 'applanating suction cup' which was essentially an applanation tonometer held in place by a suction ring. Both these devices were only suitable for short term IOP monitoring of less than 1 hour.

Other investigators have tested devices to externally measure IOP over a longer period of time.

Cooper et al. (17-20) developed a device they called a scleral guard ring. The device utilized a capacitive pressure sensor to detect deformation of the sclera with changes in IOP. A fundamental issue with this approach was apparent during animal testing showing that calibration curves varied significantly with ocular rigidity. In addition, eyes with relatively low ocular rigidities exhibited a time-dependent pressure decay that limited the IOP measurement accuracy (18). The likely reason is that sclera is a viscoelastic material that undergoes relaxation in response to changes in stress such as IOP fluctuations (13, 23). Individual eyes also exhibit significant variability in scleral rigidity (72), as well as potential regional variation in scleral thickness. These characteristics of sclera limit the utility of attempting to measure IOP by scleral applanation. A similar system has not been reported with corneal applanation, but it is likely that the cornea would also undergo stress relaxation in response to prolonged applanation (101).

Another approach has been to measure corneal deformation with changes in IOP. Greene and Gilman (32) developed silicone contact lenses with embedded strain gauges to measure the change in the meridional angle of the corneoscleral junction with variation in IOP. The authors tested the device in rabbits and reported that the strain gauge output appeared to be linearly related to IOP for physiologic pressure ranges. The authors estimated that the change in the angle, based on rigidity data for cornea and sclera, would be on the order of 0.016 to 0.020 radians per mmHg. To detect changes this small, the contact lenses needed to be custom molded for individual eyes in order minimize artifactual movement of the strain gauges.

Leonardi et al. (47) have updated the concept of using strain gauges embedded in soft contact lenses to measure deformation of the cornea associated with IOP changes. The authors were able to detect changes in the radius of curvature of enucleated porcine eyes of approximately 3 μm per mmHg of pressure using a temperature compensated strain gauge embedded in the circumference of a silicone contact lens. At this sensitivity, however, the system would likely be subject to significant motion artifacts unless the contact lenses were custom molded as described by Greene and Gilman (32). No reports of *in vivo* animal or human testing have been published.

An issue with temporary pressure monitoring is the assumption that 24-hour IOP patterns are conserved. The circadian IOP patterns appear to be highly reproducible for groups of patients (52, 54, 56). However, if individual 24-hour IOP patterns are not conserved, then a single usage of an IOP monitor would be of limited utility. The reproducibility of individual 24-hour IOP profiles remains to be demonstrated.

10 Permanent IOP monitoring

Permanent IOP monitoring involves collection of IOP data over an indefinite period of time. The concept of a permanent, implantable IOP monitor is also not new. Forty years ago, Collins (16) pioneered the development of an implantable capacitive pressure sensor for monitoring IOP. It consisted of a pair of parallel spiral coils encased within a gas-filled plastic "pill." As the pressure in the eye changed, the distance between the coils changed due to compression of the gas bubble, resulting in a change of the capacitance and resonant frequency of oscillation which could be detected externally. Svedbergh et al. (5, 78, 86) updated this concept by placing a pressure sensor on an intraocular lens (IOL), taking advantage of the potential space created within the lens capsule during cataract extraction, and eliminating the need for a separate surgical procedure. Walter et al. (80, 90, 91) and Stangel et al. (84) have further refined this concept, adding telemetry and micro-chip technology to the intraocular sensor to solve the problems of signal noise.

Other possible permanent IOP sensors have been proposed. Two groups of independent researchers investigated the concept of measuring IOP variations by incorporating strain gauges into a silicone band scleral buckle. The goal was to measure changes in the circumference of the sclera due to variations in IOP. Wolbarsht et al. (96) tested the system in cats and found that IOP could be measured accurately, but individual *in vivo* calibration was required due to significant variability in scle-

ral rigidity. Flower et al. (28) described the use of a similar system for monitoring IOP in conscious unrestrained primates. However, due to the need for surgical implantation, the authors viewed it as a research tool for gaining information on IOP patterns instead of a method that could be used clinically in humans.

The best location in the eye for a permanent pressure monitoring device remains to be decided. Current developments would seem to favor the anterior chamber or capsular bag in the case of the IOL-based monitor. However, the vitreous has also been utilized, and one recent proposal has suggested placing a transducer at the surface of the choroid (77). As technological progress allows for smaller devices, the options for the location of a pressure sensor increase. Advancements in bioengineering, wireless communication, and biocompatible materials will likely enable the fabrication of small, efficient implantable sensors suitable for continuous IOP monitoring in the near future.

For permanent IOP monitoring, the main concern remains the safety associated with surgical implantation. Although the technology for permanent IOP monitoring is promising, the need for surgical implantation makes the indications and regulatory approval of these devices for human use uncertain. If these devices become available for clinical use, they would most likely be suitable for patients with advanced glaucomatous optic neuropathy, or those already being considered for ocular surgery. However, no human testing results have ever been reported for an implantable IOP monitor. Because of the need for surgical implantation, the clinical utility of permanent continuous IOP monitoring would more than likely need to be demonstrated before such devices can eventually gain regulatory considerations and widespread use. Acquiring this knowledge will likely require the successful development of temporary non-invasive IOP monitoring. Unfortunately, the technological issues surrounding temporary 24-hour IOP monitoring are at least as difficult as measuring pressure invasively, and likely more difficult. Problems of measurement noise, eye movement, and the need to measure IOP through closed eyelids present significant hurdles to both temporal and permanent IOP monitoring.

Another issue for both temporary and permanent IOP monitoring is the optimal time interval for measurements. Although pressure measurements at a very high frequency are technically possible, the difficult and energy requirements increase with measurement frequency. Previous attempts at continuous pressure measurement have found significant lability in IOP with eye and body movements (16, 60). The clinical significance of these brief IOP spikes is unclear and even measurements every few minutes would be a marked improvement over current clinical practice.

11 Perspective

Intraocular pressure is a dynamic parameter that varies over short and long periods of time. A clear circadian rhythm of IOP has been demonstrated in humans and several animal species. The physiologic mechanisms for the circadian IOP variation are likely related to the postural change in humans and the increase of sympathetic activities in rabbits. While the clinical significance of IOP variations remains to be fully elucidated, the need for more frequent IOP measurements than is provided with periodic office visits has long been recognized and attempts to overcome this limitation have been proposed and tested for more than 40 years.

The technological capability for permanent continuous IOP monitoring appears to exist at this time based on animal models using telemetry. The feasibility of implanting a continuous IOP sensor has been demonstrated in laboratory rabbits. However, the need for surgical implantation of pressure monitoring devices in human patients remains a significant point of concern, both from a regulatory and ethical point of view. Even if these permanent devices are eventually approved for human use, fundamental questions about the nature of IOP variations will need to be studied using other techniques since surgical implantation of permanent devices would be inappropriate for many glaucoma patients and for all normal subjects.

Temporary, non-invasive IOP monitoring is a more acceptable method of obtaining 24-hour IOP data, but the technological barriers to a clinical device are at least as difficult as permanent IOP monitoring devices. Previous attempts at 24-hour IOP monitoring have not yielded a clinically useful device. However, these efforts have identified the work that needs to be accomplished to make these instruments a reality. The development of this technology would be a critical next step in understanding and managing IOP variations in glaucoma, a leading cause of blindness.

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